THE ASSOCIATION OF RADIOGRAPHERS OF NIGERIA
EYE OF MEDICINE

JOURNAL OF RADIOGRAPHY AND RADIATION SCIENCES

SONOGRAPHIC ASSESSMENT OF KIDNEYS IN HUMAN IMMUNODEFICIENCY VIRUS SERO-POSITIVE PATIENTS: A SYSTEMATIC REVIEW

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Received: March 15th 2020 *Received in revised form: October 12th, 2020* *Accepted: November 10th, 2020*

ARTICLE INFO

Keywords: Sonography, Kidney, HIV sero-positive.

ABSTRACT

Background: Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) remains a major challenge globally, and approximately 180,000 people died from AIDS related illnesses in Nigeria in 2015. HIV associated nephropathy is the third most common cause of end-stage renal failure.

Objectives: To review published original research articles on the sonographic evaluation of kidneys in HIV sero-positive patients, identifying missing gaps and coming up with an area of further study.

Methodology: The study was retrospective and a secondary source of data from published original research articles was used. The search was performed through Google search using Google scholar, EMBASE, PubMed and Medline. All the published original research articles in English language and the availability of full text articles were included in the study.

The results: An electronic search using the search terms had identified 58 related published articles, but only 12 articles were reviewed. This study found out that human immunodeficiency virus-associated nephropathy (HIVAN) to be most predominant renal disease in HIV positive patients leaving in sub-Saharan Africa with increased renal parenchymal echogenicity and decreased corticomedullary differentiation sonographically, which correlate in raised of serum creatinine level and the degree of patients' immune competence (CD4 count).Few studies correlated the sonographic findings with histopathological feature and none uses Dopplar ultrasound.

Conclusion: This study has identified correlation of the sonographic findings with the histopathological features and the use of Doppler ultrasound as the missing gaps from the previous published research articles in the subject area.

INTRODUCTION

Human immunodeficiency virus (HIV) is a virus that attacks the human immune system, making the infected individual more vulnerable to other infectious diseases. [1] HIV is commonly spread during unprotected sexual intercourse. It can also be spread by contact with infected blood or from mother to child during pregnancy, childbirth or breastfeeding. If left untreated, HIV can lead to AIDS (Acquired immunodeficiency syndrome). [2] Acquired immunodeficiency syndrome (AIDS) is the late stage of HIV infection that occurs when the body's immune system is badly damaged because of the virus (immune-suppressed state). It

is characterized by opportunistic infections, neoplasm and neurological manifestations hence damaging the immune system, causing several types of chronic kidney diseases (CKD). [3] Human immunodeficiency virus (HIV) infection is a worldwide public health challenge. [4] The current statistics showed that nearly 37 million people around the globe are now living with HIV. The regional picture showed that more than two thirds (70%) of all people living with HIV positive live in the Sub-Saharan Africa, 25.8 million and about 3.3 million are in Nigerian. [5] Human immunodeficiency virus/acquired immunodeficiency syndrome is unique for its devastating impact on social, economic, and demographic developments. Recent studies have thrown more light on the reasons for the mortality and morbidity associated with HIV/AIDS in general and on its renal complications in particular. [6]

The kidneys are a common organ of predilection to HIV infection with end stage renal failure as the final outcome. [7] The human immunodeficiency virus has been a known cause of kidney failure, especially in patients with HIV-Associated Nephropathy (HIVAN). Risk factors for the development of HIVAN includes a low CD4 count (<200cells/mm3) and high viral burden. The biochemical features of HIVAN are rising in serum creatinine and proteinuria (>3g/24 hours). The prognosis worsens with higher proteinuria and serum creatinine. [8] The HIV-related renal impairment can present as an acute or chronic renal disease, it can be caused directly or indirectly by HIV and/or drug related effects that are directly nephrotoxic or lead to changes in renal function by inducing metabolic vasculopathy and renal damage. [8] Renal involvement in HIV/AIDS was prevalent, and HIV-related kidney disease was the third most common cause of end-stage renal disease (ESRD) in Africans between the ages of 20 and 64 years. [9] The kidneys have also been established as a reservoir for HIV. Distinct disease entities like HIV-associated nephropathy (HIVAN) have also been described. [10]

Kidney diseases remains a major challenge among patients with HIV/AIDS as they now live longer because of the antiretroviral therapy. There are many published research articles on the grayscale sonographic evaluation of kidney diseases in patients with HIV/AIDS, however, the grayscale detects pathology in the later course of the disease when compared to renal Doppler indices. Few of the published articles correlated the sonographic findings with histopathological feature and none of the studies used renal Doppler indices. This study is aimed at reviewing published original research articles on sonographic evaluation of kidney diseases in patient with HIV/AIDS, identifying a missing gap and coming up with an area of further studies.

METHODOLOGY

The study was retrospective and a secondary source of data was used from published original articles. These relevant materials were used and relevant information such as the study design, sampling methods, sample size, inclusion criteria, exclusion criteria and findings were extracted. The search was performed through Google search using Google scholar, EMBASE, PubMed and Medline. The search term used were; sonography, kidney diseases, HIV sero-positive, the effect of HIV on kidneys, patients with HIV, why HIV affects the kidneys and sonographic appearance of kidney on patients with HIV. All the published original research articles in English language, availability of full text articles and not duplicated were included in the study. All reviewed articles, articles published in different languages other than English language that were not translatable online, duplicate articles, unavailability of the full text of the articles or title not relevant were excluded.

RESULTS

Ten out of the 12 reviewed articles, the studies were conducted in Africa, 1 in North America and the remaining one in Asia. All the reviewed articles were prospective, cross sectional studies. However, the study conducted by Sidi *et al.* [2] in addition was also a comparative study, furthermore, the study conducted by Atta *et al*. [13] used both prospective and retrospective study designs. Only two out of the total reviewed articles included a control group in their studies; a study conducted by Okeke *et al.* [4] used 358 subjects as control while the study conducted by Osawe *et al.* [3] used 219 subjects as control group. Out of the 12 reviewed articles only 2 mentioned the type of sampling technique employed in their studies. Sidi *et al.* [2] employed non probability; purposive sampling technique, and Osawe *et al.* [3] also used non probability; but, convenience sampling method.

A study conducted by Atsukwei *et al*. [7] used a sample size of 500 subjects which was the largest

sample size among all the reviewed articles, followed by the study conducted by Sidi *et al.* [2] that used a sample size of 380 subjects. Studies conducted by Osawe *et al*. [3] and Eze *et al.* [6] used a sample size 358 and 340 subjects respectively. Furthermore, studies conducted by Okeke *et al.* [4] and Adeyekun *et al.* [11] used a sample size of 219 and 129 subjects respectively. However, the study conducted by Hamper *et al.* [13] used a sample size of 36 subjects which was the smallest sample size in all the reviewed articles, followed by the study conducted by Atta *et al*. [12] and then Dharvey *et al*. [8] that used a sample size of 62 and 100 subjects respectively.

Among all the reviewed articles, only four measured renal bipolar length as a way of determining renal size. A study conducted by Garko *et al.* [5] reported that 28% of the studied subjects had abnormal renal size, which was the highest percentage in all the reviewed articles followed by the study conducted by Okeke *et al.* [4] and then Adeyekun *et al.* [11] that reported 21.12% and 19.7% abnormal renal size in their studies. However, Atsukwei *et al*. [7] reported 2.6%, which was the lowest renal size reported in the reviewed articles. Furthermore, four out of the reviewed articles measured renal volume as a method of detecting abnormal renal size. A study conducted by Adeyekun *et al.* [11] reported that 15% of the selected subjects had abnormal renal volume, which was highest among the reviewed articles followed by Osawe *et al*. [3] that reported 10.9% of the studied subjects had abnormal renal volume. A study conducted by Eze *et al.* [6] reported 5.3% of abnormal renal volume among the selected subjects which was lowest renal volume reported among the reviewed articles followed by Sidi *et al.* [2] 2.1% and 7.4% among the drug dependent and drug naïve studied subjects. However, 4 out of the reviewed articles did not measure the renal bipolar length or renal volume; the studies reported only renal parenchymal echogenicity.

All the reviewed articles reported renal parenchymal echogenicity. Studies conducted by Garko *et al*. [5] and Ibinaiye *et al*. [9] each reported 96% abnormal renal parenchymal echogenicity which was the highest percentage among the reviewed articles. This is followed by Atta *et al*. [12] and then Hamper *et al.* [13] that reported 93.6% and 58% respectively as abnormal renal parenchymal echogenicity among the studied subjects. Furthermore, studies conducted by Eze *et al.* [6], Adeyekun *et al.* [11], and Dharvey *et al*. [8] reported 56.9%, 41.7% and 15.7% as abnormal renal parenchymal echogenicity of their studied subjects. However, a study conducted by Ikpeme *et al*. [10] reported 3.1% as abnormal renal parenchymal echogenicity of the studied subjects which was the lowest percentage of renal parenchymal echogenicity of the reviewed articles, followed by Sidi *et al.* [2] and then Atsukwei *et al*. [7] that reported 6.3% and 6.4% respectively as abnormal renal parenchymal echogenicity of the studied subjects.

Only two of the reviewed articles determine urea; studies conducted by Atta *et al*. [12] and Dharvey *et al*. [8] reported mean urea values of 4.4 mg/dl and 1.29 mg/dl respectively. These values are within the normal range. Out of the reviewed articles only four reported serum creatinine; a study conducted by Eze *et al.* [6] 137.5 mmol/l as the mean serum creatinine, which was the highest value reported among the reviewed articles and the was above the normal range. This was followed by Garko *et al*. [5] and Ibinaiye *et al*. [9] that reported 399 mmol/l each which was also above the normal range and then Dharvey *et al*. [8] that reported 54.4 mg/dl, which was also within the normal range. Eight out of the reviewed articles reported mean values of the CD4 counts and with the exception of the study conducted by Adeyekun *et al.* [11] the values were all above 200 cells/mm^3. A study conducted by Ikpeme *et al.* [10] reported a mean CD4 counts values of 813 cells/mm^3, which was the highest among all the reviewed articles, followed by Sidi *et al.* [2] and Atsukwei *et al*. [7] that reported mean CD4 counts values of 573.2 cells/mm^3 and 520.55 cells/mm^3 respectively. However, a study conducted by Adeyekun *et al.* [11] reported mean CD4 counts values of 189.3 cells/mm^3, which was the lowest CD4 counts value among the reviewed articles, followed by Garko *et al*. [5] and then Eze *et al.* [6] that reported mean CD4 counts values of 252 cells/mm^3 and 220.2 cells/mm^3 respectively. Out of all the reviewed articles. only two reported histopathology of the selected subjects; studies conducted by Atta *et al*. [12] and Hamper *et al.* [13] reported 39% and 53.3% abnormal histotopathological features, among the studied subjects.

Author (s) & year of Publication	Continent	Study design	Control group	Sample method	Sample size	Renal size	Renal volume (abnormal)	Parenchymal echogenicity (abnormal)	urea (mean±)	creatinine	CD4 counts (cells/mm^3)	Histopathology
Sidi*et al.* 2020	Africa	Prospective & comparative	-	Purposive	380	-	118.1	6.3%	-	-	573.2	-
Eze*et al* 2018	Africa	Prospective	-	-	340	-	196.9	56.9%	-	137.5	220.2	-
Atsukwei *et al.* 2017	Africa	prospective	-	-	500	2.6%	-	6.4%	-	-	520.55	-
Dharvey *et al.* 2017	Asia	Prospective	-	-	100	-	-	15.7%	1.29 mg/dl	54.41 mg/dl	236.14	-
Okeke *et al.* 2016	Africa	Prospective	219	-	219	21.1%	-	11%	-	-	-	-
Garko *et al.* 2015	Africa	Prospective	-	-	100	28%	-	96%	-	399	252	-
Osawe, 2014	Africa	Prospective	358	Convenience	358	-	10.9%	13%	-	-	388.3	-
Ibinaiye *et al. 2014*	Africa	prospective	-	-	100	-	-	96%	-	399	-	-
Ikpeme *et al.* 2012	Africa	Prospective	-	-	98	-	-	3.1%	-	-	813	-
Adeyekun *et al.* 2011	Africa	Prospective	-	-	120	14.9%	15%	41.7%	-	-	189.3	-
Atta *et al.* 2004	Africa	Prospective & retrospective	-	-	62	-	-	93.6%	4.4 mg/dl	-	-	39%
Hamper *et al.* 1988	North America	prospective	-	-	36	-	-	58%	-	-	-	53.3%

DISCUSSION

All the reviewed articles used prospective study design, in addition to that Sidi *et al.* [2] used comparative study while Atta *et al*. [13] used retrospective study as shown in the Table of summery. This serves as a to the two studies over the remaining 10 studies. Two study designs give more in depth information when compared to one study design. As in the table of summery Osawe *et al.* [3] and Okeke *et al.* [4] were the only studies that included control as part of their studies, which served as a strength of their studies over the other reviewed articles. Control studies are superior to descriptive studies. Only the studies conduced by Sidi *et al.* [2] and Osawe *et al.* [3] mentioned the sampling methods employed in their studies which also serves as strength over the other reviewed articles. Correct choice of sampling method ensures that the study sample gives an accurate representation of the study population. Five hundred subjects used as sample size by Atsukwei *et al.* [7] as shown in the Table of summery, this happened to be the strength of the study over the other articles reviewed. The larger the sample size used in a study the accurate and reliable of the obtained results, but, the smaller the sample size the less accurate and reliable of the obtained results. The studies conducted by Sidi*et al.* [2], and Osawe [3] Eze *et al.* [6] and Adeyekun *et al.* [11] evaluated renal volume, which serves as a strength over the studies conducted by Okeke *et al.* [4], Garko*et al*. [6] and Atsukwei*et al*. [8] that measured bipolar length of the kidneys. Renal volume is the most precise method of determining renal size rather than bipolar length, therefore, the studies were supposed to determine the renal volume rather than the bipolar length. Renal size measurement remains an important parameter in the diagnosis of pathological conditions affecting the kidneys in patients with HIV/AIDS, therefore, the most precise method of measurement should be employed. Studies conducted by Sidi *et al.* [2], Osawe *et al.* [3], Okeke *et al.* [4], Atsukwei *et al.* [7], Ikpeme *et al.* [10], Adeyekun *et al.* [11] and Hamper *et al.* [13] did not determine the serum urea and creatinine in their studies as shown in the Table of summery, and this happened to be one the weaknesses 0f their studies in the assessment of renal changes in HIV sero-positive patients. Serum urea and creatinine are the routine laboratory investigation performed for HIV sero-positive individuals for the evaluation of renal function.

Therefore, the studies were supposed to determine the serum urea and creatinine and correlate them with the laboratory findings. Whereas, studies conducted by Garko *et al.* [5], Eze *et al*. [6] and Atta *et al.* [12] and had determined only creatinine level of the selected subjects which was one of the strengths of their studies over those that did not evaluate both the serum urea and creatinine. A study conducted by Dharvey*et al*. [8] was the only one that determined both serum urea and creatinine, which served strength over the other 11 reviewed articles. The only reviewed articles that reported histopathological features of the selected subjects were those conducted by Atta *et al.* [12] and Hamper *et al.* [13]. Histopathology is the gold standard for the diagnosis of HIV-associated nephropathy since; the sonographic features are not specific. Therefore, the studies should include the histopathological features correlated with sonographic features. None of the reviewed articles evaluated renal Doppler indices of the selected subjects, however, few reviewed articles correlate the sonographic findings with histopathological features.

CONCLUSION

Several studies have documented increase renal parenchymal echogenicity, loose of corticomedullary differentiation as renal sonographic features of patients with HIV/AIDS. This study identified correlation of the sonographic findings with the histopathological features and the use of Doppler ultrasound as the missing gaps from the previous published research articles in the subject area.

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