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CKJ REVIEW

Snow White's tale in nephrology: the emerging threat of skin-whitening creams on kidney health

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ABSTRACT

The timeless tale of Snow White, with its emphasis on fair skin as a beauty ideal, mirrors a contemporary issue in nephrology: the harmful impact of skin-whitening creams on kidney health. Fairness creams have deeply embedded themselves in global society, driven by a pervasive obsession with lighter skin tones as a symbol of beauty. This widespread use reflects deeply rooted cultural beliefs and social norms, despite the significant health risks associated with these products. Despite regulatory bans, these creams often contain hazardous substances such as hydroquinone, mercury, and arsenic, posing serious health risks. Mercury, a frequent component of these cosmetics, disrupts melanin synthesis by inhibiting tyrosinase, leading to serious health risks, including nephrotoxicity. Chronic exposure to mercury from cosmetics can harm the liver, kidneys, nervous system, and eyes, with the kidneys being particularly vulnerable. This review discusses the link between fairness creams and the occurrence of glomerular diseases. It delves into the mechanisms by which skin-whitening agents cause kidney damage. Mercury can induce kidney damage through direct cellular toxicity and immune-mediated mechanisms. We present evidence from case studies and published studies connecting mercury-containing creams to nephrotic syndrome. Minimal change disease and membranous nephropathy are the most frequently reported glomerular diseases due to these products. Treatment typically involves stopping the use of the creams and chelation therapy, with glucocorticoids and immunosuppressants for non-responsive cases. The prognosis is generally favourable, with high remission rates, and relapses are seldom reported. By highlighting the nephrotoxic effects of skin-whitening creams, this manuscript emphasizes the urgent need for stringent regulatory oversight and increased public awareness to prevent further health complications.

Keywords: fairness creams, kidney health, MCD, membranous nephropathy, mercury, nephrotic syndrome

INTRODUCTION

The pursuit of fair skin, deeply rooted in cultural and historical contexts, has persisted throughout centuries. Since ancient Rome, toxic substances such as white lead mixtures, 'white lightning', and 'moonshine' powders have been used to achieve a pale complexion [1–3]. In many parts of the world today, the desire for lighter skin remains a dominant beauty standard, with skin-whitening creams widely used across Africa, Europe, North America, and Asia, showing a prevalence of 27%–77% in community samples [4–6]. These products, while often marketed as cosmetic enhancers, might carry significant health risks. They

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may contain hazardous substances such as heavy metals, the content of which may exceed recommended limits. The kidneys are particularly susceptible to injury from toxic metals present in skin-whitening creams. This damage can manifest as glomerular diseases, acute kidney injury resulting from acute tubular necrosis, and chronic kidney disease (CKD). Although the nephrotoxic effects of heavy metals have been well-documented in the literature, recent case reports and studies underscore a growing concern over the link between skin-whitening cream usage and glomerular diseases, such as membranous glomerulopathy (MGN) and minimal change disease (MCD). This review places a specific emphasis on the association between fairness cream use and the development of glomerular diseases, integrating recent research findings. It explores the characteristics features, and potential mechanisms driving this correlation and offers insights into current treatment options and possible clinical outcomes.

Fairness creams and heavy metal content

Skin pigmentation is due to melanin produced by melanocytes present at the dermal-epidermal junctions and distributed to the keratinocytes of the skin. Melanin itself is synthesized from L tyrosine through enzymatic reactions with tyrosinase, a copper-containing enzyme acting as the rate-limiting enzyme of melanin biosynthesis [7]. This enzyme is the potential target for various skin-lightening agents, including hydroquinone, arbutin, azelic acid, kozic acid, etc. [8, 9]. Most skin-lightening creams claim to reduce the melanin content and lighten the skin. These fairness creams commonly contain waxes, moisturizers, antioxidants, and preservatives, but may also contain various pharmaceuticals such as hydroquinone, unknown herbal products, and even steroids [10, 11], Several heavy metals, such as lead, cadmium, arsenic, nickel, cobalt, and mercury, can also be found in a wide range of cosmetic products, such as lipsticks, mascaras, hair dyes, and skin-whitening creams [7, 8, 12–15]. Further, these cosmetics may contain different content or higher content of the ingredients than mentioned in the product label. A study on unregulated and unlabelled Omani cosmetics revealed significant amounts of chromium, copper, and lead [15]. Similarly, research from Pakistan showed that various brands of sunblock creams had the highest concentrations of nickel, lead, and chromium, while lipsticks had elevated levels of iron, and lotions contained maximum levels of cadmium [16]. Studies have also shown elevated levels of urinary biomarkers for potentially toxic elements (PTEs) in women who are occupationally exposed to cosmetics. The levels of arsenic and cadmium biomarkers showed a strong and significant positive correlation with kidney damage markers, including urine kidney injury molecule-1 (uKIM-1) and tissue inhibitor matrix metalloproteinase 1 (uTIMP-1) [17]. The presence of such heavy metals in cosmetics poses a latent threat to consumers of all demographics. Hydroquinone, for instance, inhibits melanin production but is associated with severe complications, including carcinogenesis, ochronosis, and DNA damage, leading to its ban in numerous countries [8, 9]. Cadmium toxicity may both tubular and glomerular damage [18]. Chronic exposure to lead can adversely affect the nervous system, liver, and kidneys and result in anaemia, hypertension, cardiovascular disease, immune deficiency, and developmental problems such as cognitive deficits, learning disabilities, and memory loss [19]. Similarly, mercury and arsenic, potent nephrotoxins, disrupt cellular processes and can cause acute and chronic kidney damage, neurotoxicity, and even cancer. The 'Crema de Belleza—Manning' debacle in 1996 serves as a cautionary tale, emphasizing the need for rigorous regulatory oversight on the compositions of cosmetics [20]. Following the discovery of alarmingly high mercury levels within the cream, the Mexican Secretary of Health issued an epidemiologic alert to enhance surveillance against acute and chronic mercury toxicity in border states [20]. Despite a ban on its use in cosmetics in many countries and the Minimata convention limiting a concentration of 1 mg/kg (1 ppm) for lightening products, many such products contain far higher concentrations of mercury and are available easily in the market [21]. The rules for cosmetic products about licensing and sale are not as strict as those for drugs in most countries. A systematic review examining mercury exposures from 787 skin-lightening products showed the prevalent use of mercury as a key ingredient in such products globally. The overall pooled median mercury level was found to be 0.49 μg/g with an interquartile range (IQR) from 0.02 to 5.9 [22]. In a community-wide case series from Hong Kong, urine mercury concentrations were high among individuals who had recently used the cream within 45 days, while blood mercury concentrations showed an increase as early as 2 days post-cream application [23]. Narayanan *et al*. reported more than 10 000 ppm of mercury in all five of the analysed fairness creams, substantially greater than the 1 ppm permitted by WHO [24].

Health hazards due to mercury in cosmetics

Heavy metals are known to cause kidney injuries. For example, mercury has been associated with kidney injuries, including the public health disaster of Minimata in Japan [25]. Mercury is well-established as both a nephrotoxin and a neurotoxin [26, 27]. Apart from kidney toxicities mercury can cause central nervous system toxicities that can manifest as hypodynamia, insomnia, headache, dizziness, tremors, hypomnesia, and numbness [27]. Chronic fatigue, weight loss, and anorexia have been reported. Neurological complications are more common than kidney disorders. In a case series involving 16 Chinese patients with mercury intoxication, six patients developed proteinuria as a result of skin-lightening products, and all of the patients also had neurological symptoms [28]. Patients might experience gastrointestinal symptoms such as nausea, metallic taste, gingivostomatitis, and hypersalivation [29]. The FDA has already issued warnings regarding the possibility of vision loss due to mercury poisoning from unregulated beauty products [30].

Glomerular diseases associated with skin-whitening products

The seminal case reported by Barr *et al*. in 1972 represents a significant milestone, shedding light on the correlation between skin-lightening creams and nephrotic syndrome [31]. Subsequent investigations have corroborated these findings, with a plethora of case reports and studies implicating fairness creams in the pathogenesis of glomerular diseases [24, 32–37]. Histopathological examinations have revealed associations between the use of these cosmetic agents and glomerular diseases such as MCD, MGN, and focal segmental glomerular sclerosis (FSGS). In a retrospective series of mercury-associated glomerulonephritis by Qin *et al*., involving 35 Chinese patients, renal histopathology showed that 60% had MCD, 37.1% had MGN, and 2.9% presented with FSGS [36]. Similarly, Gao *et al*.'s retrospective analysis of 172 patients diagnosed with mercury poisoning showed that 26.74% had kidney dysfunction, with

89.13% of cases presenting with nephrotic syndrome [32]. MGN was the predominant pathological finding found in 51.43% of the patients. Remarkably, cosmetics emerged as the primary culprit, accounting for 71.74% of these cases. See Table 1 for a detailed list of important studies on the use of cosmetic agents and their association with glomerular diseases.

Membranous glomerulonephritis

MGN is one of the most commonly associated GN with the use of cosmetics. Most cases of such MGN cases are characterized by the absence of serum anti-PLA2R antibodies and glomerular PLA2R antigens [22, 34]. Deposits of IgG1 and IgG4 are observed along the glomerular capillary loops [36]. In a series of Li *et al*. on mercury-associated MGN, out of 10 patients, three had acute tubulointerstitial injury and immunofluorescence findings showed granular deposits of IgG1 (predominantly) and IgG4 and C3 (mostly accompanied by deposits of C4 and C1q) along the glomerular capillary wall [34]. In a study by Qin *et al*. comparing ultrastructural features between patients with mercury-associated MGN (M-MGN) and idiopathic MGN (I-MGN), the effacement of the foot process was less severe in M-MGN than in I-MGN. The cut-off foot process width of $<$1654 nm differentiated M-MGN from I-MGN with high sensitivity (92.3%) and specificity (83.3%) [37]. In a recent series reported by Narayanan *et al*., an association was observed between the use of fairness creams and 13 out of 15 cases of Neural Epidermal Growth Factor-like Protein 1 (NELL-1)-associated MGN [24]. The cohort of individuals using fairness creams was predominantly young, showed no particular gender preference, and presented with relatively subtle symptoms despite nephrotic-range proteinuria. NELL-1 serves as an autoantigen linked to both primary and secondary MGN. Examination of the skin creams revealed exceedingly high levels of mercury ($>$104 times the permissible limit of 1 ppm).

MCD and FSGS

Following MGN, MCD is another commonly reported cause of nephrotic syndrome associated with the use of fairness creams. In a series by Zang *et al*., four cases of MCD were identified following exposure to mercury-containing skin-lightening creams for 2 to 6 months [33]. Treatment involved discontinuing the creams and administering chelation therapy with D-penicillamine; two patients also received steroids. Blood mercury levels normalized within 1 to 7 months, while urine mercury levels took 9 to 16 months to normalize. All patients experienced complete remission of proteinuria within 1 to 9 months. In another series by Qin *et al*., MCD was found in 21 patients (60% of cases) and FSGS in one patient (3% of cases) [36]. The remission rates for MCD were lower compared to MGN, and the duration of mercury exposure was shorter. Additionally, urinary mercury concentrations in MCD patients were significantly higher than in those with MGN.

Regarding IgA nephropathy, the evidence for the association of IgA nephropathy with cosmetic products and heavy metals is much weaker compared to that with MGN and MCD being limited to case reports and case series [38, 39]. Gao *et al*. reported only one case of IgA nephropathy out of 35 patients who underwent renal biopsy after developing nephrotic syndrome due to chronic mercury intoxication [32]. Another series of 41 patients with glomerular diseases presumably caused due to mercury-containing cosmetics reported IgA nephropathy in conjunction with MCD in five patients [40]. Given that IgA nephropathy is the most common glomerular disease and mesangial IgA staining is common, whether these observations are coincidental or there is some association between IgA nephropathy and cosmetics containing mercury is debated.

Pathogenesis

Mercury prevents melanin formation by competing with copper in the enzyme tyrosinase [41]. Inorganic mercury is absorbed from the stratum corneum of the skin. The amount absorbed directly correlates with the amount of mercury in the product. Excretion occurs primarily through urine with a half-life of 1–2 months [42]. Whereas mercury can cause various systemic side effects, the kidneys, having a high affinity for mercury ions, bear most of the toxicity. Inorganic mercury is readily absorbed as Hg^{2+} in the proximal tubular cells, with $\sim$50% of a nontoxic dose found in the kidneys after a few hours of exposure [43] (Fig. 1). Mercury-induced MGN is speculated to be caused by a complex interplay between immunomodulation and direct cellular damage [44]. Organic forms of mercury more commonly affect the nervous system. After systemic absorption and filtration at the glomerulus, mercury is taken up by the OAT1 and OAT3 in the proximal tubule of the kidney [45]. Once mercuric ions gain access to the intracellular compartment of cells, they form strong bonds with protein and non-protein thiol-containing biomolecules like glutathione. Binding to these biomolecules reduces the export of mercuric ions from the cell. Acute toxicity causes tubular necrosis. It disturbs cellular resting membrane potential and cellular integrity. There is disruption of tight junctions by causing their phosphorylation via protein kinase A dependent mechanism [46]. Both these events lead to altered proximal tubular cell permeability and proteinuria in acute exposure to high quantities of mercury. Based on this mechanism of oxidative injury, urinary levels of *N*-acetyl-β-D-glucosamidase and B2microglobulin can serve as biomarkers of kidney injury in the early stages [43]. The pars recta is the segment most frequently affected. The temporal association between mercury entry and injury pattern has been documented by electron microscopy at 6 hours after exposure, cells begin to lose microvilli with swelling of mitochondria, 12 hours after exposure there is rupture of the plasma membrane, decreased contact with the basement membrane and distortion of cell shape, and after 24 h, cellular fragments can be identified in the tubular lumen, junctional complexes between cells are absent, and nuclear structure is compromised [47]. Chronic mercury exposure, however, can cause proteinuria by immune mechanisms. It binds to proteins, which can act as haptens, to form antigen-antibody complexes, that get deposited in the glomerulus and incite inflammation, leading to mesangial proliferation, MGN, or MCD. This ultimately results in nephrotic syndrome [48]. Mercury can also directly damage podocytes, potentially contributing to proteinuria. Animal models have shown the immunogenic effects of mercury. Genetically susceptible mice demonstrate a T helper 2-predominant immune response with increased production of interleukin-2 and interleukin-4 when presented with T cells from mercury-exposed mice [49]. Increased interleukin-4 levels cause B cell proliferation with the production of IgG1 autoantibodies in mice, the same IgG subclass that is predominant in patients with MGN due to Hg toxicity. This leads to impaired T cell survival and peripheral tolerance due to impaired apoptosis and oxidative stress. Moreover, exposure to mercury components triggers an abnormal immune response, leading to polyclonal B and T cell activation and the production

Table 1: Detailed list of important studies on the use of cosmetic agents and their association with glomerular diseases.

Study	Population	Exposure	Duration of exposure	Presentation	Kidney disease	Treatment	Evolution	Mentions	Ref
Li SJ, 2010	11 patients, Chinese population Follow-up 6–48 months	Mercury from pills (5), fairness cream (4), hair-dyeing (1), vapours (1)	2–60 months Fairness cream 4–12 months	3 patients—NS, 8–proteinuria All patients had normal kidney function	All patients had MGN LM: thickened GBM and mildly proliferative mesangial cells. ATIN- in 3 patients. IF: granular deposits of IgG and C3 along the glomerular capillary wall, mostly accompanied by deposits of C4 and C1q. IgG1 and IgG4 (predominantly IgG1) deposits along the glomerular capillary loops	All patients halted the exposure 5 patients were treated with ACEI/ARB 4 patients received chelation therapy (urinary mercury concentration higher than 100 μg/l)	9 patients- complete remission during follow-up (1–4 years) 1 patient who was exposed to mercury again after remission and had a relapse after 1 month	The urinary mercury concentrations were 1.5 to 50 times higher than reference value 6 women with pre-existing autoimmune diseases	[34]
Tang HL, 2013	4 patients, all females, Hong Kong	Mercury-containing skin-lightening cream	2–6 months	NS and heavy proteinuria (8.35–20.69 g/day)	All patients MCD	Stop cosmetic cream use and chelation therapy with D-penicillamine. Two patients received steroids.	All patients achieved complete remission of proteinuria within 1–9 months.	Mercury content of the facial creams was very high (7420–30 000 parts per million) Blood mercury levels normalized in 1–7 months; urine mercury levels took longer (9–16 months).	[33]
Qin AB, 2019	35 patients, China	Mercury from skin lighting cream, mercury pills, hair-dyeing agents	1–120 months	All patients had proteinuria and normal kidney function 62.9% had NS Median proteinuria 4.6 g/24h	60% MCD 37.1% MGN (negative for PLA2Rc Ab and glomerular Ag) IgG1 (61.5%) and IgG4 (46.2%) deposits were noted along the glomerular capillary loops. 2.9% FSGS	16 patients did not receive immunosuppressives or glucocorticoids before chelation (9 with MCD, 7 with MGN)/Received 4.5 ± 2.8 (range 1–12) rounds of mercury detoxification. Achieved complete remission in 4.5 months (range 0.3–23) Monotherapy with mercury detoxification had an 87.5% complete remission rate. 11 patients initially receiving immunosuppressive treatment (7MCD, 4MGN). Received 3 rounds of mercury detoxification (range 2∼8). Achieved complete remission in 2.5 months (range 1.0–18.0).	2 with MCD- no remission until glucocorticoids 1 case of MGN- no remission until glucocorticoids and cyclophos-phamide	The remission rate of patients with MCD and MGN was 77.8 and 100%, respectively. No significant difference in rounds of mercury, or remission duration between patients with MCD and MGN Patients with MCD had a significant shorter duration of mercury exposure than patients with MGN 4 (range 1.0–120.0) versus 9.5 (range 2.0–120.0) months.	[36]

Table 1: Continued

Study	Population	Exposure	Duration of exposure	Presentation	Kidney disease	Treatment	Evolution	Mentions	Ref
Chan TYK, 2020	Multiple case reports: 30 Asian females from Hong Kong, China, UK	Mercury from lightning skin	2–60 months	Predominant NS, media proteinuria 5.7 g/24h	16 with MCD 2 with MCD/IgA 7 with MGN 1 with FSGS	7 received chelating agents 16 received chelating agents plus steroids	7 patients with no chelation therapy 23 patients received chelation therapy, from which 12 received steroids	Time to remission of proteinuria reported in 9 subjects following treatment with chelating agents or chelating agents plus steroids (median 2 months, range 1–9 months) Time to remission was longer in 3 subjects (cases 8–10) not treated with chelation therapy (≥12 months).	[35]
Gao Z, 2022	46 patients, China Follow-up 6 months	Mercury industrial exposure in 2 patients (4.35%), cosmetics in 33 (71.74%), application of folk prescription in 10 (21.74%), and mercury pollution in the living environment in 1 (2.17%)	Medium duration 12 months	41- nephrotic syndrome, 5- proteinuria	51.4% MGN, 37.4% MCD 8.57% MPGN 2.86% IgAN	25 patients—chelation therapy 12- mercury chelation and glucocorticoids + chelation + glucocorticoids and immunosuppressives	No difference in complete remission among 3 methods.	Gradual decline of urinary mercury concentrations, 24-hour urinary total protein level declined.	[32]
Qin AB, 2021	13 patients, China	Mercury exposure by skin-lightening creams in 38.5% mercury-containing pills 30.7% Mercury from hair-dyeing agents in 23.1% unknown 7.7%	2–120 months Fairness cream unknown/2–7 months	Medium proteinuria /24 h: 3.67 (2.87–5.93)	All patients had MGN	All patients received chelation therapy 10 (76.9%) received glucocorticoids combined with cyclophosphamide 2 (15.4%) received glucocorticoids combined with cyclosporine A	1 patient achieved complete remission without immunosuppressive agents 2 patients were lost to follow-up The remaining 11 (84.6%) achieved complete remission after an average of 20.3 ± 9.8 months	Mercury exposure linked to less severe foot processes effacement vs idiopathic MGN Better prognosis in M-MGN due to minor podocyte damage.	[15]
Narayanan R, 2024	NELL-1 MGN cohort, 13 of 15 patients using skin fairness creams, India	Mercury from fairness creams	2–24 months (median 4 months)	nephrotic-range proteinuria (mean, 13.33 ± 4.45 g) Normal kidney function	All patients MGN	All patients stopped using the cream + RAS blockade. 2 patients received empiric corticosteroids before diagnosis. One patient received rituximab due to persistent nephrotic state.	The face cream group: 6 patients achieved complete remission. 7 patients achieved partial remission. Mean duration to partial remission: 4.8 (±3.25) months. Mean duration to complete remission: 10.3 (±2.73) months.	Fairness creams with high content of mercury (>104 times higher than permissible limits of 1 ppm).	[24]

LM: light microscopy, IF: indirect immunofluorescence, ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, NS: nephrotic syndrome, RAS: renin-angiotensin system, MPGN: membranoproliferative glomerulonephritis.

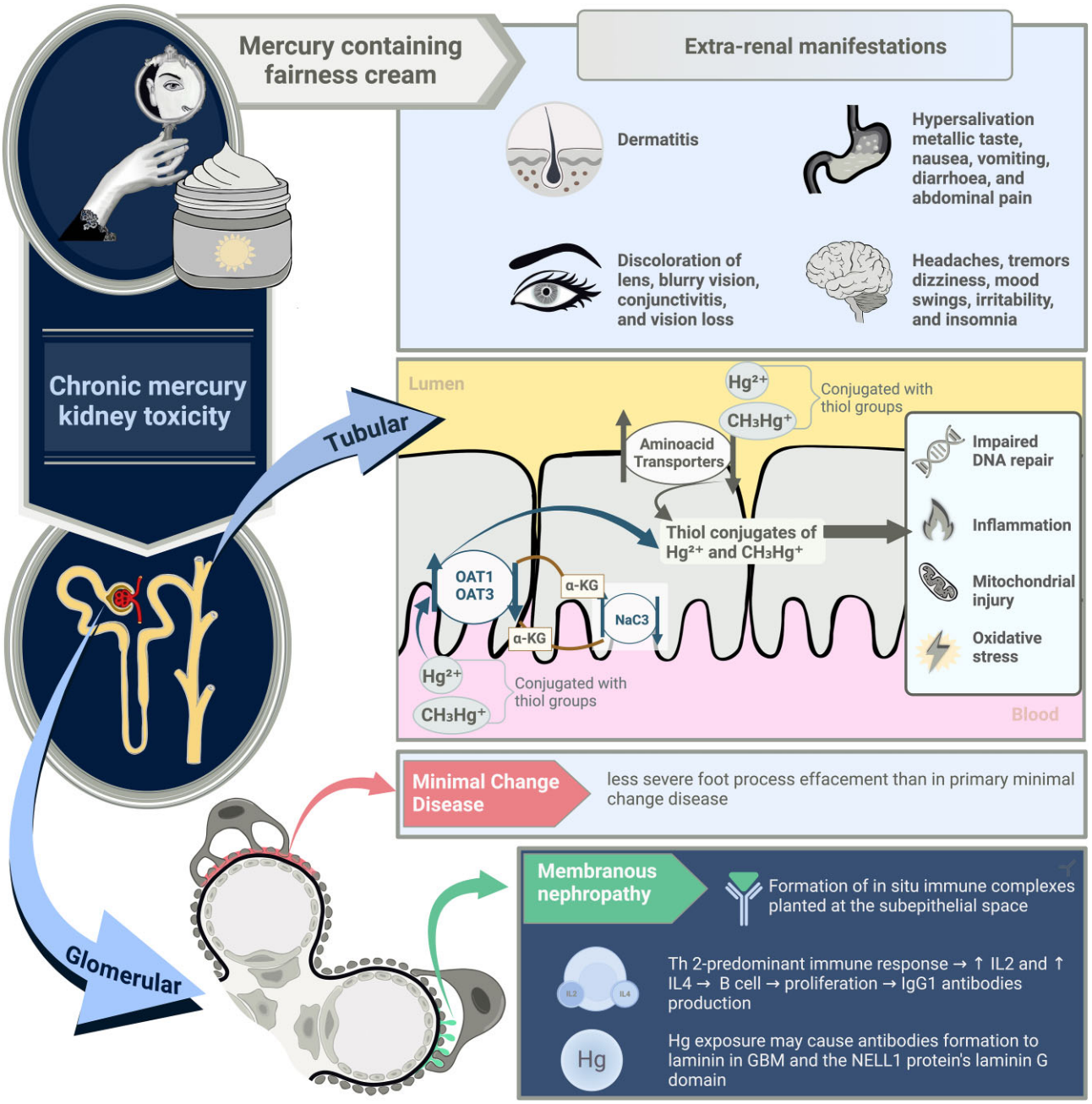

Figure 1: The mechanism of mercury-induced kidney injury along with extrarenal manifestations.

of various autoantibodies such as serum IgG1 and Ig E, anti-DNA, antiphospholipid, anti-laminin-1, and antithyroglobulin, including those targeting glomerular basement membrane (GBM) components [50, 51]. Mercury itself is not detected in the immune complex suggesting that the glomerular damage is secondary to immune activation. Antibodies then react with the basement membrane proteins in the setting of Hg exposure leading to proteinuria. Animal models have shown that mercury has an immunosuppressive effect on T lymphocyte function and can induce autoantibody formation [52]. As mercury itself has a high-affinity binding to sulfanyl groups of proteins, it interferes with multiple cellular processes, including podocyte to GBM crosstalk, which may disturb the integrity of the basement membrane by altering protein conformation. These include cationic proteins such as laminin and fibrillarin that develop strong interactions with negatively charged GBM components. Immune complexes interact with the negatively charged GBM components and transverse to the subepithelial space or act as weak reducing agents to modify protein folding. This may incite complement, supported by an increased frequency of C4 and C1q deposition and IgG1-predominant antibodies within immune complexes in Hg-induced MGN [44]. In addition to IgG1 predominance and C1q expression, Hg-induced MGN often has mesangial immune deposits and is phospholipase A2 receptor negative, distinguishing it from idiopathic MGN [36]. The association of NELL1 positivity in MGN due to mercury exposure is an

area of growing interest. NELL1 is a podocyte antigen identified in a subset of MGN cases characterized by distinct histologic and immunologic features, notably segmental glomerular capillary loop subepithelial deposits with IgG1-dominant staining [53, 54]. While NELL1 is primarily studied for its role in osteoblast differentiation [55], it has also been detected in the kidneys of healthy humans, particularly in the loop of Henle, distal tubular cells, and glomerular podocytes, with minimal expression in mesangial or endothelial cells [56]. In cases of mercury-associated MGN, the mechanism may involve mercury's high-affinity binding to sulfhydryl groups, potentially leading to autoantibody development against laminins, which are important components of the GBM [57] (Fig. 1). This is particularly significant considering the presence of a laminin G domain in the NELL1 protein, suggesting a possible pathogenic link between mercury exposure by using cosmetics and the development of NELL1-positive MGN. The accumulation of mercury in proximal convoluted tubules, where NELL-1 is abundant, may also contribute to autoantibody formation [58]. Pathogenic alterations in the kidney due to mercury have thus far been primarily observed in genetically susceptible mice. This suggests that genetic polymorphisms might also contribute to susceptibility to kidney injury in humans. Mercury exposure from the use of fairness creams could then serve as a 'second hit' to this underlying predisposition, exacerbating the development of nephrotic syndrome.

Other heavy metal exposure, particularly by lead, arsenic, and cadmium also primarily involves kidneys through tubular injury, though glomerular involvement can occur as well. Lead-induced nephrotoxicity due to acute exposure, mostly targets the proximal tubules where intranuclear inclusion bodies containing lead-protein complexes form [59]. This proximal tubular damage impairs reabsorption processes, often resulting in Fanconi syndrome, characterized by the loss of electrolytes in the urine [60]. Chronic lead exposure exacerbates kidney injury by increasing urate secretion, promoting vasoconstriction, and eventually leading to glomerulosclerosis, hypertension, and interstitial fibrosis [61].

Similarly, arsenic exposure, with ~70% being excreted through the kidneys, has been identified as a significant risk factor for CKD. Chronic arsenic exposure is associated with reduced estimated glomerular filtration rate (eGFR), proteinuria, and, in some cases, kidney cancer [62]. In the kidneys, arsenic cause oxidative stress, mediated by increased production of reactive oxygen species and reactive nitrogen species (RNS) [63]. These reactive species cause oxidative damage to lipids, proteins, and DNA, leading to tubular cell vacuolation, interstitial nephritis, and glomerular enlargement.

Cadmium toxicity similarly affects renal function, with ionized cadmium impairing phosphate and glucose transport, disrupting mitochondrial respiration, and causing membrane rupture in proximal tubular cells [59]. Prolonged cadmium exposure results in chronic tubular-interstitial nephropathy, with cadmium accumulating in the kidney medulla and proximal tubule's S1 segment, contributing to progressive renal dysfunction [18].

Treatment and prognosis

Treatment of glomerular diseases caused by fairness creams has a multifaceted approach, implying stopping the use of the cream, chelation therapy, glucocorticoids, and additional immunosuppressive agents. Cessation of mercury exposure and chelation therapy are the cornerstones across all studies, effectively removing mercury concentrations and reducing proteinuria. For example, the study by Li *et al.* demonstrated that chelation therapy led to complete remission in nine out of 11 patients, normalizing urinary mercury concentrations [32]. The response rate to chelation was notably high. In Qin AB's study, 87.5% of patients who underwent mercury chelation achieved complete remission within a median duration of 4.5 months [34]. Similarly, Chan *et al.* reported faster remission rates in patients treated with chelating agents compared with those not receiving chelation therapy [33]. When chelation was not used, there were observed longer time to remission, persistent proteinuria, and kidney function impairment.

In an older Kenyan cohort study, 53% of participants diagnosed with nephrotic syndrome had a history of using skin-lightening creams. Prognosis appeared favourable, with 50% achieving remission, of which 77% did so spontaneously after discontinuing the creams [29].

Although chelation might be insufficient as a standalone treatment for mercury-induced nephrotic syndrome, as the primary source of glomerulonephritis is known and treatable, glucocorticoids should not be recommended as a first-line treatment. Their use should be reserved for cases where chelation therapy failed to alleviate severe/refractory nephrotic syndrome, or for patients with severe clinical characteristics such as renal dysfunction, severe hypoalbuminimea and oedema [30]. Data comparing the effects of chelation therapy with and without immunosuppression are limited. In a study by Gao *et al.*, no significant difference in complete remission rates was observed between patients receiving chelation therapy alone and those treated with a combination of chelation therapy and glucocorticoids or other immunosuppressive agents [30]. However, there are cases of mercury-induced MCD or MGN persistent after chelation therapy, where remission was obtained after corticosteroid therapy [34] and rarely other immunosuppressives [22, 34].

The overall prognosis was favourable, with high remission rates achieved through chelation therapy alone (Table 1). Patients often responded well to glucocorticosteroids and immunosuppressants, frequently attaining complete remission quickly. Most reported cases had normal baseline kidney function. Relapse was rarely observed and was typically linked to mercury re-exposure [30].

Here, we uniquely compile data from most published literature on the nephrotoxic effects of skin-whitening creams. While the link between heavy metals and nephrotoxicity is well-established, recent reports highlighting the development of glomerular diseases concerning these products make this topic particularly urgent. This is the first comprehensive review to move beyond isolated studies and case reports, offering a broader perspective on the issue and emphasizing the emerging patterns of glomerular disease cases worldwide. By addressing the global impact of these harmful practices, we call attention to the urgent need for increased awareness among the general population and policymakers about the potential health risks posed by using skin-whitening creams.

Gaps in the literature

The current literature on the association between cosmetic agents and glomerular diseases has several key gaps. Most studies are small, with sample sizes ranging from 4 to 46 patients, and are typically retrospective and single-centre, limiting their generalizability. There is a need for larger cohort studies to better understand patient characteristics and outcomes.

Additionally, most studies lack long-term follow-up data, which is crucial for determining prognosis and relapse rates. The duration of exposure to harmful cosmetic agents, is often unclear, leaving questions about how long it takes for glomerular damage to develop. Although some studies have measured mercury levels in blood, serum, and urine, there is no consensus on threshold levels linked to proteinuria or renal dysfunction. Treatment approaches also remain ambiguous, with no comparative data on the efficacy of chelation therapy alone, versus its use with immunosuppression, or simple discontinuation of the cosmetic agent. Nearly all patients in the existing studies had normal GFR, which might explain the preference for chelation therapy without immunosuppression; however, this may differ in cases where proteinuria is associated with renal dysfunction. Mechanistic insights are largely extrapolated from animal models, as no study has definitively linked cosmetic agents to specific pathogenic processes in humans. While NELL-1 has been identified in some MGN cases, the role of other antigens and the precise role of NELL-1 in this context remains unclear. Larger, multicentric studies with longer follow-up periods are essential to bridge these gaps and guide clinical management.

CONCLUSION

This review highlights the growing nephrotoxic threat posed by skin-whitening creams, particularly due to their toxic metal content such as mercury. These creams, driven by cultural beauty standards, are increasingly implicated in the development of glomerular diseases like MGN and MCD. The urgent need for global awareness, stricter regulation, and public education is underscored, as continued exposure threatens kidney health worldwide, linking cosmetic practices with severe health outcomes. Clinicians must remain alert to the possibility of heavy metal toxicity in patients with new-onset proteinuria and should specifically inquire about the use of skin-lightening products. A detailed exposure history and elevated serum and urinary mercury levels are critical indicators of mercury poisoning. These environmental toxins are reversible causes of nephrotic syndrome, highlighting the importance of cessation of exposure and/or chelation therapy.

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CONFLICT OF INTEREST STATEMENT

None declared.

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