Skin Lightening and Chronic Kidney Disease: A Tale or A Fact?

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ABSTRACT

***Introduction*:** Skin-lightening (a.k.a. bleaching or whitening) agents have the potential of causing adverse health effects, including skin diseases, high blood pressure, and kidney disease. Nigerian women have the highest rate (77%) of skin lightening practice, while almost 40% of people in countries of Asia use these products. This paper is a systematic review aimed at appraising the evidence on the association of topical skin bleaching agents and CKD in humans.

***Materials and Methods*:** References of relevant articles from the earliest record to October 2019 were obtained following a search of Pubmed, HINARI, and GOOGLE Scholar. Search terms such as skin lightening, skin bleaching, skin whitening, cosmetics were combined with kidney-related terms like kidney, kidney disease, renal, CKD, kidney failure, and renal failure.

***Results*:** Mercury was the specified skin-lightening agent in 13 of the 16 studies, while others did not specify the chemical agent. The most frequent histopathologic patterns of glomerular disease associated with topical application of mercury were MCD (6/11) and MN (6/11). Seven out of 11 studies reported remission after withdrawal of mercurial cosmetic and use of a chelating agent, 2/11 showed remission after only withdrawal of mercury agent while in 2/11 some patients achieved remission only with the addition of steroids, alkylating agents or both.

***Conclusion*:** There is limited high-grade evidence on the effects of topical skin lightening agents on the human kidneys. Majority of available studies are case reports but have demonstrated that MCD and MN are the commonest GN associated with topical mercury exposure, and withdrawal of the mercury agent and chelation results in remission in most patients.

INTRODUCTION

Skin-lightening (a.k.a. bleaching or whitening) agents have the potential of causing adverse health effects, including skin diseases, high blood pressure, and kidney disease. [1] Skin bleaching has become a common practice particularly common among dark-skinned women around the world; however, fair-skinned individuals, men and children are not spared. [1-5] Low self-esteem, believe that lighter skin is associated with beauty, attractiveness, privileges, higher economic and social status; and eradication of racial discrimination amongst others are some reasons for cosmetic skin whitening. [2, 6]

Skin lightening is reportedly most prevalent in West Africa, South Africa, and Asia; although some dark-skinned population in Europe and North America also use them. [1] Nigerian women have the highest rate (77%) of skin lightening practice, while prevalence is almost 40% in Asian countries.7 Commonly used skin-lightening cosmetics contain

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various organic and inorganic agents including mercury, steroids, hydroquinone, tretinoin, arbutin (hydroquinone B-D glucose), Kojic acid, azelaic acid, glutathione, alpha hydroxy acids, niacinamide, amongst others. [8] Mercury, steroids and hydroquinone are the most studied and are associated with adverse effects.

The dermatological adverse effects of these agents are well-known; however, there are still uncertainties regarding the effect of these agents on the kidneys. Although chronic topical exposure to mercury has been associated with secondary glomerular disease and varying degrees of proteinuria, the available evidence from human studies is scarce. [9] Hydroquinone has been linked with increased cell proliferation and adenomas in some animal studies while other studies dispute this; however, this association is not established in humans. [10-12] Not much is known about other agents with regards to kidney damage.

This paper is a systematic review aimed at appraising the evidence on the association of topical skin bleaching agents and CKD in humans.

CRITERIA FOR CONSIDERING STUDIES

Design: This systematic review accepted a wide range of studies that passed a threshold of quality:

- o Cohort studies
- o Case-control studies
- o Cross-sectional studies.
- o Case-controls

Population: Human studies with no age, racial, ethnic or gender restrictions.

Exclusion: Animal studies, reviews, reports, book chapters.

METHODOLOGY

Search Strategy: References of relevant articles from the earliest record to October 2019 were obtained following a search of Pubmed, HINARI, and GOOGLE Scholar. Search terms such as skin lightening, skin bleaching, skin whitening, cosmetics were combined with kidney-related terms like kidney, kidney disease, renal, CKD, kidney failure, and renal failure.

The search strategy was constructed by grouping the free texts and MeSH terms into categories and then combining those using BOOLEAN operator terms in order to capture articles of most relevance. The strategy was used for all databases searched. Articles of most relevance were captured, i.e. the inclusion of crucial references identified through reviews addressing a similar research question. The review was limited to studies presented in the English language only. A series of google internet searches using combinations of the above-stated search words identified other relevant unpublished and grey literature. Authors were contacted when necessary to obtain full copies of articles.

Data Extraction

A data abstraction form was used to standardize the extraction process, limit bias, maximise reliability and ensure identification of all relevant details. Data extraction focused on: study location, study design, sample size, the skin-lightening agent reported, associated kidney disease, evidence for association, and effect size where relevant.

Methodological Quality Assessment

Quality assessment was performed for all included studies using the Quality Assessment Tool for Quantitative Studies (EPHPP, 1998). [13] This tool helped to rate the studies as weak, moderate or strong in various criteria. The criteria assessed were study design, selection bias, confounders, data collection methods, withdrawals and dropout, and power calculation.

Data Synthesis

After a qualitative assessment of the variety of study characteristics, quality, and results, a formal meta-analysis was inappropriate due to the heterogeneity of the study designs and the full range of methods employed and outcomes assessed.The organisation of data and description of patterns across included studies were presented in tables and texts. Given the wide array of objectives and measurements, it was not possible to give and compare overall effect sizes for all studies.

RESULTS

A total of 16,507 studies were identified, out of which 16 relevant studies spanning from 1987 to 2019 were included. [14-29] (Table 1) Nine were case

reports, while only one was a retrospective case-control study (Table 2). Majority of the studies were 'weak' (81.2%). Mercury was the specified skin-lightening agent in 13 of the 16 studies, while others did not specify the chemical agent. None of the studies specifically provided evidence of toxic effects of topical hydroquinone or other bleaching agents on the kidney.

Table 1: Summary of Search Results

DATABASE	SEARCH RESULT	INCLUDED
PubMed	253	8
HINARI	504	2*
GOOGLE SCHOLAR	15,300	6*
TOTAL	16,507	16

** Studies already included from PubMed and/or HINARI search were not duplicated*

Table 2: Types of Studies included

STUDY DESIGN	Frequency (n)
Case-control	1
Retrospective	2
Cross-sectional	3
Case-series	1
Case-report	9
TOTAL	**16**

The clinical presentation of patients reported in the majority of the studies (13/16) was proteinuria, while in 9/16 studies, patients presented with nephrotic syndrome. Eleven out of 13 studies reported the histopathologic pattern of glomerular disease associated; these included MCD (6/11), MN (6/11), FSGS (1/11), and IgA nephropathy (1/11). One study reported acute tubulointerstitial nephritis.[20] Seven out of these 11 studies reported remission after withdrawal of mercurial cosmetic and chelation with sodium dimercaptosulfonate (DMPS) OR D- penicillamine, while 2/11 showed remission after only withdrawal of mercury agent. [17,25] In 2/11, some patients achieved remission only with the addition of steroids, alkylating agents or both. [19,29] Table 3 and 4 summarises the studies included in this review.

DISCUSSION

This study confirms the scarcity of robust evidence regarding topical skin lightening agents and kidney disease in humans. The majority of studies reviewed were case reports/case series, while others were cross-sectional and retrospective studies.

Although case-reports are weak evidence, in some of these studies, the researchers demonstrated an improvement of clinical presentation (reduction in proteinuria/remission of nephrotic syndrome) and reduced urine and serum mercury, after withdraw of mercury-containing agent and chelation. The retrospective studies similarly showed remission of nephrotic syndrome following the withdrawal of mercury-containing agent and chelation. However, in two studies, there were a few patients who required steroids and alkylating agents to achieve remission.[19,29]

The reversibility of symptoms after withdrawal and chelation may suggest a causal role. However, one must consider the drawbacks of case-reports/series such as lack of generalisability, inability to establish a cause-effect relationship, the danger of over-interpretation, and publication bias amongst others. However, case reports are useful for detecting novelties, generating hypothesis and pharmacovigilance as may have been the case in some of the earlier reports. Retrospective studies are also not without disadvantages such as recall bias, missing information. Longitudinal studies with renal biopsies are ideal for establishing a causative

Table 3: Summary of Studies Included

S/N	Author	Location	Date	Design	Sample Size	Strength of Study	Sex or M:F Ratio	Age or Mean Age
1.	Lauwerys R[14]	Belgium	1987	Case report	1	Weak	M	3months
2.	Oliveira DB et al[15]	UK	1987	Case report	1	Weak	F	46yrs
3.	Pelclova D, et al[16]	Czech Republic	2002	Case report	1	Weak	M	21yrs
4.	Soo YOY et al[17]	China	2002	Case report	1	Weak	F	34yrs
5.	Tang HL et al[18]	Hong Kong	2006	Case report	1	Weak	F	34yrs
6.	Chakera A, et al[19]	UK	2010	Case report	2	Weak	F	26 yrs, 44yrs
7.	LI SJ et al[20]	China	2010	Retrospective study	11	Weak	1:10	15-45yrs
8.	Iyanda AA et al[21]	Nigeria	2011	Comparative cross-sectional	23 users, 25 controls	Weak	F	29-55yrs
9.	Okoye et al[22]	Nigeria	2011	Cross-sectional	476	Moderate	1:5*	46 ± 17yrs
10.	Tang HL et al[23]	China	2013	Case series	4	Weak	F	26yrs, 29yrs, 34yrs, 45yrs
11.	Zhang L et al[24]	Saudi Arabia	2014	Case report	1	Weak	F	28yrs
12.	ETL HO et al[25]	Hong Kong	2015	Case report	1	Weak	F	31yrs
13.	Ladi-Akinyemi et al[26]	Nigeria	2017	Retrospective case-control	150 cases, 300 control	Moderate	1.5:1	40±???? yrs
14.	Niu HX, et al[27]	China	2017	Case report	1	Weak	F	39yrs
15.	Okwuonu CG, et al[28]	Nigeria	2017	Cross-sectional study	328	Moderate	1:2.6*	54±???? yrs
16.	Qin A [29]	China	2019	Retrospective study	35	Moderate	1:4.8	36±8yrs

*For skin lighteners alone

Table 4: Summary of Renal Effects in Studies Reviewed

S/N	Author	Lightening Agent	Urine Hg	Proteinuria	Effect on kidney	Treatment	Remission	Time to Remission
1.	Lauwerys R [14]	Mercury	High-level kidney mercury	Absent	Tubular damage	Not stated	N/A	N/A
2.	Oliveira DB et al [15]	Mercury	330nmolHg/mmol	Proteinuria 2.2g/day	MN	Steroids	Yes	8 weeks
3.	Pelclova D, et al [16]	Mercury (10% mercuric ammonium chloride)	2336mg/day	Proteinuria 11.1g/day	MN	Withdrawal and chelation with DMPS	Yes	1 year
4.	Soo YOY et al [17]	Mercury (200x above allowable limit)	Not stated	Nephrotic range	MN	Withdrawal	Yes	N/A
5.	Tang HL et al [18] parts/million)	Mercury (300	Not stated	8.35 g/day	MCD with D-penicillamine	Withdrawal and chelation	Yes	9 months
6.	Chakera A, et al [19]	Mercury	16.5-77.5nmol/mmol	>9.0g/day	MN	Withdrawal	No	N/A
7.	LI SJ et al [20]	Mercury(2%w/w)	12->400mg/L	1.2-4.76g/day	MNATIN	Withdrawal and chelation with DMPS (4 out of 9 patients). ACE/ARB (5 patients)	Yes	1-4years
8.	Iyanda AA et al [21]	Not specified	Not stated	Absent	Mean urea and creatinine were higher in users compared to controls. (42.05±2.17mg /dl and 127.65±2.60 ìmol/L VS. 13.60±0.85mg /dl and 76.09±1.70 ìmol/ L.P= 0.005)	None	N/A	N/A
9.	Okoye et al [22]	Not specified	Not stated	Present, not quantified	Reduced risk for CKD None (low GFR and proteinuria) among users of skin lighteners, not sustained after adjusting for confounding OR=1.76, 95% CI=0.39-8.04	N/A	N/A	
10.	Tang HL et al [23] parts/million	Mercury7420-30,000	316-2521nmol/day	8.35-20.69g/day	MCD with D-Penicillamine	Withdrawal, chelation and steroids	Yes	1-9months
11.	Zhang L et al [24]	Mercury	469mmol/L	8.25g/day	MCD	Withdrawal, chelation with DMPS and steroids	Yes	6months

12.	ETL HO et al [25]	Mercury	334 nmol/day	8.97g/day	MCD	Withdrawal ACEI	Yes	3 weeks
13.	Ladi-Akinyemi et al [26]	Not stated	Not stated	Not stated	CKD13.4% of CKD patients versus 0.7% of controls used bleaching agent. P-value- 0.001	None	N/A	N/A
14.	Niu HX, et al [27]	Mercury	High	Present	IgA nephropathy with MCD	Withdrawal and chelation	Yes	1 month
15.	Okwuonu CG, et al[28]	Mercury	Not stated	Present	Increased risk of CKD among Skin lighteners, not sustained after adjusting for confoundingOR– 1.5, CI: 0.11-3.10	None	N/A	N/A
16.	Qin A [29]	Mercury	10-138.2mg/L	1.6-19.7g/d (median 4.6g/day)	MCD (60%) MN (37.1%) FSGS (2.9%)	Withdrawal and chelation with DMPS. Two out of 16 patients required Steroids and cyclophosphamide /cyclosporin	Yes	1-18months (median 2.5months)

N/A=not applicable, MN=membranous nephropathy,
MCD=minimal change disease, ATIN=acute tubulointerstitial nephritis,
DMPS=dimercaptosulfonate, ACEI=angiotensin converting enzyme inhibitor,
ARB=angiotensin receptor blocker, GFR=glomerular filtration rate.

relationship between topical skin-lighteners and glomerular disease.

Some of the studies reported that a high level of mercury in urine and serum of exposed patients reduced significantly following withdrawal and chelation; an observation which may explain the improvement in symptoms. However, some patients required steroids, ACEI/ARB or alkylating agents, suggesting that the kidney damage may be due to other causes or that mercury-induced glomerular damage requires additional treatment in some patients. It is not clear from the available evidence what clinical or pathologic factors predict the need for additional treatment besides failure to respond to withdrawal and/or chelation. Histological diagnosis of glomerular involvement was available in more than 50% of studies reviewed, revealing MCD and MN as the most frequent histologic patterns of GN. There was no report of repeat biopsy at any time, to confirm histologic recovery after the withdrawal of the mercurial agent. Although other secondary forms of GN were excluded through clinical interviews and evaluation, it is not guaranteed that the glomerular damage was due to mercury exposure. All potential causes of GN were not excluded, and primary GN is still a consideration.

Madsen et al [30] demonstrated increased renal weight and size in rats chronically exposed to mercury; there was an associated increase in proximal tubule volume, dilatation of tubular lumen, and thinning of the tubular basement membrane. Other in vitro studies have shown that mercury chloride inhibits cell proliferation, generates free oxygen radicals and induces apoptosis via cytochrome c release from the mitochondria of proximal renal tubules. [31,.32] One of the studies reviewed reported acute tubulointerstitial nephritis co-existing with MN in one of the patients. [20] There is no pathognomonic histopathologic pattern of mercury-induced glomerulonephritis, several patterns have been reported including MCD, MN, FSGS, IgA nephropathy.

Three cross-sectional studies were included in this review [21,22,28]; one showed a significant increase in serum copper, urea and creatinine in persons using skin-lightening agents (not specified) compared to non-users. [21] One Nigerian community-based study showed a 4.6 fold increase in the risk for CKD in patients using mercury-containing skin lighteners; however, this effect disappeared after controlling for confounding factors. [28] Another community-based study by the author of this review reported a reduced risk of CKD in patients using skin-lighteners, and this observation did not persist after controlling for confounding such as age.[22] In this study, CKD was significantly more prevalent in the older age group, while skin lightening was commoner in the young.

The only case-control study (retrospective) included in this review, reported that the use of skin lightening cosmetics was significantly higher (13.4%) amongst CKD patients compared to controls (0.7%). [29] The retrospective nature of the study introduces recall bias, and there was no histologic evidence of glomerular damage. Finally, this review did not find any human studies reporting the effect of hydroquinone nor the other skin lightening agents on the kidneys. Although some animal studies have shown mutagenic effects of topical hydroquinone in rat kidneys, [33-35] others have disputed this finding. [36,37]

CONCLUSION

Although there is ample literature on the toxic health effects of mercury, there is limited high-grade evidence on its toxic effects on the human kidneys. Majority of available studies are case reports, but these have demonstrated that MCD and MN are the commonest GN associated with topical mercury exposure; and withdrawal of the mercury agent and chelation results in remission in most patients.

Use of skin-lightening cosmetics is a common practice that requires effective interventions that will discourage the public from continuing this potentially hazardous habit. There is a need for high-quality case-control or cohort studies that will provide strong evidence of glomerular damage from topical use of skin-lightening agents, as this may be a strong deterrent to this dangerous practice.

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