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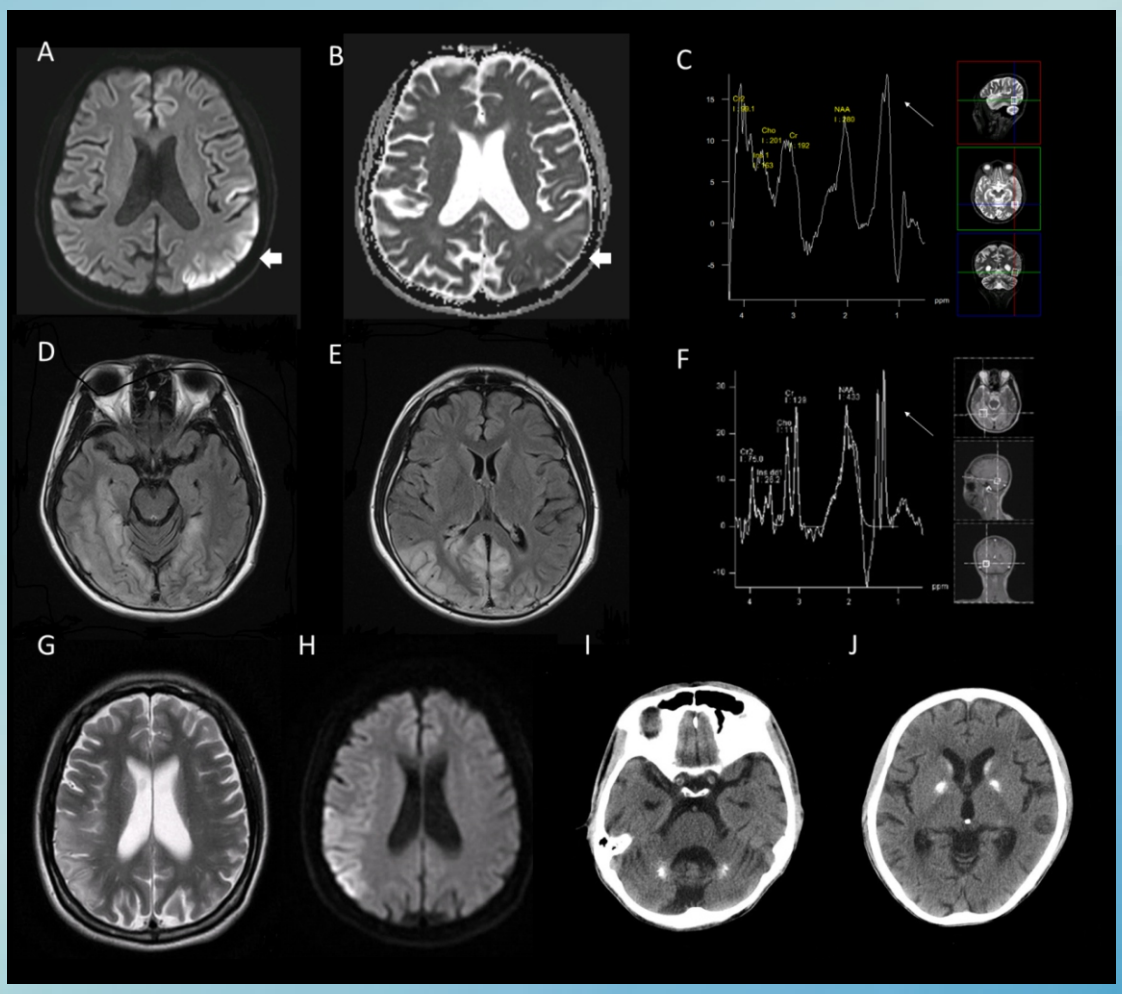

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End Stage Renal Disease in a Child with Epidermolysis Bullosa

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Abstract

Epidermolysis bullosa (EB) is an inherited connective tissue disease causing blisters in the skin and mucosal membranes. In severe cases, EB may be associated with renal damage through several mechanisms, mainly immunological ones. The present case described a young male with dystrophic recessive EB who developed an advanced chronic renal damage secondary to tubulointerstitial nephritis that was demonstrated by a renal biopsy. Unpublished previously, this complication should be considered among the possible causes of renal damage in EB. Also it is recommended a protocoled surveillance of renal and urinary tract complications in children with EB.

Keywords

Epidermolysis Bullosa, Tubulointerstitial Nephritis, Chronic Renal Failure, Dialysis

1. Introduction

Epidermolysis bullosa (EB) syndromes are a group of genetic mechanobullous skin disorders that share a common feature of blister formation occurring with little or minor trauma, and are classified nowadays under the group of genodermatoses. EB may be broadly differentiated into four main groups by the level at which the separation occurs: at the intraepidermal level (EB simplex), intra-lamina lucida (junctional EB), sub-basal lamina level (dystrophic EB) and Kindler syndrome. Further distinctions are made according to mode of inheritance, extent of disease (localized, generalized), associated features, and underlying genetic alterations [1]. New EB phenotypes, genotypes and modes of transmission have been identified recently, each of which has its own relative risk for the development of specific extracutaneous complications and/or premature death [2]. Among these,

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a small but important proportion may develop significant renal and urological complications which can have a major impact on their quality of life, morbidity and mortality [3]. The present article describes a child with dystrophic EB who developed end stage renal disease (ESRD) secondary to a chronic, although undetected, tubulointerstitial nephritis (TIN), an unreported renal complication of EB.

2. Case Report

A 13-year-old white male affected with severe generalized recessive dystrophic EB was evaluated in a regular health control by the medical team of DEBRA (Dystrophic Epidermolysis Bullosa Research Association)-Chile. He had a homozygous mutation (+/+) COL7A1: c.7708delG, exon 103 and clinically characterized by bilateral pseudo syndactyly, esophageal stricture, which required dilatation, recurrent corneal ulcers, chronic anemia and severe malnutrition. He was doing fine, asymptomatic, but with many skin lesions and blisters in his extremities. No laboratory test regarding renal function or abdominal ultrasound was done in the last 6 months. He had been receiving multivitamins, hydroxyzine, chlorpheniramine, zinc, famotidine and lactulose for the last 6 months, and occasionally non-steroidal anti-inflammatory drugs (NSAIDs) and systemic antibiotics for inter current infections. His urine output was normal, with no edema, blood pressure in normal range for age, sex and height. Among the lab test done, drew attention a serum creatinine of 2.4 mg/dl and BUN 48 mg/dl. His phosphorus was 6 mg/dl, calcium 8.2 mg/dl, hematocrit 20.8%, normal plasma electrolytes, venous blood pH of 7.28 and bicarbonate 16 mEq/L. Urinalysis without hematuria, leucocyturia or casts, urine protein/creatinine ratio of 1.77. Renal ultrasound showed kidneys of normal size but with increased cortical echogenicity, the parenchymal blood flow was normal, with resistive index in normal range. Repeated serum creatinine one week later was 2.74 mg/dl. A renal biopsy was performed (**Figure 1**) showing multifocal tubular atrophy and interstitial fibrosis involving up to 50% of the examined tissue. Some of the atrophic tubules had prominently thickened and wrinkled basement membrane with a reduced diameter and a narrow lumen filled with eosinophilic homogeneous proteinaceous material. Non-atrophic tubules showed dilated and irregular lumen. Also a focally dense inflammatory cell infiltrate made up mainly of lymphocytes was seen. There was more than 50% of global glomerular sclerosis with thickening and delamination of Bowman's capsule of the remaining glomeruli and retraction of the glomerular tuft. By immunofluorescence, weak mesangial positivity for C_3 and IgM was seen; there was no C_3 or immunoglobulin deposition in tubulointerstitial compartment. On ultraestructural examination, the glomeruli showed slight wrinkling of the basement membrane, without irregular contours or dense deposits. The pathologist's findings were consistent with chronic tubulointerstitial nephritis. A tentative treatment with oral prednisone 2 mg/kg/day was initiated, with mild improvement of renal function (serum creatinine of 2.17 mg/dl) for 3

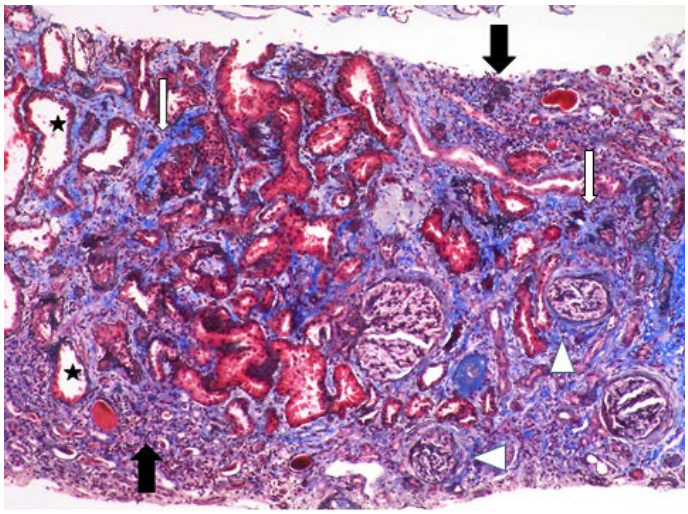

Figure 1. Renal histology stained with Masson's trichrome + Jones methenamine silver showing diffuse tubulointerstitial mononuclear infiltrate (black arrows), peri glomerular fibrosis (white arrow heads), interstitial fibrosis (white arrows) and tubular atrophy (asterics). (× 200).

months, but with further worsening of azotemia. Finally, the patient's renal function worsened progressively to the level of end stage renal disease, and was started on chronic peritoneal dialysis two years after the biopsy. Two more years later and due to a big communicating hydrocele, the patient was switched to chronic hemodialysis. Currently the patient is stable on dialysis but without perspective of kidney transplantation because of parents refusal.

3. Discussion

The genodermatoses are a large group of inherited single-gene disorders with skin manifestations. Many of these disorders are rare. However, the recognition of their skin findings is important not only for the initiation of appropriate dermatologic therapy, but also for the detection of other associated abnormalities in these frequently multisystem disorders, including malignancy [1]. Genitourinary involvement in EB has been widely reported [3] [4]. The renal parenchyma itself may be affected in patients with EB, particularly those with the more severe forms.

The pathogenesis of renal damage is complex and several factors are involved: a) frequent antibiotic therapies based on aminoglycosides, notoriously nephrotoxic, used to treat renal and skin infections; b) cytokine release, particular amyloid A protein, which, in EB patients, may lead to renal failure; c) immunocomplexes, deposited in glomerular capillary basement membranes, or in the mesangium, resulting in post-infectious glomerulonephritis, IgA glomerulonephritis, or mesangial proliferative glomerulonephritis [5], besides the renal damage secondary to urinary tract stenosis/obstruction and associated infections [3] [4]. All these conditions can lead to chronic renal failure, although it is a rare cause of death in pediatric population [6].

In our patient, the cause of severe renal dysfunction was identified histologically as a chronic TIN, an association not reported previously in children with EB. TIN is an immune-mediated cause of renal damage characterized by the presence of inflammatory cell infiltrate in the interstitium of the kidney. According to the etiology, TIN can be classified into two main types: non-infectious and infectious. Concerning the non-infectious causes, the use of certain drugs is either directly responsible for TIN or indirectly by creating a hypersensitivity reaction, mainly after the use of NSAIDs or β-lactam antibiotics [7]. The manifestation of the disease is either of sudden onset or, rarely, chronic with slow evolution leading to end-stage renal disease, as it occurred in our patient. We could not clarify the cause of this chronic TIN, being most probably related to the chronic (or acute) use of some drugs, as the way it happened with this child. Among the main possible culprit drugs we should include prescribed and unprescribed ones, as non-steroidal anti-inflammatory drugs and antibiotics frequently used in this disease. No evidence of characteristic infections associated with TIN [7] was detected previously. Besides that, chronic TIN might occur after a systemic disease that causes immunity disequilibrium such as sarcoidosis, lupus, Sjögren's syndrome, vasculitis and Crohn's disease [8]. EB may cause immunological alterations due to persistent inflammation and recurrent infections but its direct relationship with TIN has not been probed. With exception of EB acquisita, an autoimmune disease, the common EB is a genetic disorder without an autoimmune origin demonstrated so far [1].

Direct injury, high metabolic demands, or stimuli from various other forms of renal dysfunction activate tubular cells. These, in turn, interact with interstitial tissue elements and inflammatory cells, causing further pathologic changes in the renal parenchyma. The tissue response to these changes thus generates a feed-forward loop of kidney injury and progressive loss of function [9]. The treatment of TIN is very controversial, being the withdrawal of the offending agent the most important issue. The use of steroids in TIN has shown benefits in cases of drug-induced TIN within the first 2 weeks of diagnosis and before the progression of interstitial fibrosis [10]. In our case, the steroids were initiated too late and the renal failure continued progressing as expected, despite an initial improvement of the serum creatinine.

As mentioned before, the clinical presentation of chronic TIN uses to be slow and unrecognized. In our patient, without overt clinical symptoms/signs suggesting renal dysfunction, the diagnosis of this complication was greatly delayed, a situation that could be avoided if the patient had been in a tighter follow-up plan. It is recommended that a nephro-urological surveillance should be part of the routine evaluation from childhood EB [11]. In this sense, there are currently no published guidelines on how to monitor these patients. Almaani and Mellerio recommend a 6-monthly serum urea and electrolytes, blood pressure, and urinalysis be performed in all patients with recessive dystrophic EB and junctional EB. Annual ultrasound imaging in patients with junctional EB may also be warranted. If any abnormalities are detected, appropriate imaging or functional tests should be performed and specialist urological or renal opinions sought [12].

4. Conclusion

Nephro-urological complications are not uncommon in severe cases of EB. Renal damage from different mechanisms and pathogenesis may lead to advanced chronic renal failure. Our patient represents an unrecognized and unpublished cause of ESRD, diagnosed by a renal biopsy. Because patients with EB are frequently on many drugs, NSAIDs and antibiotics among them, TIN should be considered as a possible cause of kidney injury. This complication could have been recognized much earlier if it had followed a protocol tracking periodically nephro-urological complications in these children. We strongly recommend a protocoled surveillance of renal and urinary tract complications in children with EB.

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Disclosure

The authors of this manuscript declare to have no conflict of interest for its publication.

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Comparative Costs of Different Renal Replacement Therapies in Lower Middle Income Countries on the Example of Georgia

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Abstract

End-Stage Renal Disease (ESRD) represents one of the most challenging social and medical problems mainly due to substantial treatment-associated costs. The chronic nature of the disease needs expensive continuous care that majority of the patients cannot afford. Therefore, in many countries expenses associated with the ESRD treatment is paid by state government. These treatment options include: hemodialysis, peritoneal dialysis and kidney transplantation. Multiple studies have been conducted throughout the world to assess cost-effectiveness of these treatment modalities. The studies suggest that kidney transplantation not only reduces mortality and morbidity but improves a quality of life of ESRD patients. Furthermore, it is the most cost-effective treatment for the ESRD at least in high-income countries. The goal of our study was to determine whether above-mentioned is true for lower middle income countries, where the cost of the ESRD treatment is substantially lower. Despite the low dialysis costs, transplantation remains the cheapest form of renal replacement therapy RRT in lower income countries like Georgia. Our results reveal, that kidney transplantation is most expensive modality of Renal Replacement Therapy (RRT) at month 1, but count of costs reveals that after the 10th month of treatment, the cumulative cost of transplantation is less than the cumulative cost of peritoneal dialysis and after the 23rd month, cumulative cost of hemodialysis also surpasses the cumulative cost of transplantation-related treatment and this cost comparison is in line with global data from upper-middle and high income countries.

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Keywords

End-Stage Renal Disease (ESRD), Renal Replacement Therapy (RRT) Costs, Hemodialysis, Peritoneal Dialysis, Kidney Transplantation (KT)

1. Introduction

Worldwide, End-Stage Renal Disease (ESRD) represents one of the most challenging social and medical problems due to substantial treatment-associated costs. The chronic nature of the disease requires expensive continuous care that majority of the patients cannot afford. Therefore, in many countries expenses associated with the ESRD treatment is paid by state government. The main modalities of renal replacement therapy include: hemodialysis, peritoneal dialysis and kidney transplantation. Governments, mostly in developed countries, each year face increase of total ESTD treatment costs due the surge of disease incidence and prevalence fed by the factors as aging population trend and raise of diabetes morbidity. Therefore, searching for most efficient ways of treatment is highly demanded globally. Multiple studies have been conducted throughout the world to assess cost-effectiveness of these treatment modalities. These studies suggest that kidney transplantation not only reduces mortality and morbidity but improves a quality of life of ESRD patients. Furthermore, it is the most cost-effective treatment for the ESRD at least in upper-middle and high income countries. The goal of our study was to determine whether above-mentioned is also true for lower-middle income countries, where the overall costs of the ESRD treatment is substantially lower. Also we aim to suggest policy improvements that would promote cost-effective methods of treatment, which will help relatively low-income Governments such as of Georgia to make available better possible treatment services to the greatest possible number of people with ESRD.

1.1. Global Picture of ESRD

Constantly rising number of ESRD patients on all continents drive the global cost of ESRD treatment. In the UK, the annual incidence of ESRD has doubled during 1995-2005 to reach about 100 new patients per million of population. The annual incidence of people older than 65 years in the USA is more than 1200 per million of population [1]. There are two factors that augment the increasing number of ESRD patients. First is the ageing of the population; the incidence of ESRD is higher in elderly people than in general population. The second factor is the global epidemic of type 2 diabetes mellitus. Patients with diabetes mellitus have higher chances of developing ESRD [2]. In 2009, costs of ESRD rose by 3.1% to 29% billion within US [3].

It is doubtless that higher incidence rates of ESRD patients will result in ever-growing expenditures. There are several ways to avoid ever-growing costs of ESRD treatment. In some countries, hemodialysis can be replaced by cheaper peritoneal dialysis as a main modality of treating ESRD. Moreover, a shift from in-center hemodialysis to home-based dialysis is another potential strategy that could enhance the cost-effectiveness of ESRD care. Overall, studies from various upper-middle to high income countries demonstrate that kidney transplantations is the most cost-effective way to treat ESRD, resulting in reduced expenditures that could be used more productively elsewhere.

The severity of prevalence and incidence of End-Stage Renal Disease is even more alarming in developing countries [4]. Despite the similar incidence rates, the prevalence rates vary from less than 100 per million population in sub-Saharan Africa and India to about 400 per million population in Latin America and more than 600 per million population in Saudi Arabia4. Thus, prevalence is largely a matter of survival made possible by renal replacement therapy, which in turn depends on healthcare expenditures and economic strength of these countries/continents.

1.2. End-Stage Renal Disease Financing Options

Various countries have different financing options for End-Stage Renal Disease. A study by Dor, Pauly, Eichleay and Held provides comprehensive review of several financing models that countries participating in ISHCOF (International Study of Health Care Organization and Financing) use. These countries include Australia, Belgium, Canada, France, Germany, Italy, Japan, New Zealand, Spain, Sweden, United Kingdom and United

States. Health care systems in these countries appear to be markedly different, ranging from the relatively market-based system in the United States to the National Health Service models that have the government as the sole owner and payer for health care (United Kingdom, Sweden, Spain, and Italy).

Three types of models tend to dominate payments to dialysis centers. The first model uses per-treatment prices that are administratively set at a national level. In the second model, payment systems may be based on capitation, *i.e.*, a fixed payment per patient or episode of care. The third model is global budgeting, whereby a regional administrative authority or a major hospital at the head of a local network is responsible for allocating an overall budget to various activities and units under its administrative control [5].

In contrast to the often-complex payment rules for dialysis providers, payments for kidney transplantation tend to be simple and straightforward. For the most part, transplant costs are paid fully by the relevant national health authority [5].

1.3. Comparative Cost-Effectiveness of ESRD Treatment Options

Multiple studies have been conducted throughout the world exploring the cost-effectiveness of End-Stage Renal Disease treatment options. These studies unanimously suggest that kidney transplantation is the most cost-effective treatment method for ESRD. Below we will review cost-effectiveness of RRT options in high- and upper middle income countries. Thereafter we will review Georgia, as an example of lower middle income country for the comparative cost-effectiveness of renal replacement therapy options.

Austria-A study conducted in Austria developed a Markov model of costs, quality of life and survival to compare three different assignment strategies of Renal Replacement Therapy. The authors used three strategies to construct their model. Strategy 1 represents the current assignment policy in Austria. 90.6% of new ESRD patients were treated with hemodialysis, 7.2% with peritoneal dialysis, 0.1% received a renal transplantation from a live donor and 2.1% from a deceased donor. The hypothetical alternative Strategy 2 was set as 20% of the incident, ESRD patients were allocated to peritoneal dialysis. In the other alternative Strategy 3, 20% of incident ESRD patients were allocated to peritoneal dialysis and additional 10% for preemptive renal transplant from a living donor (see **Table 1**) [6].

Overall, cost-effectiveness study showed that kidney transplantation and peritoneal dialysis perform better when compared to hemodialysis. Strategy 2 (20% peritoneal dialysis) and Strategy 3 (20% peritoneal dialysis and 10% kidney transplantation) can save €26 million and €38 million discounted respectively and gain 839 QALYs and 2242 QALYs respectively over the next 10 years when compared to Strategy 1 (hemodialysis dominated) [6].

Denmark-Similar study in Denmark also used decision analytic tree of Markov model and established the cost-utility analysis (CUA). The analysis was conducted based on data acquired in Denmark from 2012. At the end of year 2012, 4829 patients were being treated for end-stage renal disease (ESRD) in Denmark. Of these, 2330 patients had received kidney transplantation, whereas the remaining 2499 patients were in dialysis. Instead of US dollars, however, the analysis was built on Danish Crones [7].

The CUA shows that when comparing the total average costs and effects of the two alternative treatments, transplantation holds a dominant position as it yields both lower costs (810,516 DKK versus 1,032,934 DKK) and higher effects (4.4 QALY versus 1.7 QALY). Thus, the cost-utility analysis showed that transplantation is more cost-effective compared with dialysis; it yields both lower costs and better effects [7].

Serbia—A study conducted in Serbia aimed to compare ratio of costs and effects (Cost Effectiveness Analysis—CEA) of hemodialysis and kidney transplantation in patients with End-Stage Renal Disease. The study included 150 patients totally, divided into two groups. The study group consisted of 50 patients with kidney transplantation and the control group consisted of 100 patients on hemodialysis. There was no statistically significant age difference between the dialyzed (in average 42.92 years) and transplant (in average 40.58 years) patients ($p = 0.154$, t test) [8].

An effect of kidney transplantation in relation to hemodialysis as treatment selection was expressed in the form of Incremental Cost-Effectiveness Ratio (ICER), according to the equation: $ICER = CTR - CHD/ETR - EHD = \Delta C/\Delta E$, (where CTR—costs of transplant patients for a 10-year period, CHD—cost of patients on hemodialysis for a 10-year period, ETR—QALY years of life for transplant patients, EHD—QALY years of life for patients on hemodialysis).

According to the equation for calculating ICER the costs of kidney transplantation and patient maintenance therapy are considerably lower than costs of hemodialysis within a 10-year period, as well as that the difference

Table 1. Four calculated outcomes for three different treatment strategies.

Treatment Strategies	Treatment Outcomes			
	Discounted Costs	Total Life Years Saved	Total Years Free of Dialysis	Discounted QALY Years
Strategy 1	€8083 M	259,731	103,387	203,407
Strategy 2	€8057 M	260,435	103,875	204,245
Strategy 3	€8046 M	261,511	107,157	205,648

in patient life quality is in favor of patients with kidney transplantation 8. Overall the study concluded that kidney transplantation strategy is far more cost-effective since it saves EUR 132256.25 per one year of QALY contribution within 10 years period [8].

Spain—A prospective study conducted in Hospital Clínic de Barcelona compared the costs of Live -Donor Kidney Transplantation (LDKT) during the first year of the treatment with those of hemodialysis during the first year. Total of 106 patients (57 undergoing HD and 49 who receiving LDKT) participated in the study 9. The mean age of transplant recipients was 46 ± 15 years and that of donors was 52 ± 10 years. The study found that the mean annual cost of LDKT in the first year after transplantation was 29,897.91€. Of this sum, 27% (8128.44€) amounted to costs associated to donor. The rest of the 73% (21,769.47€) represented costs associated to kidney transplant recipient. The cost of hemodialysis was 43000.88€, of which 37,917 V corresponded to HD procedure and activities and the remainder (5082€) to transportation. Overall, the study concluded that live donor kidney transplantation is more cost-effective than hemodialysis, representing a savings of 13,102.97 per patient/y. The study further reported two findings; a. the costs of kidney transplantation shrink after year one, while the costs of hemodialysis remain the same, b. kidney transplantation is associated with higher quality of life (QALY) than hemodialysis treatment, although the study did not report any numerical values associated with QALY [9].

Australia—A study conducted in Australia used a dynamic population-based Markov model to assess the costs and health outcomes of proposed changes in service provision. Specifically, from the viewpoint of a central healthcare funder, study assessed the incremental health sector costs and benefits of i) an increase in the number of new ESKD patients receiving a transplant and ii) increasing the number of new dialysis patients receiving home-based, rather than hospital-based services, compared with current clinical practice for treating people with ESKD. These two proposed changes to clinical practice for new ESRD patients in Australia were assessed over 2005-2010 10. Overall the study concluded that increasing number of kidney transplantations has tri-fold effect; it reduces the costs, improves patient's quality of life (QALY) and increases the patient survival rate. The study also made favorable conclusions towards the home based hemodialysis—that it can produce net savings of $A46.6 million by 2010 without affecting the quality of treatment [10].

Chile—A study conducted in Chile used the Markov model to assess the net benefits of cadaveric kidney transplantation within the country11. The study found that the expected present value of costs associated with dialysis is approximatelyUS$134,000, whereas the expected costs of a transplant amount to nearly US$106,000. Overall, the study concluded that cost savings associated with cadaveric kidney donation are positive and substantial, thus cadaveric kidney transplantation is highly encouraged as a primary strategy of renal replacement therapy [11].

Portugal—A retrospective study conducted in Portugal analyzed cost-effectiveness of kidney transplantation, hemodialysis and peritoneal dialysis 7. The study found that at a 10 year (estimated graft average survival) interval, kidney transplantation costs 120,395.02€ and dialysis 278,091.12€. Thus, over the span of 10 years, renal transplantation saves the Portuguese health system an average of 157,696.1€. Thus, the study concluded that since the renal transplantation is the most cost-effective treatment of End-Stage Renal Disease, the Portuguese government should shift its attention and resources on promoting more organ donation [12].

Italy—A study conducted in Italy assessed the costs and health outcomes of proposed changes in service provision for ESRD patients. Specifically, authors assessed the incremental health care costs and benefits of the following: 1) an increase in the number of new ESRD patients receiving atransplant from donation after cardiac death (DCD); and 2) an increase in the total number of transplants (all types) supplied to new ESRD patients, compared with current clinical practice for treating patients with ESRD in the same setting [13]. The study was based on a dynamic population-based Markov, estimating the costs and benefits of proposed changes in service delivery to ESRD patients. Overall, the study concludes that changing the actual practice pattern for new patients

with ESRD by increasing the availability of kidneys from DCD should result in a cost-effective policy to expand the kidney donor pool. Thus, the authors argue that their results should encourage a health policy expressively tailored to reach markedly higher rates of kidney transplants by using extended criteria to select donors such as those experiencing cardiac death [13].

The eight studies above argue that kidney transplantation represents the most cost effective treatment option for End-Stage Renal Disease compared to hemodialysis and peritoneal dialysis. This opinion based on evidence is now widely shared among the countries of different development level including medium and high income countries. However, universality of this principle is yet to be tested also in lower-income countries. In this paper we will try to examine and compare RRT cost in Georgia, which is lower-middle income country based on World Bank ranking.

2. Methods and Results

2.1. ESRD Treatment in Georgia

Georgia, being a small post-soviet country is regarded as a lower middle income economy. The current funding model for ESRD treatment has been inaugurated in 2011 as a result of a wide reform, which amid at universal and accessible medical care for all patients with ESRD. The prevalence of dialysis-dependent patients in Georgia is about 570 per million populations and this number is progressively increasing due to factors such as increased access to treatment and overall increase in life expectancy.

For instance, the total number of beneficiaries of the state hemodialysis program has increased by 16% and 11% in years 2014 and 2015, respectively. These figures reflect a substantial growth in burden of costs as well.

Georgia is a good example for comparing costs associated to ESRD treatment in a lower income country. As the state is providing funds for all three modalities of Renal Replacement Therapies, we are able to perform detailed analysis of the cost-structure associated to each of those. The goal of this paper is to provide evidence that along with upper-middle and high income countries such as above reviewed Serbia and USA, Kidney Transplantation is the most cost-effective method of RRT also in lower income countries, which have a different cost structure and expectedly lower per patient expenditure compared to richer countries.

Although public funding is ensured for each of RRT, the allocation and drivers of financing varies across the modalities because of legal and other limitations, which will be discussed further in this paper especially with regard to kidney transplantation.

2.2. Hemodialysis in Georgia

State provides 100% funding for hemodialysis treatment in Georgia, which covers dialysis sessions, basic lab tests and medications and renal anemia therapy (Erythorpoeitin and IV iron) and the services are immediately available for all patients diagnosed with ESRD. The principle of funding is per dialysis session per patient and covers up to 157 hemodialysis procedures per year (based on frequency of three sessions per week) and the total funding consists of two different parts:

1) Reimbursement of service per hemodialysis sessions; and

2) Centralized state purchase of the dialysis disposables and anti-anemic medications;

For the reimbursement of dialysis the state currently pays GEL 40.0 (US$ 18) per hemodialysis session to service provider directly, which should cover the cost of dialysis service, including salaries, management, equipment as well as lab tests and medications (usually limited to basic tests and generic antihypertensives, phosphate binders and antibiotics). For the medication and other materials needed for hemodialysis government centrally makes purchases and makes allocations to service providers based on request as per usage incurred. Centrally purchased medications comprise anticoagulants and anti-anemic drugs (generic erythropoietin and generic iron sucrose), as well as dialysis disposables, which typically include dialyzer, dialysis blood set, needles, bicarbonate, acid concentrate and disinfectant. We have calculated the cost of centralized state purchase per patient per hemodialysis session based on the allocations made during last 12 months to National Centre for Urology—a major ESRD treatment provider in Georgia, which handles approx. 10% of country's total yearly hemodialysis budget and 50% of peritoneal dialysis and 50% of Kidney Transplantations in Georgia. National Centre for Urology data from last 12 months (April 2015 to March 2016) suggest that Government allocated on average GEL 44 (US$ 20) worth of centrally purchased medications and materials per hemodialysis session per

patient. Combining the funding of dialysis sessions (GEL 40) and allocated medications and materials (GEL 44) amounts to GEL 84 (US$ 37) total hemodialysis budget per session per patient, which multiplied by the reimbursed number of hemodialysis sessions entitled to a patient results in GEL 13,236 (US$ 5883) average hemodialysis budget Per Patient Per Year (PPPY) as of year 2016.

2.3. Peritoneal Dialysis in Georgia

Public funding of peritoneal dialysis in Georgia also consists of two parts:

1) Reimbursement to clinics providing peritoneal dialysis—amount defined per patient per month; and

2) Centralized state purchase of the dialysis disposables and anti-anemic medications;

Fixed funding which state directly pays to service providers amounts to GEL 105.0 (US$ 47) per patient per month. For the medication and other materials needed for peritoneal dialysis government centrally makes purchases and makes allocations to service providers based on request as per usage incurred. National Centre for Urology data from last 12 months (April 2015 to March 2016) suggest that Government allocated on average GEL 2115 (US$ 940) worth of centrally purchased medications and materials per peritoneal dialysis patient per month, which together with monthly fixed reimbursement per patient amounts to GEL 26,639 (US$ 11,840) average peritoneal dialysis budget Per Patient Per Year (PPPY) as of year 2016. Thus, the cost of peritoneal dialysis in Georgia is double of hemodialysis making it significantly inefficient from the costs point of view and how this circumstance affects access to peritoneal dialysis is subject to further analysis.

As displayed on **Table 2**, peritoneal dialysis in Georgia is at least double the cost of hemodialysis, whereas in Austria, the ratio is exactly the opposite, hemodialysis being significantly more expensive. This is to be attributed to difference in the cost structure associated with these treatment methods. Hemodialysis has been observed as a labor-intensive treatment, with salaries taking significant part of the cost, whereas the biggest contributor to peritoneal dialysis expense is its material [14]. NayakKaropadi *et al*. have compared the costs of hemodialysis and peritoneal dialysis in 46 counties (20 developed and 26 developing) and found out that hemodialysis to peritoneal dialysis ratio tends to be higher in developed countries, implying high labor costs [15]. In Georgia low salaries drive the low cost of hemodialysis, while the cost of peritoneal dialysis stands on par with global prices of its prime materials.

2.4. Kidney Transplantation in Georgia

Kidney transplantation is the third method of Renal Replacement Therapy in Georgia, which is publicly funded, however the number of cases is limited by available funds to the maximum of 36 surgeries per year.

Its mechanism of financing also consists of two parts:

1) Reimbursement of surgery and early post transplatation period; and

2) Centralized state purchase of immunosuppressive medications;

Government directly pays to service providers fixed amount of GEL 20,000 (US$8.889) per kidney transplantation surgery, and provides patients with centrally purchased very basic immunosuppressive medications, limited to generics of CNI (both Cyclosporin and Tacrolimus are used) lifelong and MMF only for the first 6 post-transplant months (lifelong only in selected cases), with no induction therapy or alternative drugs covered. Based on data from the National Centre for Urology, the average cost of immunosuppressive medications during firs 6 post-transplant months amounts to GEL 240 (US$ 107) per month. After the 7th moth the average cost per patient per month decreases to GEL180 (US$ 80).

As we want to compare economics of dialysis and kidney transplantation as alternative methods of Renal

Table 2. Comparison of TTP costs in three different income level countries.

Year	Country	Income Level	HD Cost PPPY (EUR)	PD Cost PPPY (EUR)	KT Cost PPPY (EUR)
2008	Serbia	Upper-middle	10 year average—16,533	N/A	10 year average—4895
2010	Austria	High	1st year—43,600 2nd year—40,000 >2nd year—40,600	1st year—25,900 2nd year—15,300 >2nd year—20,500	1st year—51,000 2nd year—17,200 >2nd year—12,900
2016	Georgia	Lower-middle	Yearly—6765	Yearly—13,600	1st year—12,670 From 2nd year—1835

Replacement Therapies, we put those costs on a single chart to review the cost-effectiveness over years of treatment (see **Figure 1**).

As we can observe from the **Figure 1**, kidney transplantation is most expensive modality of RRT at month 1, but count of costs reveals that after the 10th month of treatment, the cumulative cost of transplantation is less than the cumulative cost of peritoneal dialysis and after the 23rd month, cumulative cost of hemodialysis also surpasses the cumulative cost of transplantation-related treatment and this cost comparison is in line with global data from upper-middle and high income countries as we reviewed above (**Table 2**). This effect is possible because after initial high cost of surgery and intensive immunosuppressive engagement, the monthly cost of treatment from the seventh month drops to just 16% and 8% of monthly costs of peritoneal dialysis and hemodialysis, respectively.

However, despite being the most cost-effective method of treatment for ESRD, kidney transplantation is paradoxically the only financially restricted RRT in Georgia, as currently the state makes available funds for maximum of 36 surgeries per year. Other objective restrictions to kidney transplantation include legal framework on organ donation in Georgia, which only allows donations from living relatives, including parents, siblings, spouse, children and some other close relatives. Dating back from grim past of warfare, criminal and economic hardship after the collapse of the Soviet Union, Georgia enacted strict donor laws, forbidding not legally related donor transplantation to avoid illegal market for organ trade. Nonexistence of state funded potential donor examination programs farther discourages kidney transplantation.

3. Recommendations to Promote Kidney Transplantation in Georgia

As demonstrated by the case of Georgia, transplantation represents the cheapest form of RRT also in lower income countries. This is a good financial argument for the Georgian government to try to maximize the number of kidney transplantations and reduce the number of patients on maintenance dialysis. Following measures can help promote kidney transplantation as the method of choice of RRT:

1) Removing financial obstacles and providing universal coverage for kidney transplant surgeries without delay, much as in case of hemo- and peritoneal dialysis. As funds are restricted only for kidney transplantations, it is creating the barrier to accessibility. Removing the limit of yearly kidney transplantations would increase RRT cost in the first year, which would be offset by significantly lower post-transplantation medication costs;

2) Providing funds for potential living donor examinations would help increase the number of successful kidney transplantations by reducing health risks and thus attracting more living donors;

3) Expanding the potential donors' circle by removing legal obstacles and promoting altruistic living donations to friends and other emotionally close but not legally related patients. This proposal is currently under active consideration and could potentially double the number of living donors for an average patient;

4) Improving post-transplant care coverage by providing better and more modern immunosuppression, comprehensive post-transplant surveillance and treatment programs for complications;

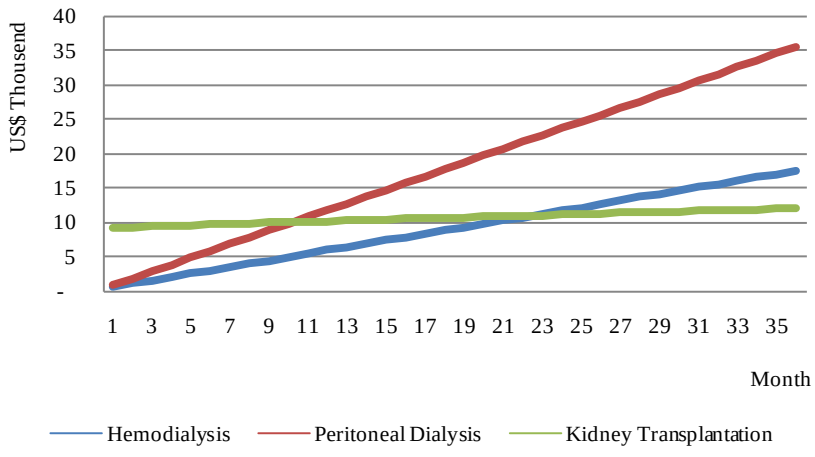

Figure 1. Cumulative cost of treatment, US$.

5) Taking reasonable initial steps to introduce a state program of deceased donor transplantations. Studies 6 have shown that live donor and deceased donor kidney transplantations have comparable effects on the patients in terms of cost-effectiveness, graft viability and survival rates. Georgia could start preparations involving the work on public opinion, infrastructure and legal frameworks to put a basis for future decease donor transplantations.

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Excessive Weight Loss Following Laparoscopic Gastric Mini Bypass or Roux-En-Y Gastric Bypass Surgery

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Abstract

Background: More than 90 percent of obesity surgery is done using a laparoscope. This method is superior to open surgery and lead to fewer complications, shorter hospital stay and faster recovery. This study compared course of weight loss following laparoscopic Gastric Mini Bypass or Roux-En-Y Gastric Bypass surgery, after one year of follow up. Materials and Methods: This randomized clinical trial was conducted among obese patients admitted to Rasoul Akram Hospital Obesity Clinic, Half underwent laparoscopic Roux-En-Y Gastric Bypass and the rest were undergoing laparoscopic Mini Gastric Bypass. The amount of weight loss during the first year after surgery will be discussed. Results: In this study, 75 obese patients were studied. Most of the participants were female (82.7%). Participants aged between 18 and 59 years old (average = 36.8 ± 9.8 y/o). Before the surgery, there was no significant difference in weight between the two groups. Excessive weight loss after one month, six months nine months and one year between the two groups was significant and was more in Mini Gastric Bypass ($p < 0.05$). Conclusion: Respecting the benefits of Mini Gastric Bypass compared to the Roux-En-Y Gastric Bypass technique, it is suggested for patients with morbid obesity.

Keywords

Morbid Obesity, Laparoscopic Mini Gastric Bypass, Laparoscopic Roux-En-Y Gastric Bypass

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1. Introduction

Obesity is defined as excessive weight and body fat due to environmental factors and individual genetic predisposition factors. According to the body mass index (BMI) categories, obesity defined as BMI more than to 30 kg/m^2 [1]. Obesity is not a disease of known cause, but several factors are involved in its formation. Genetic factors, internal secretions, psychological factors and environmental factors play important roles in causing obesity. Energy imbalance is the most important factor in weight gain and obesity.

Scientific studies approved weight loss surgery for patients with a BMI more than 35 kg/m^2. More than 90% of the obesity surgeries performed by laparoscopy which is preferred to open surgery: It leads to fewer complications, shorter hospital stay and faster recovery. Gastric bypass surgery by loop method was first done by Mason & Itoh in 1960, then Griffin and his colleagues introduced the open technique of Roux-En-Y Gastric Bypass. In 1994, first laparoscopic gastric bypass was performed in America and now America's most common bariatric surgery is gastric bypass. The operation is usually done as Roux-en Y, stomach is approximately divided into two small areas (30 - 50 cc) and large (The remaining stomach) and food enter the small area. In mini gastric bypass the surgeon does not cut the small intestine. The smaller stomach is connected to the 150 to 200 cm of small intestine. This new bypass has fewer side effects than the old method and length of stay after surgery is less [2].

In mini gastric bypass surgery, duration of surgery is about 30 minutes and hospital stay between 1 to 3 days while in the method of Roux-En-Y Gastric Bypass, duration of surgery was more than an hour and length of stay in hospital is between 4 and 8 days [3] [4]. In this study, candidate for bypass surgery referred to obesity clinic of Rasoul Akram Hospital during year 2013-2014, were randomly divided into two groups and one group underwent Roux-En-Y Gastric Bypass and the second group Mini Gastric Bypass and the difference between the two groups were studied.

2. Material and Methods

In this study, all patients with obesity who were referred to the obesity clinic since March 2013 to March 2014 in Rasoul Akram Hospital were enrolled. Half of the group was randomized to undergo laparoscopic Roux-En-Y Gastric Bypass and the rest undergone a Laparoscopic Mini Gastric Bypass. In both groups, the duration of surgery based on the minutes and weight loss over a year after surgery were recorded in kilograms. In this study, a researcher-made questionnaire was used for data collection. All questionnaires have been completed based on direct interviews with patients or relatives of patients who had full information of the patient's condition. Exclusion criteria included patients not wanting to participate in the study, lack of access to follow-up the patient's health status during follow-up, any severe illness in which surgery or anesthesia was impossible for the patient, mental instability and inability to understand the procedure, drug and alcohol addiction and eating disorders. SPSS software was used for data analysis and the results of the P-Value less than 0.05 significantly was considered.

3. Results

In this study, 75 patients with obesity who underwent surgery by one of the mini-gastric bypass or Roux-En-Y Gastric Bypass were studied. 62 participants were female (82.7%). Participants were between 18 and 59 years old and the average age of the participants was 36.8 ± 9.8. Before the surgery, there was no significant difference between weights in two groups (**Table 1**). The weight loss between the two groups based on Independent Samples Test is shown in **Table 2**. The weight loss after 10 days and three months did not differ significantly between groups while weight loss after one month, after six months, after 9 months and one year was significantly higher in the mini gastric bypass group than the other group (**Table 2**). Duration of surgery in mini gastric bypass surgery significantly was less than the other group (**Figure 1**).

4. Discussion

Gastric bypass surgery was more common in the late 1990s. Effects of gastric bypass surgery are actually a combination of stomach volume reduction and mal-absorption of nutrients. This applies especially in people who consume large quantities of sweets and simple carbs and do not respond to bonding. Bypass surgery was more effective than bonding so that 60% to 70% of patients lose their excessive weight in 9 to 14 months after surgery. Studies have shown that mini gastric bypass was effective for the treatment of obesity and favorable

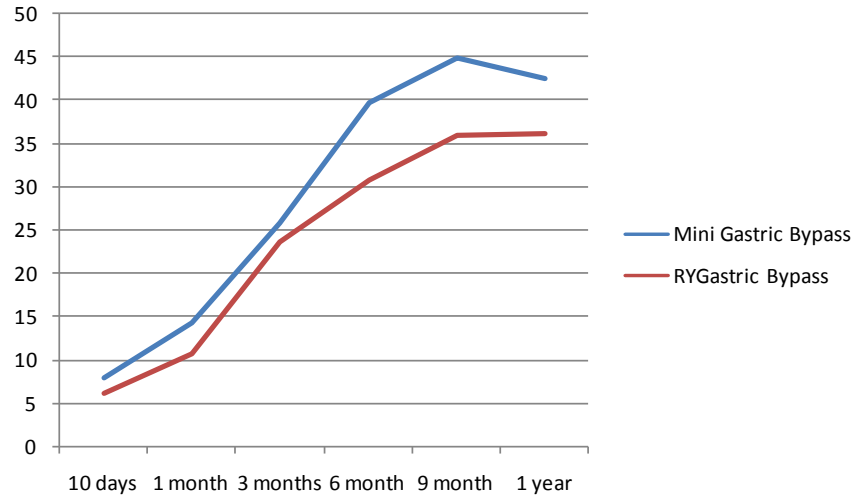

Figure 1. Weight loss (kg) after surgery.

Table 1. Weight and duration of surgery in two groups.

		Min	Max	Mean	SD	p
Weight	Mini Gastric Bypass	83	227	129.28	25.662	0.183
	Roux-En-Y Gastric Bypass	93	146	121.10	14.913	
Duration of Operation	Mini Gastric Bypass	60	160	101.97	24.204	0.016
	Roux-En-Y Gastric Bypass	90	200	124.55	30.778	

Table 2. Mean weight loss (Kg) and mean excessive weight loss according to time in two groups.

Weight Loss	Surgery	Mean (Kg)	SD	Sig. (2-tailed)	Mean (%)	SD	Sig. (2-tailed)
10 days	Mini Gastric Bypass	7.98	3.578	0.056	18.867	19.7309	0.365
	Roux-En-Y Gastric Bypass	6.26	2.261		14.722	6.0903	
1 Month	Mini Gastric Bypass	14.35	5.480	0.009	29.130	10.9085	0.426
	Roux-En-Y Gastric Bypass	10.85	2.624		26.596	11.9506	
3 Month	Mini Gastric Bypass	25.75	9.084	0.040	54.436	29.7664	0.661
	Roux-En-Y Gastric Bypass	23.82	7.295		58.040	24.0787	
6 Month	Mini Gastric Bypass	39.58	15.791	0.040	76.516	17.4284	0.499
	Roux-En-Y Gastric Bypass	30.88	7.053		71.011	24.3041	
9 Month	Mini Gastric Bypass	44.83	11.036	0.032	93.246	22.2293	0.335
	Roux-En-Y Gastric Bypass	35.96	7.781		82.293	25.8923	
Weight loss after one year	Mini Gastric Bypass	42.55	25.809	0.095	93.600	5.0912	0.478
	Roux-En-Y Gastric Bypass	36.23	10.693		84.665	29.1695	

results in the removal of diabetes type 2 in patients with obesity [5]-[8] and lead to improve the quality of life in these patients [9]. However mini gastric bypass is easier and safer procedure compared with Roux-En-Y Gastric Bypass in two-year follow-up period, any Achilles' heel for it has not been reported yet [10] [11]. Since the mini-gastric bypass in the stomach has not been cut and small intestine connected to 150 to 200 cm of small intestine, this method has fewer complications than the traditional Roux-En-Y Gastric Bypass [12], but the possibility of bile reflux in this method is higher than the conventional bypass method. In a study published in 2012, 1657 patients evaluated. Under the scheme, operation time and postoperative hospital stay and the rate of post-

operative complications in patients with Roux-En-Y Gastric Bypass was more and weight loss in this group was less through a 5-year follow-up [12].

Excessive weight loss in mini gastric bypass after one year in our study was similar to other published studies [4]. In another study in 2008 on 16 patients under mini gastric bypass surgery results showed that patients had 78-minute surgery and postoperative hospital stay 1.2 days. There were no long-term complications and mortality after surgery and weight loss at two years after surgery was 72 kg [13]. Excessive weight loss in mini-gastric bypass surgery was reported as much as 70 percent in various studies over one [14] and 5 years [4] which was consistent with our results. Another study published in 2012 evaluated 1000 patients who had undergone mini gastric bypass surgery between 2005 and 2011 were studied. According to the study, mini gastric bypass was low-risk and effective method that can be performed easily and with little associated side effects. In this study, all patients had experienced reflux following surgery [15]. Previous studies have shown that mini gastric bypass surgery over the short-term, was safe and successful in excessive weight loss [16] [17], this point was confirmed in our study.

5. Conclusion

According to recent study and adapt these results with studies in other countries, mini gastric bypass seems to be the easier way than the Roux-En-Y Gastric Bypass, which is less time consuming procedures and hospital stays are shorter. Also, due to the lack of anastomosis between the stomach and the jejunum, is a safer way and the effects and duration of surgery and hospitalization is less than Roux-En-Y Gastric Bypass, to the extent effective in weight reduction for patients with obesity. The effect of this method in the treatment of obesity complications such as low back pain, sleep apnea, high blood pressure, diabetes and depression have been proven and so could act as a substitute, among bariatric surgery considered.

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Holmes Heart and HIV: A Rare Combination of Two "H"s in a 23-Year-Old Widow

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Abstract

A 23-year-old, lean, scoliotic female presented to our hospital with a history of shortness of breath and cyanosis on exertion. Her 2D echocardiography revealed single left ventricle with both atrio-ventricular valves opening in it. She had normally related great arteries, with severe pulmonary artery hypertension, without pulmonary stenosis. Her blood tests indicated that she was reactive to human immunodeficiency virus (HIV-1). The patients died within 2 months despite treatments with anti-retroviral therapy and decongestive therapy.

Keywords

Double-Inlet Left Ventricle, HIV, Holmes Heart, Left Ventricular Hypertrophy, Rudimentary Right Ventricle

1. Introduction

Single ventricle, an unusual cardiac malformation, is usually associated with transposed great arteries [1]. Holmes heart is a rare variety of single ventricle, in which the great arteries are normally related [2]. Despite being recognized for more than a century, only few cases of Holmes heart have been reported till date [2]-[6]. Herein, we report a case of a 23-year-old lean scoliotic HIV-positive female who was diagnosed with Holmes heart. To the best of our knowledge, no case with a combination of HIV and Holmes heart has been reported previously.

2. Case Report

A 23-year-old thin-built female presented with a history of shortness of breath and palpitations, which were mainly exertional. She was poorly nourished with aphthous ulcers in mouth. Family history revealed that she was a second child of healthy consanguineous parents; her other siblings being normal. At the age of 15 years,

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she got married to a man who was a lorry driver by profession. We were informed that her husband had passed away due to some unknown illness a year after their marriage. Physical examination of the patient suggested that she had mild scoliosis of dorsal vertebrae, without any kyphosis. Her body was cyanotic. In addition, she had grade-II clubbing. One year ago, she was admitted for acute heart failure and was treated with decongestive therapy. No other significant past illness was noted.

Cardiovascular examination of the patient showed left ventricular apex with a huge parasternal shift. Upon auscultation, a single second heart sound and medium pitched ejection systolic murmur (grade 3/6) in the left parasternal area were heard. Other systems were found normal. Chest X-ray in the posterior-anterior view revealed cardiomegaly with increased pulmonary vascularity along with a prominent convexity on left margin of cardiac shadow, suggestive of rudimentary outlet chamber (**Figure 1**). Electrocardiogram showed a right axis deviation with a deep S wave in anterior precordial leads (**Figure 2**). The 2D echocardiography indicated a single left ventricle with both atrio-ventricular valves opening in it (*i.e.* double-inlet left ventricle; **Figure 3**). The functional morphological left ventricle was hypertrophied, with normal situs and with severe pulmonary arterial hypertension, without pulmonary stenosis. A rudimentary outlet chamber was seen anteriorly and a dilated pulmonary artery was arising from it to the left of the ventricle. Accordingly, Holmes heart was diagnosed. In view of history of heart failure, the patient was planned to be treated with decongestive therapy.

Additional laboratory investigations suggested neutrophilic leukocytosis. The total white-blood cell (WBC) count was 12,500 with neutrophils showing 78% and lymphocytes 20%. We could not perform a detailed infectious screening in view of financial constraints. The enzyme-linked immunosorbent assay (ELISA) was found to be positive for the detection of antibodies for human immunodeficiency virus (HIV-1). Her CD4 count was 29 cells per cubic millimeter of blood. We confirmed the diagnosis of acquired immunodeficiency syndrome (AIDS). Since patient's family refused further in-hospital treatment, she was discharged from the hospital with prescription of medical therapy comprising zidovudine 300 mg BD, lamivudine 150 mg BD, and efavirenz 400 mg OD in addition to decongestive therapy. Two months later, we were informed by her relatives that the patient had died at home.

3. Discussion

Double-inlet left-ventricle accounts for about 1% of all congenital heart malformations. Holmes heart, *i.e.* double-inlet left ventricle with normally related great arteries, is still rare. There is no precise information regarding the prevalence of Holmes heart, apart from a few case reports in the modern literature. The characteristic features of Holmes heart include absence of the sinus (body or inflow tract), double-inlet left-ventricle, and

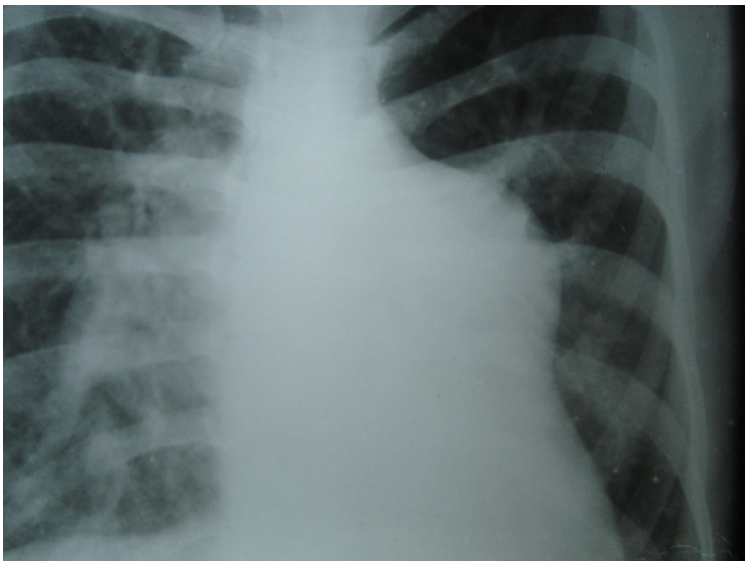

Figure 1. Chest X-ray showing cardiomegaly with increased pulmonary vascularity along with a prominent convexity on left margin of cardiac shadow, suggestive of rudimentary outlet chamber.

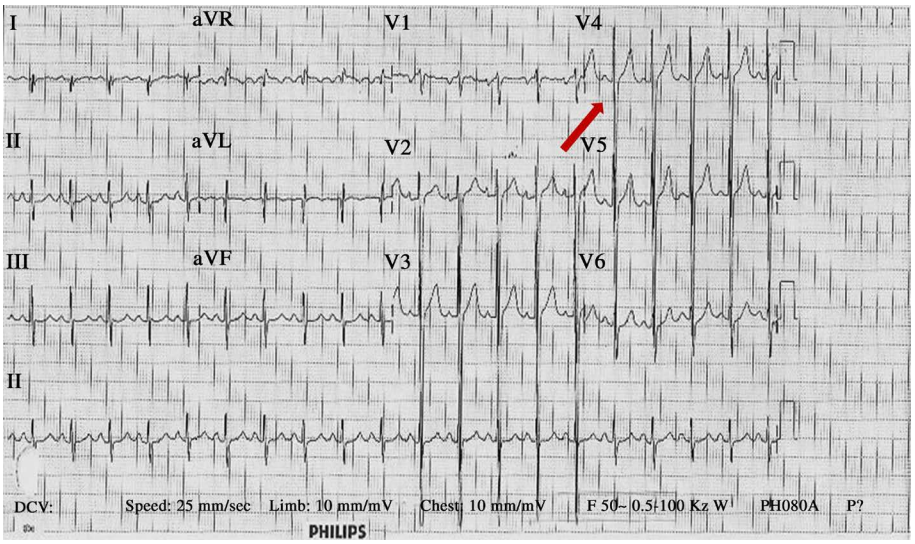

Figure 2. Electrocardiogram showing a right axis deviation with a deep S wave in anterior precordial leads.

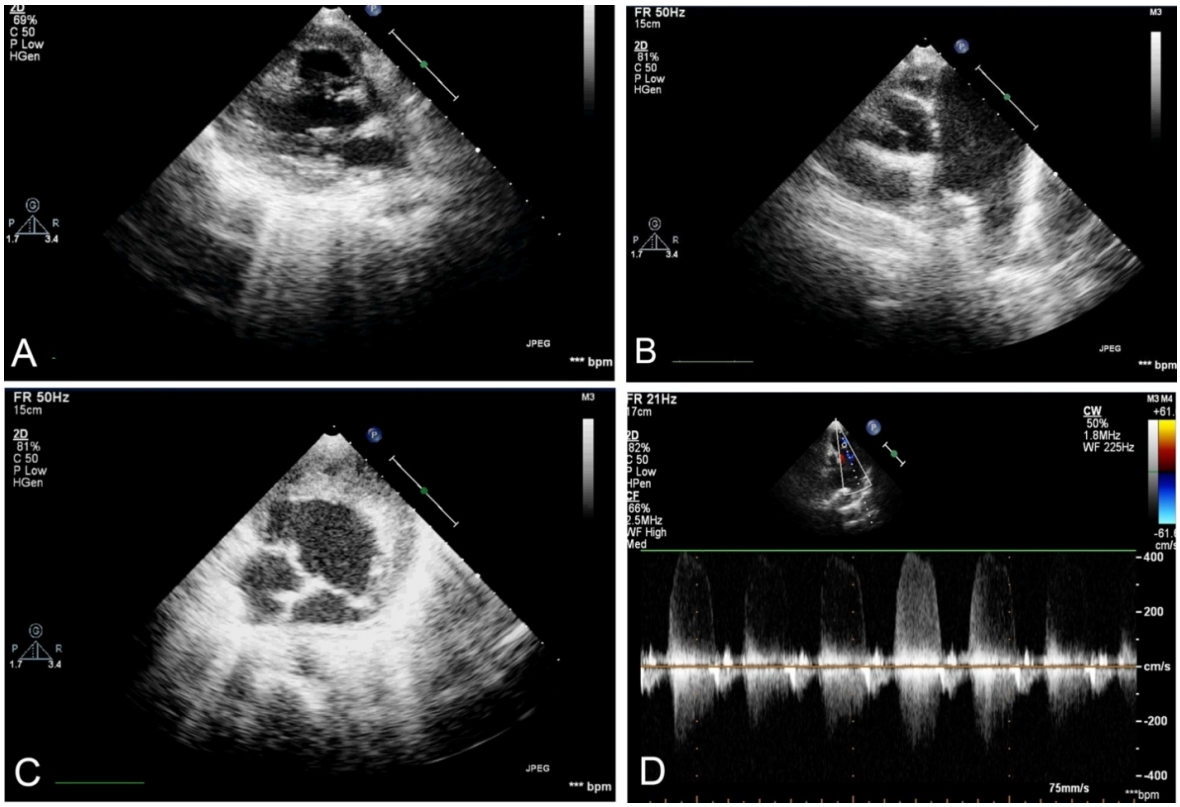

Figure 3. 2D echocardiography showing hypertrophy of left ventricle (A) Morphological left ventricle with rudimentary right ventricle (B) Normally related great vessels (C) Opening of both atrioventricular valves in single ventricle (D) Dilated pulmonary artery with moderate-to-severe pulmonary regurgitation.

normally related great arteries, with the pulmonary artery arising from the infundibular outlet chamber and the aorta arising from the single left ventricle [7]. Such patients with single ventricle usually die from heart failure, arrhythmia, or sudden death during infancy or childhood; however, only some patients reach adulthood [6].

In recent years, Sethi *et al*. have reported a case of a 10-year-old boy with effort dyspnea and cyanosis who was diagnosed to have Holmes heart type of univentricular heart with parachute mitral valve. They demonstrated

the usefulness of 2-dimensional and 3-dimensional echocardiography and multidetector computed tomography in the diagnosis of Holmes heart [8]. In another recent report, Weichert *et al*. described the echocardiographic findings of three fetuses with Holmes heart and addressed the pre- and perinatal management as well as additional abnormalities [9]. Conversely, Coasts *et al*. reported a case of double-inlet left-ventricle with concordant ventriculoarterial connections and a straddling tricuspid valve adherent to the malaligned ventricular septum in a 59-year-old woman [10]. However, reports of Holmes heart in adult patients are very rare.

Klaus *et al*. reported a case of single ventricle with normally related great arteries with sub-pulmonary stenosis in a 26-year-old adult patient [5]. In contrast, the 23-year-old patient in the present case did not exhibit pulmonary stenosis. Similar to our patient, a review of 14 cases of single ventricle with normal great arteries, without pulmonary stenosis, had reported that the oldest individual was 17 years in clinical group and 23 years in necropsy group [1]. Survival to even sixth decade has been reported by Gabbarini in a patient with Holmes heart without pulmonary stenosis [6]. Rahimtoola *et al*. explained the probable reasons for longer survival in Holmes Heart patients without pulmonary stenosis stating that only 16% of such patients displayed complete mixing, while more than half of the patients had their oxygenated blood selectively streamed to systemic circuit and unoxygenated blood selectively streamed to the lungs (favorable streaming) [11].

Apart from long survival, presence of scoliosis and diagnosis of AIDS along with the Holmes heart are distinctive features in the present case. Although the source of HIV infection or duration of suffering from HIV could not be identified, we believed that it could have been transferred from her deceased husband. Unfortunately, the patient died at her home within 2 months from the presentation at our hospital. The information related to her death was retrieved verbally through her relatives with no access to information related to her postmortem. We are of opinion that precise details about HIV infection or postmortem report could have offered more valuable insights regarding the patient discussed in the present case.

Overall, the distinctive features of the present case include long survival with Holmes heart (*i.e.* up to 23 years) and co-presentation of HIV and scoliosis with Holmes heart. Our case also provides valuable diagnostic information of Holmes heart by 2D echocardiography.

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Comparison of Blood Pressure Patterns of Teaching and Non-Teaching Staff of a Nigerian University

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Abstract

Objective: Differences in jobs descriptions and responsibilities may contribute to varying degree of exposure to diseases including high blood pressure. There is dearth of studies comparing blood pressure patterns and anthropometric parameters between teaching and non-teaching staff of university. Therefore, this study was designed to assess and compare the blood pressure and the anthropometric parameters of both teaching and non-teaching staff of a Nigerian university. Materials and Methods: A cross-sectional study was conducted to assess blood pressure pattern and anthropometric parameters among 324 apparently healthy teaching (n = 120) and non-teaching (n = 202) staff of Obafemi Awolowo University, Ile-Ife, Nigeria. Anthropometric parameters including height, weight and hip and waist circumferences were measured. Blood pressure was measured thrice during office hours (9.00 - 11.00 hours) using standard procedures and hypertension was defined as ≥140 ≥90 mmHg. Descriptive and inferential statistics were used to analyze the data at $p < 0.05$ alpha level. Results: The mean of ages of teaching and non-teaching staff were 46.8 ± 9.8 and 45.6 ± 10.9 years. The prevalence of high blood pressure was 34.9% with a distribution of teaching to non-teaching rate of 20.1% and 14.8% respectively. There were significant correlations between blood pressure and each of weight, body mass index and waist circumference in both groups ($p < 0.05$). Conclusion: Prevalence of high blood pressure was higher among teaching than non-teaching staff and significant correlations were found between blood pressure and some anthropometric parameters. Public health including regular physical activity enlightenment programmes to reduce blood pressure is recommended.

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Keywords

Blood Pressure, Anthropometric Parameter, Teaching, Non-Teaching Staff, Nigerian University

1. Introduction

Hypertension or high blood pressure is the most common treatable risk factor for cardiovascular disease which accounts for about 25% of deaths globally [1] [2]. Indeed, it has already been projected that up to three-quarters of the world's hypertensive population will be in economically developing countries by the year 2025 [3]. The sudden increase in the prevalence of hypertension in sub-Saharan Africa (SSA) has been attributed to urbanization, industrialization, economic transition as well as globalization which bring about lifestyle changes and consequent predisposition to cardiovascular disease and other chronic diseases [4]. Thus, it is regarded as a serious public health problem being the leading cause of morbidity and mortality in SSA [5] [6].

Although hypertension risk factors are numerous, sedentary lifestyles, poor dietary intake and occupational stress are now considered as risk factors for high blood pressure [7] [8]. More importantly, obesity resulting from physical inactivity has been linked with increased prevalence of hypertension [9]. Furthermore, significant association between work-related stress and cardiovascular complications has been reported [10] [11]. Similarly, university staff are continually subjected to high level of psychological stress leading to chronic psychological disturbances such as excessive anger, anxiety, irritability and frustration [12] [13].

Previously, Adedoyin *et al*., [14] reported moderate cardiovascular risk among university staff. They attributed this to reduced physical activity due to reduction in the active transportation such as walking and biking which have being replaced with proliferation of Tokunbo cars (fairly used imported cars) and Okada (commercial motor bike). Their study did not compare the level of cardiovascular risk between the academic (teaching) and non-teaching staff. We hypothesized that the academic staff would have higher risk of been hypertensive than the non-academic. Academic staff responsibilities include teaching, research, administration and community services while that of non-academic staff are mainly routine administrative works. Differences in jobs descriptions and responsibilities may contribute to varying exposures to diseases including high blood pressure. Presently, there is dearth of studies comparing blood pressure patterns and anthropometric parameters between teaching and non-teaching staff of universities. Therefore, this study was designed to assess and compare the blood pressure and the anthropometric parameters of both teaching and non-teaching staff of a Nigerian university.

2. Materials and Methods

2.1. Participants

2.1.1. Research Design

This cross-sectional study recruited three hundred and twenty four (324) staff (academic = 122; non-academic =202) of the Obafemi Awolowo University, Ile-Ife, Nigeria using purposive sampling technique.

2.1.2. Population and Participants

The Obafemi Awolowo University was established in 1962. It is one of the first generation Federal Government Universities. There are two colleges and 13 faculties with 103 academic departments and units as well as seven specialized centres and institutes. The central campus comprises the academic, administrative units and service centers while the student residential area is made up of 10 undergraduate hostels and a postgraduate hall of residence [15]. Both teaching and non-teaching were approached to participate in this study.

Inclusion criteria

Eligibility for inclusion was apparently healthy individuals free of obvious disabilities and full-time workers of the institution.

Exclusion criteria

Pregnant women and causal workers were excluded from the study.

2.2. Procedure

Ethical approval was sought and obtained from the Health and Research Committee, Institute of Public Health,

College of Health Sciences, Obafemi Awolowo University, Ile-Ife, Nigeria. The purpose of the study was explained to the participants and informed consent was obtained. Data collection took place between 9:00-11:00 hours.

2.2.1. Assessment of Blood Pressure

Blood pressure of participants was measured using a validated electronic blood pressure kit (Omron Intelli Sense M6 Comfort, Japan) after about 10 minutes of quiet sitting. The blood pressure was measured in sitting position with the feet flat on the floor and the arm placed on the table so that the arm is at the same level as the heart. The cuff of the sphygmomanometer (of appropriate size) was wrapped around the left upper arm and the participants were instructed to remain calm and not to talk during the measurement while the palm was turned upward [16]. Three readings were taken at five minutes interval and the average was used for the analysis.

2.2.2. Assessment of Anthropometric Parameters

The weight of each participant was measured using a portable weighing scale (Seca 761, CE: 0109 0123, United Kingdom). The participant was asked to stand erect on the weighing scale bare-footed with light clothing without holding or carrying anything with them. The participant stood erect, looking straight ahead with as minimal amount of clothing and accessories as possible, considering the site of data collection. The height of participants was measured using a height meter with the participant standing upright, both arms lying by the sides, eyes looking straight without shoes while standing against the height meter placed against the wall with the participant's heels, back and the occiput touching the height meter. Waist and hip circumferences of participant was measured in centimeters using a measuring tape. The waist circumference was measured with the participants standing upright with their feet together arms by side with the palm facing inward and the measuring tape wrapped around the participants' abdomen horizontally and positioned at the level of the umbilicus. Instruction was given to the participant to relax and breathe normally and with the tape measure aligned together horizontally. Measurement was then taken from zero line of tape at the end of expiration when the diaphragm is in neutral position. The hip circumference was measured at the widest diameter of the buttock; the greatest concavity of the buttock and measurement taken from zero line of the tape [17].

2.3. Data Analysis

Descriptive statistics of frequency, percentage, mean and standard deviation was used to summarize data. T-test was used to compare blood pressure and anthropometric parameters between teaching and non-teaching staff. Pearson Product Moment Correlation Analysis was used to determine the correlation between anthropometry and blood pressure among participants. Significant difference was set at $p < 0.05$. Data analysis was performed using Statistical Package for Social Science (SPSS 17.0 version).

3. Results

The sample comprised 324 participants with 122 teaching and 202 non-teaching staff. **Table 1** showed physical characteristics of all participants. The mean age of academic and non-academic staff were 46.8 ± 9.8 and 45.6 ± 10.9 years respectively. All participants were comparable in age but significantly different in physical characteristics of weight, height, waist circumference and body mass index ($p < 0.05$).

Table 2 showed the prevalence of hypertension among teaching and non-teaching staff using the 140/90 mmHg cuff-point. The result showed that the prevalence of hypertension was higher among teaching than non-teaching staff. The total prevalence rate of hypertension among teaching and non-teaching 34.9% with an academic-to-non-academic distribution of 20.1% to 14.8% respectively. Furthermore, percentage of systolic hypertension among teaching and non-teaching staff were 25.4% and 17.4% respectively. Similarly, the percentage of diastolic hypertension in both groups were 14.7% and 12.1% respectively. The comparison of blood pressure profile between teaching and non-teaching staff showed that the academic staff has significantly higher systolic blood pressure than non- teaching staff ($t = 2.268$; $p = 0.025$). However, there was no significant difference in the diastolic blood pressure in both groups ($t = 1.326$; $p = 0.187$).

The Pearson Product Moment Correlation test was used to determine the relationship between anthropometry (height, weight, body mass index, waist and hip circumferences) and blood pressure among academic staff. Among teaching staff, **Table 3** showed that both systolic and diastolic blood pressure significantly correlated

Table 1. Physical characteristics of the participants.

	Teaching staff	Non-teaching staff		
Variables	**Mean ± S.D**	**Mean ± S.D**	**t-cal.**	**p-value**
Age (years)	46.8 ± 9.8	45.6 ± 10.9	1.652	0.101
Height (m)	1.72 ± 0.08	1.65 ± 0.08	6.079	0.010*
Weight (kg)	74.96 ± 13.6	67.19 ± 11.4	5.600	0.010*
Waist Circumference	90.7 ± 11.1	88.3 ± 10.8	2.463	0.015*
Hip Circumference	99.8 ± 8.8	98.6 ± 8.9	1.789	0.076
Body mass index	25.4 ± 4.0	24.2 ± 4.7	2.079	0.040*

*Significant at $p < 0.05$.

Table 2. Prevalence of hypertension and comparison of blood pressure profile between teaching and non-teaching staff.

Variable	**Teaching staff**	**Non-teaching staff**		
Blood Pressure	**%**	**%**		
SBP (mmHg)	25.4	17.4		
DBP (mmHg)	14.7	12.1		
	Teaching staff	**Non-teaching staff**		
Blood Pressure	**Mean ± S.D**	**Mean ± S.D**	**t-cal**	**p-value**
SBP	130.94 ± 14.6	126.97± 18.8	2.268	0.025*
DBP	77.7 ± 10.7	75.7 ± 11.3	1.326	0.187

*Significant at $p < 0.05$. Key: SBP; Systolic blood pressure. DBP; Diastolic blood pressure.

Table 3. Correlation between anthropometry and blood pressure among teaching staff non-teaching staff.

	SBP	**DBP**
Variable	**r**	**r**
Teaching Staff		
Height	0.044	0.061
Weight	0.253**	0.309**
BMI	0.265**	0.315**
Waist Circumference	0.248**	0.278**
Hip Circumference	0.141	0.245**
Non-teaching staff		
Height	0.010	0.032
Weight	0.212**	0.253**
BMI	0.189**	0.195**
Waist Circumference	0.243**	0.261**
Hip Circumference	0.154*	0.157*

**Correlation is significant at $p < 0.01$. Key: SBP; Systolic blood pressure. DBP; Diastolic blood pressure.

with each of weight (r = 0.253; 0.309), body mass index (r = 0.265; 0.315) and waist circumference (r = 0.248; 0.278) ($p < 0.01$) and between diastolic and hip circumference (r = 0.245) ($p < 0.05$). Similarly, correlation between anthropometry and blood pressure among non-teaching staff, the results showed that both systolic and diastolic blood pressure significantly correlated with each of weight (r = 0.212; 0.253), body mass index (r = 0.189;

0.195), waist circumference (r = 0.243; 0.261) ($p < 0.01$) and waist circumference (r = 0.159; 0.154) ($p < 0.05$).

4. Discussion

This study assessed the blood pressure of staff of the Obafemi Awolowo University, Ile-Ife, Nigeria and compared the blood pressure and the anthropometric parameters of both teaching and non-teaching staff. The study shows a significant difference in systolic blood pressure of teaching and non-teaching staff but no significant difference in the diastolic blood pressure in both groups. Also, this study shows the prevalence rate of hypertension among teaching to be higher than that of non-teaching staff. It has been reported that a high level of psychological stress during certain occupational activities (public speeches like lectures in class and at meetings and seminars) contributes to blood pressure increase among certain professionals predominantly those with high intellectual activity like university lecturers [18] [19]. This is supported by study done by Fauvel *et al*., [20] in which psychological stress is related to high blood pressure as well as unfavourable cardiovascular profile.

Kulkami *et al*., [21] explained that stress can cause hypertension through repeated blood pressure elevations as well as by stimulation to the nervous system to produce large amounts of vasoconstricting hormones that increases blood pressure. Furthermore, when one risk factor is coupled with other stress producing factors, the effect on blood pressure is multiple. Some of the factors affecting blood pressure through stress include white coat hypertension, job strain, race, social environment, and emotional distress. Development of high blood pressure may be associated with the poor knowledge on the risk factors for hypertension which may also result into inability of the staff to manage hypertension effectively. In the study conducted by Abdullah *et al*., [22] on the knowledge of hypertension of the University of Ibadan staff, they found that the staff has low knowledge of some of the risk factors.

Our study shows that there were strong significant correlations between weight, body mass index, waist circumference and systolic blood pressure as well as diastolic blood pressure among the teaching and non-teaching staff. These findings corroborate the study of Adebayo *et al*., [23] which indicated a trend towards increase prevalence of risk of hypertension in Nigeria. Furthermore, Adebayo *et al*., [23] reported increased body mass index (BMI) significantly increase blood pressure in adults and this was supported by other authors [24]-[27]. Additionally, Adedoyin *et al*., [16] reported similar findings in which weight and BMI were significantly correlated with systolic blood pressure and diastolic blood pressure but the correlations were weak contrary to that found in this study. Contrast to our findings, independent association between body mass index and systolic and diastolic blood pressure has been reported [28] [29]. Furthermore, Janssen *et al*., [30] reported that waist circumference and not BMI explains obesity related health risk including hypertension. Increased blood pressure has been linked to the influence of modernization with concurrent increase in western lifestyle which increases the prevalence of obesity [16] [31].

According to study by Adebayo *et al*., [21] a significant correlation was found between hip circumference and diastolic blood pressure whereas no significant correlation was found between hip circumference and systolic blood pressure. This is consistent with the finding among teaching staff; however, hip circumference shows a significant correlation with both the systolic and diastolic blood pressure. In contrast to study conducted by Snijder *et al*. [32] an inverse relationship was found between hip circumference and blood pressure.

The increased prevalence of hypertension has also been associated with economic, dietary and lifestyle change which are by-products of the influence of modernization which have become perennial in the society [16]. It has however been noticed among the academic staff that they have little or no time for physical activity due to the nature of their work and as such are more prone or susceptible to increased blood pressure. Transition to a sedentary lifestyle as strong risk factor for hypertension has been reported, however a change from a sedentary lifestyle to an active one can reduce blood pressure level and subsequently lower cardiovascular risk by 30% [33] [34]. Therefore, it has been recommended that routine assessment could be of help to detect people that are at high risk of developing hypertension and approaches to reduce the risk of hypertension such as prevention of overweight and obesity and promotion of physical activity should be encouraged [16].

Findings from our study should be interpreted with caution due to some inherent limitations. Firstly, this is a cross-sectional study and its generalizability may be limited. Furthermore, blood pressure varies differently during daily activities, our study was conducted during 9.00 and 11:00 hours which might be different from other hours of the day. Laboratory and other clinical tests were not conducted prior to this study to identify individuals with high risk of hypertension and may affect the outcome of this study.

5. Conclusion

It was concluded that the academic staff have higher blood pressure than non-academic staff. Furthermore, anthropometric characteristics were significantly associated with blood pressure. It is therefore recommended that a periodic re-assessment be made to keep abreast of the changes in the blood pressure as well as to detect those that are at risk of developing hypertension so that preventive measures could be put in place. Therefore, more emphasis should be placed on prevention than treatment of hypertension.

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Disclosure of Interest

The authors declare that they have no conflicts of interest concerning this article.

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Perineal Electric Burn Reconstruction Using Modified Thoraco-Umbilical Flap*

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Abstract

Perineal reconstruction is an essential component of the overall treatment plan of perineal electric burn, but it is a very difficult and complex job. The modified thoraco-umbilical flap may be a perfect way of repairing perineal area. It is based on the deep inferior epigastric artery and vein and the superior epigastric artery and vein, which look like the "reverse TRAM flap". The large flap could be fashioned into a perfect perineal area without the need for free flap. It left a satisfactory donor scar, and it avoided the need to change the patient's position during the operation. Four cases were reconstructed by modified thoraco-umbilical flap after perineal electric burn, and all of them were satisfied with the results. The modified thoraco-umbilical flap has been emerged as a very useful reconstructive tool and is particularly valuable in reconstruction of the perineal electric burn.

Keywords

Perineal Electric Burn, The Modified Thoraco-Umbilical Flap

1. Introduction

The perineal area serves an important function. Perineal reconstruction is an essential component of the overall treatment plan of perineal electric burn. When perineal electric burn occurs, it is very hard to reconstruct. Skin graft is not the best way because the contract scar will happen. Local flap transfer may be the best way for perineal electric burn, but there is no proper local flap when the local skin, muscle and artery were destroyed [1]. Due to the special function and appearance of the perineal area [2], reconstructive options for perineal trauma are not very satisfactory.

*The study was approved by ethics committee of our hospital, and all the 4 patients signed informed consent before the operation.

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2. Methods

The TRAM flap has emerged as a very useful reconstructive tool and is particularly valuable in reconstruction of the breast following masterctomy [3] [4]. From the point of view of form, the modified thoraco-umbilical flap looks like the “reverse TRAM flap”, is based on the deep inferior epigastric artery and vein and the superior epigastric artery and vein [5]. Flaps are typically marked approximately 12 cm high at the midline and extend approximately 22 - 24 cm laterally from the midline (**Figure 1**). The modified flap can extend the midline if there is necessary. The large flap could be fashioned into a perfect perineal area without the need for free flap. It left a satisfactory donor scar, and it avoided the need to change the patient’s position during the operation (**Figure 2**). The modified thoraco-umbilical flap has emerged as a very useful reconstructive tool and is particularly valuable in reconstruction of the perineal electric burn.

3. Case Report

Four cases were electrician, and were hurt by electric when they sat on the ladder. Four cases were reconstructed by the modified thoraco-umbilical flap, and all patients were satisfied with the results. With the patient in a supine position, a doppler probe is used to identify the deep inferior epigastric artery and the superior epigastric artery. The size and the shape of the flap were designed according to the wound area of perineum. During flap harvest, the superficial inferior epigastric vessels are approached first. The anterior rectus sheath is opened around the perforators and the vessels are carefully dissected down through the rectus muscle to the deep inferior epigastric artery and vein. The flap was transferred from the subcutaneous tunnel. All of the patients were satisfied with the function and appearance of the flap.

4. Discussion

The reconstructive goal of perineal trauma is to obtain durable coverage and function. Axial pattern skin flap and local random flap are the main ways for perineal area. But to the electric burning patients, the wound area are large and irregular, the soft tissue and artery near the wound area are often destroyed, local axial pattern skin flap and local random flap are very difficult to be designed and peformed. The modified thoraco-umbilical flap

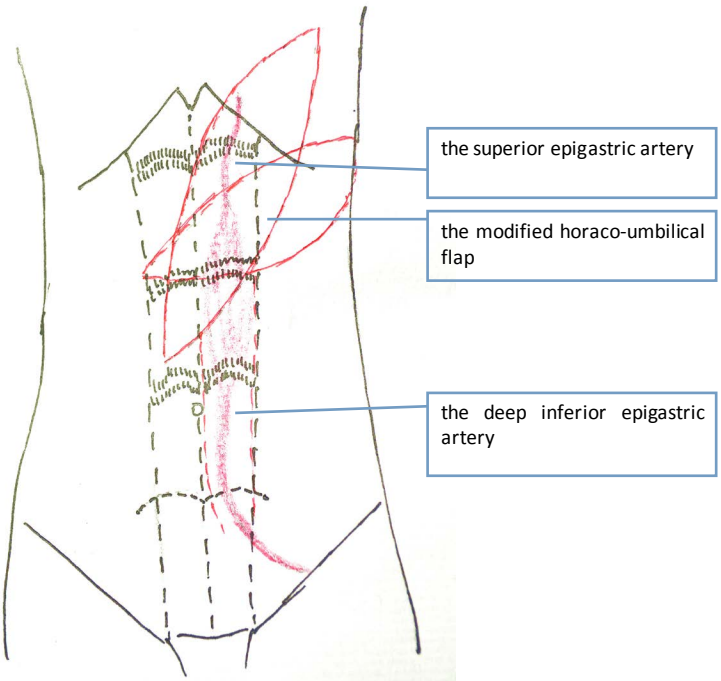

Figure 1. The modified horaco-umbilical flap is based on the deep inferior epigastric artery and vein and the superior epigastric artery and vein. Flaps are typically marked approximately 12 cm high at the midline and extend approximately 22 - 24 cm laterally from the midline.

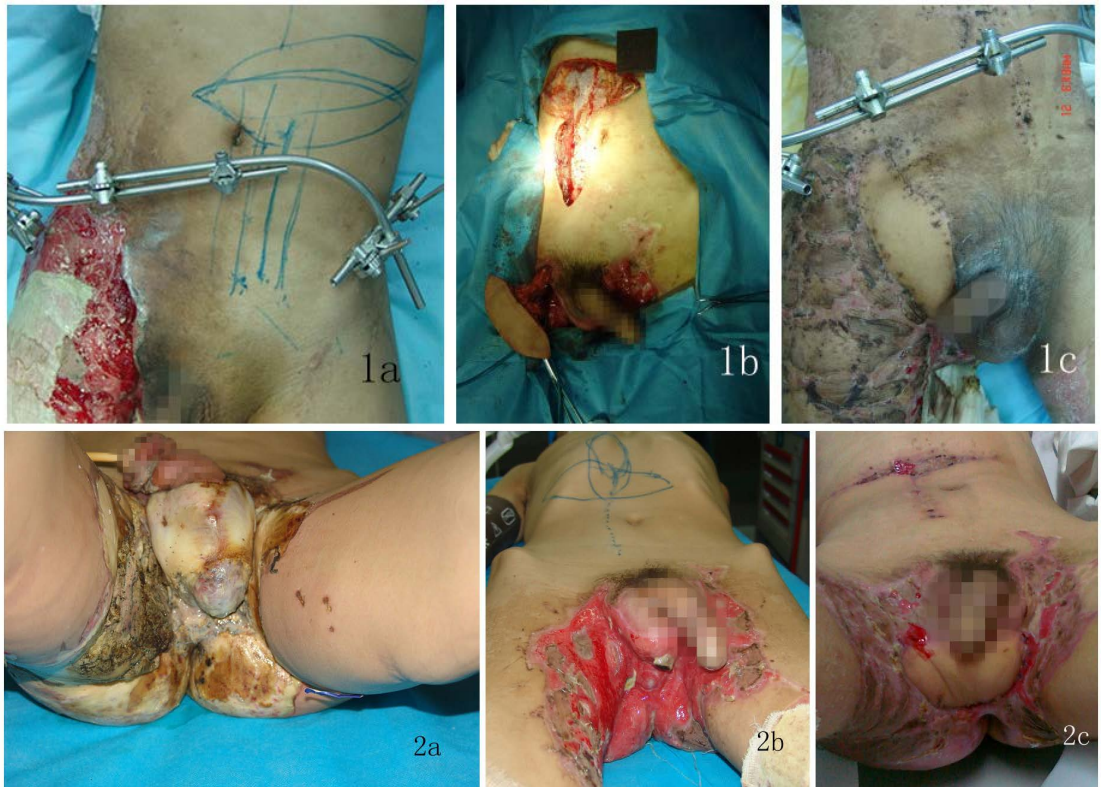

Figure 2. (1a) the serious perineal trauma after electric burn; (1b) the modified thoraco-umbilical flap was transferred to perineal area; (1c) the appearance of the flap after 4 weeks. (2a) the electrical injury of perineal area; (2b) the perineal trauma area was repaired by the modified t horaco-umbilical flap; (2c) the appearance of the flap after 3 weeks.

may be the perfect flap to repair perineal, especially to the serious and large perineal trauma. In addition, the modified thoraco-umbilical flap can extend the midline and be more flexible compared to the traditional thoraco-umbilical flap.

5. Conclusion

The modified thoraco-umbilical flap is a very useful reconstructive tool for the reconstruction of the perineal electric burn, and this way is worth promoting.

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Functional Capacity and Psychosocial Correlates of Exercise in Nigerian Patients with Hypertension

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Abstract

Objectives: Psychosocial factors are important determinants of cardiovascular health outcomes in rehabilitation. However, the relationship between exercise performance and individual factors remained poorly understood. This study investigated the relationship between functional capacity and psychosocial correlates of exercise in Nigerian patients with hypertension. Study Design and Setting: This quasi-experimental study recruited 120 patients with hypertension (≥140/90 ≤ 179/109 mmHg) from the Cardiac Care Unit of a Nigerian university teaching using purposive sampling technique. Functional capacity was assessed using the 6-minute walk test and maximum oxygen consumption (VO_2 max) was estimated. Participants also underwent a 30-minute self-paced walking exercise. Thereafter, psychosocial correlates of exercise including exercise self-efficacy (ESE), social support (SoS), perceived exercise barrier (PEB) and socio-economic status (SES) were assessed using validated questionnaires. Descriptive and inferential statistics were used to analyze data. Alpha level was set at $p < 0.05$ of significance. Results: A majority of the participants demonstrated high ESE (75.0%), moderate SoS (60.9%) and low PEB (71.7%). More than half (58.4%) of the participants were in the middle SES. Male and female participants were comparable in ESE scores ($p = 0.554$), SoS ($p = 0.362$) and six-minute walk distance (6-MWD) ($p = 0.194$) except in body mass index ($p < 0.05$). The mean 6-MWD and VO_2 max were 350.6 ± 54.7 m and 9.74 ± 1.5 ml/kg/min respectively. There were significant correlations between functional capacity and each of ESE ($r = 0.184$; $p = 0.026$) and SoS ($r = 0.374$; $p = 0.021$). Conclusions: Psychosocial correlates

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of exercise including self-efficacy and social support were significantly associated with functional capacity among Nigerian patients with mild to moderate hypertension.

Keywords

Functional Capacity, Psychosocial Correlate, Exercise, Hypertension

1. Introduction

Regular exercise practice such as brisk walking, cycling or jogging of moderate intensity and 30 minutes per day has been reported to be effective for blood pressure (BP) control [1]. Exercise alone has been reported to be capable of lowering systolic blood pressure up to 15 mmHg and reduces risk of cardiovascular mortality by 30% [2]. Although hypertension impairs endothelial function and poor functional capacity, regular exercise participation has been reported to improve aerobic performance and exercise tolerance [3]. Physiotherapists often prescribe exercise training based on cardiovascular parameters and functional status of patients with hypertension. However, individual factors as regard initiation and maintenance of exercise programme are still a challenge in rehabilitation care [4].

Engagement in regular physical exercise may be influenced by many factors including personal and health challenges, lack of recreational facilities, environmental factors and socioeconomic status (SES) [5]. Socioeconomic disparity is a strong determinant of health, and has been reported as an aetiological factor in the development of hypertension [6]. Low SES could negatively impact on self-esteem and ability to engage in self-regulatory task such as exercise [7]. In addition, the social cognitive theory explains that self-efficacy, perceived exercise barrier and social support are central to behaviour change [8].

Exercise as a health behaviour is associated with one's self-efficacy perception and one's ability to overcome self-reported perceived barrier to exercise [9]. King [10] observed that psychosocial factors are important personal attributes that may predict current and future participation in regular physical exercise. However, there is no evidence to suggest that psychosocial factors are taken into consideration in designing exercise training during rehabilitation of patients with hypertension. Furthermore, there is dearth of information on the relationship between functional capacity and psychosocial correlates of exercise among patients with hypertension in different socioeconomic strata. Hence, this study investigated the relationship between functional capacity and psychosocial correlates of exercise among Nigerian patients with hypertension.

2. Methods

2.1. Study Sample

Participants for this study were patients with clinical diagnosis of essential hypertension. Eligibility for participation included patients with mild to moderate hypertension (≥140/90 ≤ 179/109 mmHg) receiving treatment at OAUTHC and whose ages range from 40 - 70 years. They were excluded from the study if presented with musculoskeletal or neurological conditions that may affect walking or cognitive problem affecting ability to recall personal information.

This quasi-experimental study recruited 120 patients with mild to moderate hypertension from the Cardiac Care Unit, Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile-Ife, Nigeria using purposive sampling technique. The OAUTHC was founded on integrated comprehensive health-care services based on a pyramidal structure designed to secure excellent and efficient health-care services in the area of cardiovascular disease. The hospital has more than 600 beds space. The institution provides health-care to more than 10 million Nigerians in the South West Zone of Nigeria. It covered Ondo, Osun, Oyo, Ekiti, Edo and part of Kwara State [11].

2.2. Procedure

Ethical approval for this study was obtained from the Health and Research Ethics Committee of the Institute of

Public Health, Obafemi Awolowo University, Ile-Ife. The Head of CCU gave permission to recruit patients with hypertension for participation in the study. The purpose of the study was explained to respective participants and an informed consent was obtained. Anti-hypertensive medications and dosage prescribed by the attending cardiologist were recorded. Participants' anthropometric characteristics were measured using standard procedures. After ten minutes of quite sitting, participants' cardiovascular parameters including resting heart rate, systolic and diastolic blood pressure were measured in sitting position using standard procedures.

Functional capacity was assessed using the six minute walk test on a 30 m level ground floor. After five minute of resting, participants were instructed to perform self-paced walking exercise for 30 minutes. Thereafter, psychosocial factors related to exercise including exercise self-efficacy, social support, perceived exercise barrier and socioeconomic status were assessed.

2.2.1. Assessment of Functional Capacity

The six-minute walk test (6-MWT) was performed on a 30 meter level corridor without any obstructing object using the American Thoracic Society guidelines [12]. Participants were allowed to rest for a period of 10 minutes in sitting position before the commencement of the exercise test. Participants were instructed to walk from the starting point to the end at their own selected pace while attempting to cover as much ground as possible in six minutes [13]. Encouragement was provided every 30 seconds or more in a standardized manner by saying: "You are doing well" or "Keep up the good work". The total distance covered during the six minute walk was recorded. The maximum oxygen consumption (VO_2 max) was estimated using the American College of Sport Medicine predictive equation [14].

Computation: VO_2 max (ml/O_2kg/min) = speed (m/min) × 0.1 m/O_2/Kg + 3.5 m/O_2/Kg/min

2.2.2. Self-Paced Walking Exercise

Self-paced walking exercise was prescribed and carried out by the participants to test their understanding of ability to initiate and maintain such exercise programme on regular basis. Participants were instructed to walk on a 30 m level ground corridor for 30 minutes. They were allowed to rest briefly for 2 minutes at intervals if experiencing fatigue. At the end of 30 minutes of self-paced walking, cardiovascular parameters were assessed after 10 minutes in sitting position. Thereafter, psychosocial correlates of exercise were assessed using validated questionnaires.

2.2.3. Assessment of Psychosocial Correlates of Exercise

Exercise self-efficacy

Exercise self-efficacy (ESE) was assessed using the exercise self-efficacy scale. The scale was adapted from the study by Kroll *et al.* [15]. The questionnaire contains questions about level of confidence the participant can demonstrate to engage in exercise under specific circumstances. The questionnaire contains 10 items that describe the participant's confidence to exercise such as "when I am tired", "even if I had no access to a gym or training facility" etc. The questions were rated on a 4-point Likert scale that ranges from "Not at all true (1)" to "exactly true (4)". The maximum obtainable score is 40 while the minimum score is 10.

Social support

The amount of social support (SoS) available to the respondents was measured using the MOSSSQ. The scale is a 19-item scale developed by Sherborne and Stewart [16]. The instrument consists of four separate social support subscales and an overall functional social support index. A higher score for an individual scale or for the overall support index indicates more support. Each item is scored on a 5-point Likert scale and the scores indicate the degree to which the respondent agrees or disagrees with a particular item question (1 = none of the time, 5 = all of the time). The minimum possible score is 19 which indicates low social support and the maximum possible score is 95.

Perceived exercise barrier

The barrier component of the exercise benefits/barriers scale (EBBS) developed by Sechrist *et al.* [17] was used to assess the perceived exercise barrier (PEB) of participants. The barrier component of the EBBS which could be used separately as described by the authors consists of 14 items which is rated on a 4-point Likert-type scale. The barrier component comprised 14 barrier items categorized into four subscales: exercise milieu; time expenditure; physical exertion; and family discouragement. The minimum score for the barrier scale is 14 indicating less perceived barriers to physical activity while the maximum score is 56. Obtained scores for each of

ESE, SoS and PEB were divided by total possible score and multiplied by 100 to obtain percentage scores; 100 × (observed score − minimum possible score)/(maximum possible score − minimum possible score). Furthermore, the 25th, 50th and 75th percentiles was used to label transformed-scores into lower, middle and upper quartiles representing "low", "moderate" and "high" levels for each of psychosocial factor.

2.2.4. Socio-Economic Status

Socio-economic Status (SES) was assessed using the SES questionnaire. The questionnaire took 4 major SES indicators into consideration which include educational level, occupation, present salary, and other valuable items. Valuable properties in Nigerian context such as landed properties, type of apartment, number of rooms and persons in the household, cooking utensils, home appliances and electronics such as radio, television and computer were included. Information on vacation in the last one year was also sought. Participant's position in the society including community leader, high chief or religion leader such as priest or imam was also sought. Scores were assigned to each item on the questionnaire based on their status in the Nigerian society. The summative scores of the three socioeconomic indicators and respective valued properties and position in the community were added together to yield a maximum obtainable score of 27 points. The score was transformed as 100 × (observed score − minimum possible score)/(maximum possible score − minimum possible score). The 25th, 50th and 75th percentiles was used to label transformed-scores into lower, middle and upper quartiles representing "low", "moderate" and "high" levels of socioeconomic class. The instrument has good test re-test reliability value (r = 0.86) [18].

2.3. Statistical Analyses

Descriptive statistics of frequency, percentages, mean and standard deviation were used to summarize data. Independent t-test was used to compare male and female exercise self-efficacy, social support, perceived exercise barrier. Furthermore, paired t-test was used to compare pre- and post-exercise cardiovascular parameters (systolic and diastolic blood pressure and heart rate). Pearson product moment correlation was used to test the relationship between psychosocial correlates of exercise and functional capacity. Alpha level was set at $p < 0.05$. SPSS version 16 was used for statistical analysis.

3. Results

The socio-demographic characteristics of participants were presented in **Table 1**. **Figure 1** shows distributions of psychosocial factors of all participants. A majority of the participants demonstrated high self-efficacy (75.0%), moderate social support (60.9%) and low perceived exercise barrier (71.7%). More than half, (58.4%) of the participants were in the middle SES. **Table 2** shows the independent t-test comparison of physical characteristics, exercise self-efficacy (ESE), social support (SoS), perceived exercise barrier (PEB), socioeconomic status (SES) and six minute walk distance (6 MWD) between male and female. Both genders were comparable in physical characteristics except in body mass index ($p < 0.05$). The mean psychosocial correlates of exercise between males and females were also comparable. The mean 6-minute walk distance (6 MWD) and estimated maximum oxygen consumption (VO_2 max) of all participants were 350.6 ± 54.7 m and 9.74 ± 1.5 ml/kg/min respectively.

Table 3 shows the results of cardiovascular response to self-paced walking exercise. The results showed that there were significant differences between pre- and post-exercise, SBP ($p = 0.019$) and heart rate ($p = 0.042$) respectively. **Table 4** shows the Pearson Product Moment Correlation between functional capacity and psychosocial correlates of exercise. There were significant correlations between functional capacity and each of ESE ($r = 0.184$, $p = 0.046$) and SoS ($r = 0.374$; $p = 0.031$) and but not with PEB ($r = 0.108$; $p = 0.269$) and SES ($r = −0.03$; $p = 0.669$).

4. Discussion

The purpose of this study was to investigate the relationship between functional capacity and psychosocial correlates of exercise among patients with mild to moderate hypertension. Participants in this study were found to demonstrate high exercise self-efficacy. This is contrary to the finding of a previous study that patients with chronic non-communicable diseases usually have reduced exercise self-efficacy [19]. The plausible explanation

Table 1. Socio-demographic characteristics of participants.

Variable	n	%
Age group (years)		
40 - 50	23	19.2
51 - 60	54	45.0
>60	43	35.8
Sex		
Male	36	30.0
Female	84	70.0
Marital status		
Single	2	1.7
Married	86	71.7
Widowed	32	26.6
Educational level		
Primary	62	51.7
Secondary	46	38.3
Tertiary	12	10.0
Occupation		
Artisan/Self-employed	60	50.0
Civil servant	20	16.7
Retiree	40	33.3
Income (monthly)		
<#50K	48	40.0
#50 - #100K	65	54.2
>#100K	7	5.8

Key: K: Thousands of Naira.

Table 2. Comparison of physical characteristics, functional capacity and psychosocial correlates of exercise by gender.

	Male (n = 36)	Female (n = 84)		
Variable	**Mean ± S.D**	**Mean ± S.D**	**t-cal.**	**p-value**
Age (years)	58.3 ± 9.0	57.5 ± 7.7	0.448	0.655
Weight (Kg)	72.2 ± 10.6	71.2 ± 13.1	0.391	0.696
BMI (Kg/m^2)	25.4 ± 3.7	28.1 ± 5.6	−2.587	0.011*
ESE score (%)	74.0 ± 5.6	72.6 ± 4.9	−0.593	0.554
SoS score (%)	55.6 ± 7.1	56.6 ± 2.7	0.621	0.362
PEB score (%)	39.3 ± 4.6	41.8 ± 5.0	0.127	0.601
SES score (%)	58.4 ± 4.3	57.8 ± 4.9	1.426	0.281
6-MWD (m)	360.6 ± 48.3	346.3 ± 56.9	1.310	0.193
Est. VO_2 max (ml/kg/min)	10.1 ± 1.4	9.71 ± 1.6	1.310	0.193

*Significance at $p < 0.05$. Key: BMI: Body mass index, ESE: Exercise self-efficacy, SoS: Social support, PBE: Perceived exercise barrier, SES: Socio-economic Status, 6 MWD: 6-minute walk distance Est. VO_2 max: Estimated maximum oxygen consumption.

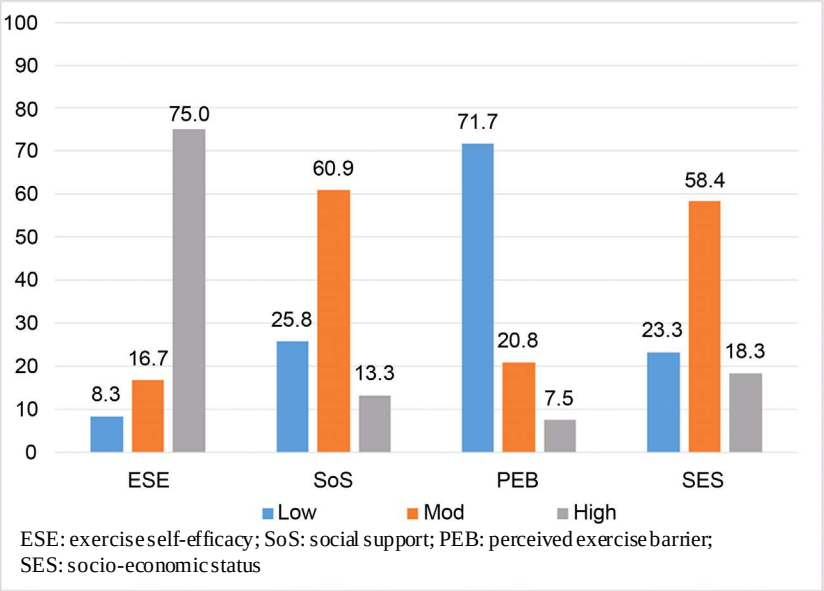

Figure 1. Distributions of psychosocial factors of all participants.

Table 3. Cardiovascular response to self-paced walking exercise.

Variable	Pre	Post	t-cal	p-value
Systolic BP (mmHg)	135.2 ± 16.3	128.9±15.3	1.292	0.019*
Diastolic BP (mmHg)	82.3 ± 10.2	80.0±10.5	0.262	0.794
Heart rate (beat/minute)	78.5 ± 11.6	72.6±11.3	1.118	0.042*
RPP ($X10^3$)	10.6 ± 2.2	10.3±1.9	0.696	0.487

*Significant at $p < 0.05$. Key: BP—Blood Pressure, RPP—Rate Pressure Product.

Table 4. Relationship between functional capacity and psychosocial correlates of exercise.

Functional Capacity		
Variable	**r**	**p**
ESE (%)	0.183	0.026*
SoS (%)	0.374	0.031*
PEB (%)	0.108	0.269
SES (%)	−0.039	0.669

*Significant at $p < 0.05$. Key: ESE—Exercise self-efficacy, SoS—Social support, PEB—Perceived exercise barrier, SES—Socio-economic status.

for the difference between our study and that of Adeniyi's findings may be that our study participants presented with less severe hypertension and were on regular antihypertensive medications with good blood pressure control. There is evidence from previous studies that self-efficacy is a strong determinant and mediating factor for high level of physical activity as well as better predictor of exercise practice [20] [21]. Kim [21] further emphasized that individuals with high self-efficacy were more likely to engage in exercise behaviour than those with low exercise self-efficacy. In addition, Bandura [22] posited that the key determinant of exercise participation is self-efficacy. Findings from our study do not suggest that there was gender difference in exercise self-efficacy. This is contrary to the findings of previous studies that men usually demonstrate higher self-efficacy than women [23] [24].

Functional capacity is a measure of cardiorespiratory fitness and determinant of survival in cardiovascular

disease. Hypertension is associated with reduction in functional capacity and impairment of aerobic exercise performance [25]. Our study shows that participants demonstrated moderate functional capacity. The mean 6-minute walk distance (6 MWD) in this study was 350.6 ± 54.7 m and estimated maximum oxygen consumption was 9.74 ± 1.5 ml/kg/min. This finding is similar to that of Cahalin's *et al.* [26] who reported a mean value of 357 m among patients with heart failure. However, Stevens *et al.*, [27] reported higher mean 6 MWD and estimated maximum oxygen consumption of 630 m and 17.5 ml/kg/min respectively among healthy adults. Several factors such as age, presence of chronic disease, initial cardiorespiratory fitness, participants' mood, body weight and individual differences may account for low functional capacity [12] [28]. Furthermore, Fagard *et al.* [29] reported that some anti-hypertensive medications including both single-dose and short-term diuretics treatments adversely affect exercise capacity and the duration of prolonged sub-maximal exercise.

Low functional capacity is associated with morbidity and mortality in cardiovascular disease [30]. The present study shows that there are positive correlations between functional capacity, exercise self-efficacy and social support. In agreement with findings of previous studies, strong relationship has been reported to be existing between functional capacity, self-efficacy and exercise behaviour in patients with coronary heart disease [31] [32]. In addition, Cromwell and Adams, [33] submitted that there is a strong association between level of exercise participation and exercise self-efficacy among older African-Americans with or without cardiac challenges.

High level of confidence to engage in regular exercise might not be enough to increase exercise participation and adherence but it is possible to initiate and sustain exercise practice among individuals with high exercise self-efficacy due to inherent self-regulatory mechanism to overcome specific task with resultant improvement in functional capacity [34]. A study by Cohen-Mansfield *et al.* [35] identified some key determinants of exercise participation and grouped them into two main categories as either increase adherence to exercise (motivators) or decrease adherence to exercise (barriers). However, our study did not find significant correlation between perceived exercise barrier and functional capacity. The type of exercise adopted in our study; self-paced walking of single exercise treatment might be responsible for no correlation.

There is significant correlation between functional capacity and social support. This finding corroborates a previous study that social support enhances regular exercise participation and improved functional capacity in patients with cardiac challenges [36]. Similarly, Ostergren *et al.* [37] reported that social support predicted improvement in physical working capacity among a small group of persons admitted with first-time myocardial infarction. Although mechanism through which social support improves functional capacity is still unclear, physical and emotional support from family, spouse or friends might be an important factor that synergies motivation for more efforts during exercise performance. This implies that social support is likely to play key role as a psychological factor that may assist in the prevention of health problems and enhance ability to initiate and sustain behaviour change. Furthermore, the evidence linking social support to health outcomes depends on the severity and nature of health problems investigated. Although mild to moderate hypertension is usually asymptomatic and might be less distressing, social support has been shown to lower cardiovascular reactivity in some laboratory studies [38] [39].

Finding from our study did not show significant correlation between functional capacity and socioeconomic status. This is contrary to finding of a previous study that socioeconomic status (SES) is significantly associated with exercise participation [40]. Socioeconomic status is also believed to be a mediator of psychosocial determinants of physical exercise which may lead to poor self-esteem [41]. In addition, Gallo *et al.* [42] reported that socioeconomic disparity is an important mediator of exercise participation. In this part of the world, SES is relatively a burgeoning area of social determinant of health and rehabilitation, and its assessment is still a challenge in determining the relationship between exercise practice and health outcomes.

Exercise plays significant role in blood pressure control. Our study affirm finding of a previous study that exercise is capable of lowering heart rate and systolic blood pressure in a single treatment [43]. This phenomenon was described as "post exercise hypotension" and many explanations including vascular responsiveness, neurohumoral and structural adaptations have been proposed as the mechanisms behind blood pressure reduction in a single exercise treatment [43] [44]. It is also possible that the role of psychosocial factors might not be unconnected with blood pressure reduction as cardiovascular reactivity decrease has been reported in some previous studies [39] [45]. Notable limitations in our study include the design; this is a quasi-experimental study and causal inferences cannot be made because of the inability to determine temporal sequence. Participants in our study were placed on different anti-hypertensive medications and it is possible that some of the medications might mask functional capacity during exercise practice. In addition, exercise self-paced walking in a single exercise

treatment might not be adequate enough to prompt exercise self-efficacy, social support and perceived barrier to exercise. Furthermore, participants in this study were recruited from hospital and were using antihypertensive medications on regular basis who might not be true representative of patients with hypertension in Nigeria.

5. Conclusion

In conclusion, exercise self-efficacy and social support were significantly associated with functional capacity but not with perceived exercise barrier and socioeconomic status in Nigerian patients with mild to moderate hypertension. Exercise prescription and training usually employ cardiovascular parameters and functional capacity as the basis to guide exercise commencement and progression, however, psychosocial factors related to exercise are becoming relevant for effective initiation and maintenance of exercise practice. Hence, psychosocial correlates of exercise should be regularly investigated and incorporated into the mainstream care of patients with cardiovascular disease prior to and during exercise rehabilitation programme in order to enhance adherence and beneficial cardiovascular health outcomes. Population based intervention studies are needed to further evaluate the role of psychosocial correlates of exercise in hypertension.

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Presentation

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Conflict of Interest

The authors declared none.

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Clinical Assessment of the Use of Propinox Hydrochloride and Scopolamine Hydrochloride in the Treatment of Abdominal Colic: A Retrospective, Comparative Study

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Abstract

Objectives: The purpose of this study was to evaluate and compare the use of propinox hydrochloride and scopolamine hydrochloride in patients presenting abdominal colic (abdominal pain), in

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terms of treatment efficacy and tolerability. Material & Methods: This was an analytical, retrospective, comparative study based on hospital records of outpatients treated at *Serviço de Clínica Médica do Hospital das Clínicas Costantino Otaviano* (HCTCO) and at *Santa Casa de Misericórdia do Rio de Janeiro*, from 1988-1998. Subjects were divided into two groups: patients from Group 1 were treated with propinox hydrochloride, while patients from Group 2 were treated with scopolamine hydrochloride. Statistical analysis was performed using GraphPad Prism version 5.0. For comparison of categorical variables, we used the chi-squared or Fisher's test, while continuous variables were analyzed using ANOVA or the Student's T test. Results: A total of 1042 subjects were included, of which 525 were allocated to Group 1 and 517 to Group 2. Mean treatment duration was 9.166 days (±4.208) in Group 1 and 8.795 days (±5.052) in Group 2, with no statistically significant difference in treatment duration between the two groups ($p = 0.198$). All subjects in Group 1 were treated with propinox 10 mg (2 coated tablets, three times per day) while all subjects in Group 2 were treated with scopolamine hydrochloride 10 mg (2 coated tablets, three times per day). There were no statistically significant between-group differences in weight, BMI, heart rate, and respiratory rate at pre- and post-treatment; with the exception of higher post-treatment systolic blood pressure in Group 1, blood pressure measures also remained homogenous. Adverse events were reported among both treatment groups with no significant between-group difference in incidence ($p = 0566$). At pretreatment, pain intensity was more severe in Group 1 ($p = 0.0257$), while at post-treatment, there was no statistically significant difference between the two treatment groups ($p = 0.895$). There was a statistically significant improvement in pain intensity within both treatment groups ($\chi^2 = 631.4$; $df = 3$; $p < 0.0001$ for Group 1 and $\chi^2 = 554.3$; $df = 3$; $p < 0.0001$ for Group 2). Conclusion: The results obtained in this study indicate a therapeutic equivalence between propinox hydrochloride and scopolamine hydrochloride. Both treatments demonstrated good efficacy and tolerability in the treatment of abdominal colic pain, in the population evaluated.

Keywords

Abdominal Colic, Propinox Hydrochloride, Scopolamine Hydrochloride

1. Introduction

The term abdominal colic is used to describe spasmodic abdominal pain, arising as a result of distension, inflammation, or obstruction. It is often characterized as a sharp, localized abdominal pain that increases, peaks, and subsides. While it is often a benign complaint, it may also be a sign of a more significant pathology, therefore a careful medical history and physical examination are crucial to the approach for a differential diagnosis. Treatment of abdominal colic includes pain relievers such as nonsteroidal anti-inflammatory drugs, as well as antispasmodic agents.

Propinox hydrochloride, also known as pargeverine hydrochloride, is an antispasmodic that presents a dual mechanism of pharmacologic action: musculotropic and anticholinergic. It functions as a musculotropic agent, acting directly on the visceral smooth muscle cells and conferring its antispasmodic activity [1]-[9]. The anticholinergic activity of propinox is derived from a moderate and non-selective blockade of muscarinic cholinergic fibers [1].

The pharmacological activity of propinox is exerted on the visceral smooth muscle cells of the digestive and genitourinary tract [1]-[9]. Its antispasmodic activity at the intestinal level presents an efficacy two to three times greater than papaverine. Its effects on digestive secretions are smaller than those produced by quaternary ammonium compounds, thus the antisylagogue action is relatively weak. In the cardiovascular system, propinox does not alter tensional values or heart rate. Additionally, there are no reported effects in the literature of effects on the respiratory tract, at therapeutic doses [2]-[5]. Propinox is indicated in the treatment of spasmodic states of the digestive, hepatobiliary, urinary or female genital tracts [1] [3].

Scopolamine hydrochloride is an anticholinergic drug that presents a high affinity for muscarinic receptors located on the smooth muscle cells of the gastrointestinal tract. Its anticholinergic activity exerts a muscle relaxant

and spasmolytic effect. Scopolamine is derived from hyoscine, an alkaloid present in the leaves of the *Duboisia* plant, native to Australia, with a pharmacological potency twice that of atropine [1].

The basis of the therapeutic action of scopolamine is blockade of the action of acetylcholine in parasympathetic sites in smooth muscle and secretory glands. With this blockade, there is a decrease in motility of the urogenital and gastrointestinal tract, which renders scopolamine particularly useful in the treatment of spasms in these regions, commonly observed in gastroenteritis, colitis, irritable bowel syndrome, diverticulitis, biliary and urethtral colic, as well as in primary dysmenorrhea. It is also used in the prevention of gastrointestinal tract spasms prior to invasive radiological and diagnostic procedures. Scopolamine also acts on the glands of the oral cavity, gastrointestinal and respiratory tract, causing a reduction of activities and consequently of secretions [1] [3]. Scopolamine hydrochloride is indicated in the treatment of spasms of the gastrointestinal tract, biliary tract spasms and dyskinesias, and spasms of the genitourinary tract [1] [3] [15].

2. Objectives

The primary objective of this study was to evaluate the use of propinox hydrochloride in patients presenting abdominal colic (abdominal pain), in terms of treatment efficacy and tolerability. The secondary study objectives were to evaluate the use of scopolamine hydrochloride in patients presenting abdominal colic (abdominal pain), in terms of treatment efficacy and tolerability, and to compare the results of the use of propinox hydrochloride with those of scopolamine hydrochloride, in terms of treatment efficacy and tolerability.

3. Material & Methods

This was an analytical, retrospective, comparative study. The study population consisted of outpatients treated at *Serviço de Clínica Médica do Hospital das Clínicas Costantino Otaviano* (HCTCO) and at *Santa Casa de Misericórdia do Rio de Janeiro*, from the period of 1988-1998, from which study data were drawn. After ethical committee approval (approval no. 523-10), data present in the hospital records of each patient were analyzed in order to fill in the clinical research form, including the results of physical exam (height, weight, heart rate, blood pressure), medical history, demographic data, the results of any laboratory exams, and the identification, pharmaceutical form, dosing and treatment duration with the study drug, in addition to the presence and severity of abdominal pain. Inclusion criteria called for subjects of both genders, above 18 years of age, who were attended at either hospital and prescribed treatment with either of the study drugs. Only data from subjects with at least two hospital visits were included. The subjects were divided into two groups, according to the drug received. Patients from Group 1 were treated with propinox hydrochloride, while patients from Group 2 were treated with scopolamine hydrochloride.

Statistical analysis was performed using GraphPad Prism version 5.0. For comparison of categorical variables, we used the chi-squared or Fisher's test, while continuous variables were analyzed using ANOVA or the Student's T test. The primary efficacy endpoint was the percentage of subjects presenting resolution (absence) of pain at the second hospital visit. Secondary endpoints included the percentage of subjects presenting mild, moderate, or severe pain at the second hospital visit in relation to the first visit, record of any adverse effects during the treatment period, and the results of any laboratory tests out of hospital reference range.

4. Results

A total of 1042 subjects were included, of which 525 were allocated to Group 1 and 517 to Group 2. Gender distribution was homogenous between treatment groups ($p = 0.386$); Group 1 included a total of 268 (51.05%) male subjects and 257 (48.95%) female subjects, while gender distribution in Group 2 was 278 (53.77%) male subjects and 239 (46.23%) female subjects. Ethnicity distribution was also homogenous between treatment groups ($p = 0.732$). Mean subject age in Group 1 was 51.65 (±7.56) while in Group 2 it was 54.4 (±7.56) ($p < 0.001$ for between-group difference).

Mean treatment duration was 9.166 days (±4.208) in Group 1 and 8.795 days (±5.052) in Group 2, with no statistically significant difference in treatment duration between the two groups ($p = 0.198$). All subjects in Group 1 were treated with propinox 10 mg (2 coated tablets, three times per day) while all subjects in Group 2 were treated with scopolamine hydrochloride 10 mg (2 coated tablets, three times per day).

The results of the physical exam performed pre- and post-treatment and the respective between-visit differences are summarized in **Table 1**. At pretreatment, there was no statistically significant between-group difference

Table 1. Pre and Post-treatment physical exam.

Variable	Group 1 Pretreatment	Post-treatment	Between-visit difference	Group 2 Pretreatment	Post-treatment	Between-visit difference
Weight (kg)	67.18 (±11.44)	67.15 (±11.39)	p = 0.284	68.19 (±11.25)	68.09 (±11.18)	p = 0.0134
BMI (kg/cm^2)	24.18 (±2.802)	24.5 (±4.945)	p = 0.0582	24.11 (±2.54)	24.1 (±2.508)	p = 0.435
Systolic blood pressure (mmHg)	122.2 (±8.25)	122.4 (±8.67)	p = 0.387	121.3 (±7.29)	121.3 (±7.304)	p = 0.875
Diastolic blood pressure (mmHg)	78.9 (±9.66)	78.23 (±9.89)	p < 0.0001	78.16 (±8.17)	78.1 (±7.662)	p = 0.781
Heart rate (bpm)	68.65 (±5.38)	68.28 (±4.93)	p = 0.0178	68.23 (±5.45)	67.91 (±5.038)	p = 0.057
Respiratory rate (ipm)	16.58 (±1.59)	16.57 (±1,142)	p = 0.974	16.61 (±1.71)	16.53 (±1.51)	p = 0.172

Data are means (±SD) and p values.

in weight (p = 0.15); this finding was maintained post-treatment (p = 0.181). BMI did not vary significantly between treatment groups at either study visit (p = 0.675 for pretreatment and p = 0.099 for post-treatment). Pretreatment blood pressure measures did not vary between treatment groups (p = 0.669 for systolic blood pressure and p = 0.1833 for diastolic blood pressure); at post-treatment, systolic blood pressure was higher (p = 0.0258) among subjects in Group 1 while diastolic blood pressure was homogenous between treatment groups (p = 0.8105). Mean heart rate was homogenous between treatment groups at both pretreatment (p = 0.2114) and post-treatment (p = 0.234). Respiratory rate was also homogenous between both groups (p = 0.725 for pretreatment and p = 0.632 at post-treatment).

There was no statistically significant between-group difference in the number of subjects using concomitant medications (p = 1.0). At pretreatment, 87 in each treatment group reported use of concomitant medications. At post-treatment, this number reduced to 27 subjects in each treatment group.

Adverse events were reported among both treatment groups, with 133 subjects in Group 1 reporting adverse events during the treatment period and 123 subjects in Group 2. The incidence of adverse events occurring during the treatment period did not vary between treatment groups (p = 0.566). **Table 2** summarizes the adverse events by system and patient group.

Figure 1 summarizes the results of the assessments of pain severity pre and post-treatment. At pretreatment, pain intensity was more severe in Group 1 (p = 0.0257), while at post-treatment, there was no statistically significant difference between the two treatment groups (p = 0.895). There was a statistically significant improvement in pain intensity within both treatment groups (χ^2 = 631.4; df = 3; p < 0.0001 for Group 1 and χ^2 = 554.3; df = 3; p < 0.0001 for Group 2).

5. Discussion

Although this was a retrospective study with inherent limitations in data availability, the study drugs were well tolerated in both treatment groups. This finding is consistent with data reported in the literature on clinical administration of both agents.

Clinical safety and efficacy studies have demonstrated a good tolerability of propinox. De los Santos *et al.* (1999) evaluated the efficacy and tolerability of propinox administered intravenously at doses of 10, 20, and 30 mg versus placebo in 350 patients presenting severe acute biliary pain. Propinox significantly and progressively reduced pain at all doses employed, 20, 60, and 120 minutes after administration, with the highest results obtained after 120 minutes at the doses of 20 mg and 30 mg. The drug was well tolerated at all doses, with no dropouts due to adverse effects. Mouth dryness was the only adverse event that occurred more frequently among the treated subjects as compared to the placebo group, and was observed only among patients receiving the doses of 20 and 30 mg. No significant changes in heart rate or blood pressure were observed among treated subjects [10].

Another clinical study evaluating the safety and efficacy of propinox by intravenous route used the same doses of 10, 20, and 30 mg versus placebo in 400 patients presenting moderate to severe colic-type abdominal pain secondary to a functional pathology (irritable bowel syndrome and dyspepsia). Propinox was more effective in reducing pain compared to placebo at the three doses administered. In the assessment performed 120 minutes following drug administration, there was a significant difference in the percentage of subjects with pain reduction in

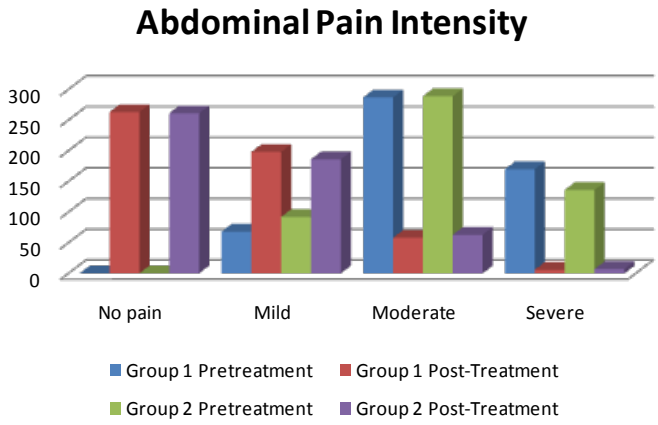

Figure 1. Abdominal pain intensity at pretreatment and post-treatment.

Table 2. Pre- and post-treatment physical exam.

System affected	Number of Subjects per Treatment Group	
	Group 1	**Group 2**
Cardiovascular system	7	7
Cardiovascular system/Nervous system	1	0
Endocrine system	43	42
Endocrine system/Cardiovascular system	1	4
Endocrine system/Nervous system	1	0
Endocrine system/Respiratory system	1	0
Endocrine system/Gastrointestinal tract	5	3
Nervous system	20	13
Nervous system/Gastrointestinal tract	1	1
Respiratory system	0	1
Gastrointestinal tract	28	25
Gastrointestinal tract/Endocrine system	2	2
Gastrointestinal tract/Nervous system	1	0
Urinary tract	21	23

Data are *n*.

favor of the 20 and 30 mg doses. The authors related dry mouth as the most frequent adverse event reported at doses of 20 mg and 30 mg. No change in blood pressure or heart rate was observed among these subjects [11].

The efficacy and safety of propinox was assessed by Mezzotero *et al*. (1995) in the treatment of patients with mild to moderate abdominal colic pain resulting from biliary, intestinal, renal-pelvic, urethral, or female genital pathology (dysmenorrhea). One hundred and six subjects were treated with a dose of 10 mg administered orally. Pain intensity decreased by 43% thirty minutes after administration of a single dose. The most frequently reported adverse effects were flushing and pruritis. One subject developed a clinical picture of cutaneous allergy with bipalpebral edema requiring parenteral administration of antihistamines [12].

The efficacy and tolerability of parenterally administered propinox was assessed by Olmos *et al*., (2003), at the doses of 20 or 30 mg, among patients presenting with colonic spasm induced by colon exam among subjects with irritable bowel. Both doses of propinox were effective in reversing the colonic spasm, increasing colonic diameter, and reducing abdominal pain. The adverse events reported during the treatment were mild and transitory, with a single case of blurred vision, one case of dry mouth and one of pruritis among the 30 subjects who

underwent treatment [13].

An oral dose of 10 mg was used by Pulpeiro *et al*. (2000) to compare the analgesic efficacy and assess changes in defecation rhythm, abdominal distension, frequency of pain crises, and sensation of incomplete evacuation as compared to treatment with a placebo. The double-blind, randomized treatment period lasted 4 weeks and included 75 subjects with irritable bowel syndrome, with 4 daily doses of the study drug. The group treated with propinox presented a significant and progressive reduction over the 28 day treatment period in intensity of abdominal pain, weekly frequency of pain episodes, and abdominal distension, greater than that observed in the group treated with placebo. The most frequent adverse effects were headaches, nausea, and dry mouth, however no dropouts due to adverse effects were recorded [14].

Several clinical studies have been performed assessing the safety and efficacy of scopolamine. Ten placebo-controlled clinical trials assessed this drug in the treatment of abdominal pain and discomfort, with a total of 3699 subjects, of which 911 received the drug in oral form (n = 868) or rectal form (n = 43) and 2788 subjects received paracetamol, placebo, or a combination of scopolamine with other drugs. Treatment duration varied in the studies from a single 20 mg dose with a 4 hour observation period to a three-month treatment period with a dose of 10 mg four times per day. The maximum daily dose varied between 20 - 200 mg over 10 days. Scopolamine was considered beneficial in all of these studies, with statistically superior efficacy over placebo in at least one variable in each study [17]-[26]. Of these ten studies, seven included a small number of subjects (<50) treated with the drug, and were performed prior to the establishment of the Good Clinical Practice and International Conference on Harmonisation Guidelines. Therefore, although the results of these seven studies were favorable, they are of limited value in assessing the efficacy of the drug.

Three more recent comparative studies, including 712 [17], 818 [21], and 1637 [23] subjects, respectively, used doses between 30 and 60 mg and treatment duration varied between 4 days and 3 weeks, respectively. The results of the first study demonstrated that scopolamine administered orally or rectally resulted in a significant improvement of pain in comparison to treatment with placebo [21]. In a double-blind, comparative, randomized study, parallel groups of patients with irritable bowel syndrome were treated with scopolamine + paracetamol, scopolamine alone, paracetamol alone, or placebo over the course of four weeks. At the end of the treatment period, 75% of the patients in the groups treated with scopolamine had significant improvement in symptoms, with a statistically significant improvement in abdominal pain intensity in the groups treated with scopolamine compared to subjects treated only with paracetamol or placebo [17]. In a clinical trial assessing 1637 subjects, the efficacy and tolerability of three daily doses of scopolamine 10 mg, paracetamol 500 mg, a combination of the two drugs, or placebo, was assessed over a three week treatment period. The intensity and frequency of the pain decreased significantly in the scopolamine treatment groups as compared to placebo, and no difference was observed between the active treatments [23].

6. Conclusion

The results obtained in this study indicate a therapeutic equivalence between propinox hydrochloride and scopolamine hydrochloride. Both treatments demonstrated good efficacy and tolerability in the treatment of abdominal colic pain, in the population evaluated.

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Sleep Quality in Non Dialysis Chronic Kidney Disease: Associated Factors and Influence on Prognosis

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Abstract

Deficient sleep quality (SQ) has been linked with a higher hospitalization rate and mortality in dialysis patients, however the prevalence of sleep disorders and their influence on prognosis in non-dialysis chronic kidney disease (CKD) has been poorly investigated. The aim of this study was to assess factors related with SQ in CKD patients (stages I-IV) followed in a nephrology outpatient clinic as well as the long-term impact of SQ on patient's outcome. Between January and May 2008, Pittsburgh Sleep Quality Index (PSQI) was self-administered by 122 patients (68 males and 54 females) with a mean age of 65 years. Patients were classified as "good" (global PSQI < 6) and "poor" sleepers (global PSQI ≥ 6). We identified 66 (54%) poor sleepers (PS), characterized by an older age (66 ± 14.2 vs 57 ± 17.0, p < 0.01), female predominance (59% vs 26%, p < 0.01) and worse renal function (49 ± 19.1 vs 57 ± 23.2 ml/min, p < 0.05). There was a significant correlation between phosphate and PSQI score (r = 0.234, p = 0.01), however no correlation with calcium or PTH. Vitamin D was also lower in PS (17 ± 7.2 vs 23 ± 15.1 ng/ml, p < 0.05). Until June 2015, hospitalization rate was higher among PS (64% vs 44%, p < 0.05). In this period, there was also a trend towards higher mortality for PS (18% vs 16%). In summary, over 50% of CKD patients have poor SQ, which was associated with older age, female gender, worse renal function, lower vitamin D and higher phosphate levels. Deficient sleep was associated with a greater probability of hospitalization and might be a prognostic marker in CKD.

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Keywords

Chronic Kidney Disease, Sleep Quality, Hospitalization, Pittsburgh Sleep Quality Index, Vitamin D

1. Introduction

Sleep impairment is frequent among dialysis patients (40% - 80%). Insomnia or insufficient sleep time, sleep latency and daytime sleepiness, restless legs syndrome (RLS) and obstructive sleep apnea (OSA) are the most common complaints [1] [2]. Factors related with sleep disturbances in these patients include those also associated with poor sleep in the general population, such as age, diabetes, depression, and obesity. Sleep disturbances in dialysis patients have also been related with uremia, anemia, phosphate and inflammation. The association between sleep quality (SQ) and renal disease may be bidirectional, since depressive symptoms and fluid overload that are common in chronic kidney disease (CKD), may also impair SQ. Besides affecting quality of life, reduced SQ has been linked with higher morbidity and mortality rates in dialysis patients, as well as with more frequent hospitalization [3].

In non-dialysis CKD, sleep disturbances may represent a novel risk factor contributing to renal and cardiovascular damage; thus, improving SQ could help to reduce progression of CKD and cardiovascular events in these patients [4]. Although a high prevalence of sleep disorders would be expected in CKD before renal replacement therapy, this question has not been investigated in depth. Sleep surveys carried out in this population were usually based in clinical questionnaires, without objective measures like polysomnography or even expert examination. For example, we've recently reported that RLS frequency (after expert examination) in non-dialysis CKD is not very different from that described in the general population [5]. Moreover, to the best of our knowledge the relationship between SQ in early stages of CKD and the use of healthcare services has not been examined.

Therefore, this study was carried out to investigate SQ in CKD patients (stages I to IV), the factors associated with poor sleep and the relationship between sleep disturbances, hospitalization and long-term patient's outcome.

2. Methods

We used a validated Spanish translation of the Pittsburgh Sleep Quality Index (PSQI), a self-rating questionnaire developed to evaluate SQ during the previous months. PSQI contains 19 questions (each scored 0 to 3) to assess seven components of SQ (subjective SQ, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications and daytime dysfunction) [6]. The total PSQI score ranges from 0 to 21. A global score of 6 or greater indicates a poor sleeper, meaning that the person suffers from moderate sleep problems in at least three sleep component areas, or severe sleep problems in two areas.

Between January and May 2008, patients with CKD (stages I to IV) attending the nephrology outpatient clinic were asked to voluntary answer the PSQI questionnaire. Only those with a complete and properly filled questionnaire were included in the study. Subjects under 18 years old, pregnant women and renal transplant patients were not included. The final group comprised 122 patients (68 men and 54 women) with a median age of 62 ± 16.2 years. According to PSQI, patients were divided into "poor sleepers" [(PS); PSQI $\geq$ 6] and "good sleepers" [(GS); PSQI < 6]. Seven years later (June 2015), the hospitalization episodes, renal function outcome and mortality rate were analyzed through retrospective evaluation of the participants' electronic medical records. The following clinical and demographic characteristics were obtained: 1) Presence of cardiovascular disease (defined as the presence of ischemic cardiomyopathy, stroke and/or peripheral arteriopathy that needed by-pass or amputation), chronic obstructive pulmonary disease (COPD), depression (defined by the need of antidepressant treatment) and diabetes; 2) Medications that might influence on symptoms, including antidepressants and hypnotic drugs. Body mass index (BMI) was calculated by the usual formula (Kg/m^2). Laboratory parameters were obtained from routine blood and urine samples, including serum creatinine, uric acid, proteinuria (albumin to creatinine ratio), calcium, phosphorus, parathormone, vitamin D, C-reactive protein (CRP), hemoglobin, folate and iron status. Glomerular filtration rate (eGFR) was estimated by the four-variable Modification of Diet in Renal Disease (MDRD-4) equation [7].

The statistical package for social sciences software (SPSS version 15.0) was used for statistical analysis of differences between GS and PS. Results were expressed as mean and standard deviation or number and percent, as appropriate. The coefficient of skewness and the coefficient of kurtosis were used to evaluate normal distribution of the data. Continuous variables were compared using the Student's t-test or Mann-Whitney *U*-test. The bivariate correlation test was performed to determine the association of demographic and biochemical data with the PSQI score, using Pearson's correlation test and Spearman's correlation test for normally and non-normally distributed variables, respectively. Chi-square test and Fisher's exact test, as appropriate, were used to compare categorical variables. The level of significance was set at $p < 0.05$. Multiple logistic regression was applied for factors that reached statistical significance in order to identify variables independently associated with SQ.

3. Results

Out of 122 studied patients, 39 (32%) were on CKD stages I-II, 65 (53%) on stage III and 18 (15%) on stage IV following the K/DOQI staging system [8]. 38 patients (31%) were diabetic. According to the PSQI score, 66 patients (54%) were classified as PS and 56 (46%) as GS. However, 94 patients (77%) considered their SQ as good or very good.

Distribution of age, gender, associated clinical conditions, medications and laboratory values among GS and PS are summarized in **Table 1**. Compared to GS, PS were older (66 ± 14.2 vs 58 ± 17.0, $p = 0.004$), were more frequently female (59% vs 26%, $p = 0.001$) and had a worse renal function (49 ± 19.1 vs 57 ± 23.2 ml/min/1.73 m^2, $p = 0.037$). There were no differences regarding diabetes, COPD, uric acid, inflammation (CRP) and albuminuria between PS and GS. Albeit not statistically significant, comorbid cardiovascular diseases, as well as depression were somewhat more frequent among PS (**Table 1**). Iron levels tended to be lower (66 ± 28.8 vs 78 ± 24.9 µg/ml) in PS, without significant impact in hemoglobin concentration. We found no differences in calcium, phosphate or parathormone values between the two groups. However, there was a positive correlation between phosphate levels and PSQI score ($r = 0.234$, $p = 0.012$), and vitamin D concentration was significantly lower in PS (17 ± 7.2 vs 23 ± 15.1 ng/ml). Multiple logistic regression analysis including all factors that reached nominal significance (age, gender, eGFR, iron, phosphate and vitamin D), revealed female gender (OR 9.929, CI 2.483 - 39.705, $p = 0.001$) as the only independently associated variable. Subsequently, a separate analysis of the data was carried out for male and female patients. Among men, vitamin D and phosphate levels were the only variables that remained statistically different between PS and GS. In contrast, PS women showed worse renal function and iron status than women who were GS, without significant difference in phosphate or vitamin D levels. Inflammation (assessed by CRP levels) was also significantly higher among PS women.

Regarding long term complications and outcome, hospitalization episodes (any cause) were significantly more frequent among PS (64% vs 44%), a difference that was more pronounced among men. Despite worse renal function at baseline, GFR decline as well as evolution to end stage renal disease (ESRD) was not significantly different between both groups. Although not statistically significant, mortality rate was somewhat higher in PS (18% vs 16%).

4. Discussion

Recent studies reported very variable prevalence of poor sleep in CKD (prior to ESRD), from 14% to as high as 85% [4]. Most of the participants in our study (54%) had indicators of poor sleep in the PSQI metrics. Interestingly, their subjective perception of SQ was significantly better than showed by the PSQI test (77% considered their sleep was good or very good). This discrepancy may help to explain the variable frequency of sleep disturbances found in surveys of CKD patients, if different questionnaires are used to assess SQ.

The aim of this study was to identify factors that may influence SQ in CKD patients, including renal function itself. Most previously reported studies found an association of older age with poor SQ, both in CKD and in the general population [9]. Although this association was also present in our cohort, a multivariate analysis failed to show age as an independent predictive factor. Our study revealed a significant difference in SQ by gender, which is consistent with previous data in the dialysis population [3] [10]. In fact, gender appears to be the single most important factor discerning between PS and GS in our cohort, an effect that was not obvious in previous investigations [9]. This difference in SQ between male and female is not specific for CKD, since it has been largely reported in other cohorts [11] [12]. Possible explanations suggested for the influence of gender in SQ include perception of social support, religious convictions, health-related behaviors and outlook that may vary

Table 1. Patient characteristics according to sleep quality.

	GS	PS	p
N (%)	56 (46)	66 (54)	
Age (yrs)	58 ± 17.0	66 ± 14.2	0.004
Female (%)	14 (26)	36 (59)	0.001
BMI (Kg/m^2)	28.8 ± 5.15	28.6 ± 4.12	0.946
Diabetes (%)	15 (28)	21 (34)	0.286
CV event (%)	6 (11)	10 (16)	0.590
COPD (%)	4 (7)	8 (13)	0.373
Depression (%)	2 (4)	6 (10)	0.279
Hemoglobin (g/dl)	13.7 ± 1.72	13.2 ± 1.55	0.109
Creatinine (mg/dl)	1.5 ± 0.57	1.5 ± 0.71	0.619
Initial GFR (ml/min)	57 ± 23.2	49 ± 19.1	0.037
Final GFR (ml/min)	53 ± 27.1	46 ± 24.5	0.160
GFR decline (ml/min)	−4.3 ± 11.4	−2.8 ± 15.1	0.543
Alb/Cr ratio (mg/g)	273 ± 556.9	482 ± 1133.9	0.221
Uric acid (mg/dl)	6.6 ± 1.87	6.6 ± 1.80	0.969
Iron (ug/ml)	78 ± 24.9	66 ± 28.8	0.039
Ferritin (mg/dl)	126 ± 117.2	106 ± 86.8	0.368
Calcium (mg/dl)	9.6 ± 0.47	9.6 ± 0.54	0.899
Phosphate (mg/dl)	3.4 ± 0.62	3.6 ± 0.64	0.117
PTH (pg/ml)	112 ± 103.0	140 ± 143.6	0.383
25 OH D3	23 ± 15.1	17 ± 7.2	0.043
PCR (mg/dl)	0.41 ± 0.506	0.69 ± 1.145	0.170
Hospitalization, any cause (%)	24 (44)	39 (64)	0.028
ESRD (%)	3 (6)	5 (8)	0.429
Death, any cause (%)	9 (17)	11 (18)	0.523

GS = Good sleepers according to PSQI; PS = Poor sleepers according to PSQI; CV = cardiovascular; COPD = chronic obstructive pulmonary disease; GFR = Glomerular filtration rate; Alb = albumin; Cr = creatinine; PTH = parathormone; PCR = C-reactive protein; ESDR = End stage renal disease.

among both genders in different geographical areas. Other confounding factors, such as education, marital state and employment status may also influence on SQ differences between genders.

Association of SQ and renal function is controversial [9] [13] [14]. We observed a correlation between impairment of sleep and renal function using calculated eGFR (and not serum creatinine) as measure of renal dysfunction. This may be explained by the female predominance of sleep problems and the factoring in of gender in the MDRD-4 formula. In fact, decline in SQ may already start in early stages of renal disease and therefore would not be simply related with the severity of renal impairment [15] [16].

We investigated whether other factors common in CKD—like anemia, diabetes and inflammation—could influence SQ. We did not find association between SQ and anemia, only a somewhat lower iron concentration in poor sleepers that was not clinically relevant. The presence of anemia has been plausibly linked with sleep disturbance in the literature. Except for the case of RLS [5], we speculate whether this might be a spurious association due to the presence of symptoms of anemia like fatigue, tiredness, lack of concentration or daytime sleepiness. Moreover, since hemoglobin values are physiologically lower in women, a gender effect may also bias the comparison of hemoglobin concentration between poor and good sleepers. Previous investigations suggested

that sleep disorders are more common in diabetic patients [17]. We did not observe significant differences in sleep quality scores between diabetic and non-diabetic patients. This discrepancy with other studies might be due to the low number of diabetics in our cohort who had severe comorbidity-such as cardiovascular problems and neuropathy-since our target population was non-dialysis CKD. Elevated CRP has been associated with increased vascular inflammation due to sleep deprivation-related hypertension [18]. Interestingly, our data suggest an association between inflammation and SQ in female CKD patients that deserves further investigation.

Mineral metabolism disturbances are common in renal disease. Some studies have shown an association between sleep problems and higher levels of phosphate and parathyroid hormone in hemodialysis and CKD patients [9] [19], that may improve after parathyroidectomy [20]. Our results suggest a correlation between PSQI score and phosphate levels, remarkably in males. Patients with poor SQ were also characterized by lower plasmatic vitamin D concentration. As far as we are aware, this is the first report underlining the association between low vitamin D levels and poor SQ in renal disease. In agreement with this observation, recent data support an inverse relationship between vitamin D levels and OSA severity [21]. Furthermore, vitamin D supplementation has been linked with RLS improvement [22]. Since both conditions (OSA and RLS) are common in CKD, it is plausible that vitamin D deficiency plays a role in sleep disturbance in renal disease.

Another finding of our study was that hospitalization rate (for any cause) in CKD patients increases markedly with the decrease of sleep quality. Poor sleep quality has been associated with an increased risk of mortality in pre-ESRD and hemodialysis patients [3] [14]. We did not find a significant correlation between SQ and mortality, perhaps due to the fact that our study population has less cardiovascular comorbid conditions than patients on dialysis or pre-dialysis. Poor sleep quality has also been related with the progression of cardiovascular disease and renal damage [4] [23]. In contrast, we did not detect an association between renal function decline and SQ. Despite progression of cardiovascular disease, sleep disturbances may start in the early stages of renal disease and thus would have less impact in renal outcome [15] [16].

5. Conclusion

In summary, this study shows that most non-dialysis CKD patients have poor sleep quality, especially women. Poor sleep is associated with worse renal function, higher phosphate and lower vitamin D levels. Sleep disturbance was also a predictor of higher hospitalization rate in our population. A limitation of our study is the use of PSQI as only measurement of sleep quality. Since a comprehensive polysomnography was not performed, it is not possible to ascertain the exact type of sleep disturbance and sleep pattern in our patients. There is no standardized consensus on criteria for subjective reporting of sleep quality. Global PSQI Scores above 5 resulted in a sensitivity of 98.7% and specificity of 84.4% to detect sleep disturbances [24]. Alcohol intake, smoking, medications and other factors that may have an impact on sleep were not evaluated. Besides renal function and other health and physical conditions, sleep is under the influence of habits and behaviors, culture, and even economic and political, thus hampering inter-study comparisons. Further large-scale, multi-center studies are needed to better address this problem.

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MELAS, MIDD and Beyond: m.3243A>G MT-TL1 Mutation in Adult Patients

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Abstract

m.3243A>G MT-TL1 mutation is the most common mitochondrial DNA mutation that results in a wide spectrum of disorders in a maternally inherited pedigree. In adult patients, many present with symptoms and signs indistinguishable from acquired diseases and the correct diagnosis is often delayed after many years. Nevertheless, clues suggesting m.3243A>G usually exist early in the disease course but are only realized late. These hints, from the evolution of symptoms and signs, family background, investigation results, or a combination of these, enable the physician to make the correct diagnosis early, which is important for appropriate treatment and better patient care. As with other inheritable diseases, genetic counselling should be offered regarding the disease management, inheritance mode, recurrence risk, usefulness and limitations of genetic testing and reproductive options.

Keywords

Mitochondrial Disease, MELAS, m.3243A>G

1. Introduction

Mitochondrial diseases are considered a category of "rare diseases", with a population prevalence of 1 in 5000 based on epidemiological studies [1] [2]. The A>G transition of the mitochondrially encoded tRNA leucine 1 (UUA/G) gene at position 3243 (m.3243A>G, MT-TL1) is the most common mutation in human mitochondrial diseases [3]. This mutation accounts for most of the severe childhood neurological phenotype mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), and maternally inherited diabetes and deafness (MIDD) in adults [4] [5]. These two discrete phenotypes are only part of the disease spectrum, many patients carrying this mutation do not fall into either group [6]. In a population epidemiological study, 1 in 400

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carried this m.3243A>G and most of them had deafness, which could actually be regarded as having mild disease [7]. In addition, these at risk persons could develop a full blown presentation in a later age, and their phenotype could also evolve. In this article, we share our experience in the clinical management of adult patients with this m.3243A>G mutation through a descriptive analysis to highlight the heterogeneity and diversity of the disease nature, and the treatment related issues.

2. Our Patients

2.1. Case 1. Diabetic Patient with Acute Stroke Presentation, with MRI Showing MELAS but Not Infarction

Mr A had a normal early development and childhood. His story started with progressive hearing loss since age 20. At 46 he was diagnosed diabetes mellitus (DM) in a health check, and he received metformin. Five years later, at 51, he had acute aphasia, and mild weakness over right side. Brain MRI revealed restricted diffusion over left temporal and parietal cortical ribbons that spared the subcortical white matters (**Figure 1(A)** and **Figure 1(B)**). This radiological finger print, together with his background comorbidity of sensorineural deafness and DM in an underweighted man with BMI 17, prompted the suspicion of MELAS with acute stroke-like episode. We treated him with intravenous infusion of L-arginine followed by oral maintenance. His serum lactate was elevated at 3.0 (ref. 0.5 - 2.2) mmol/L, and an elevated lactate peak was present in the MR spectroscopy

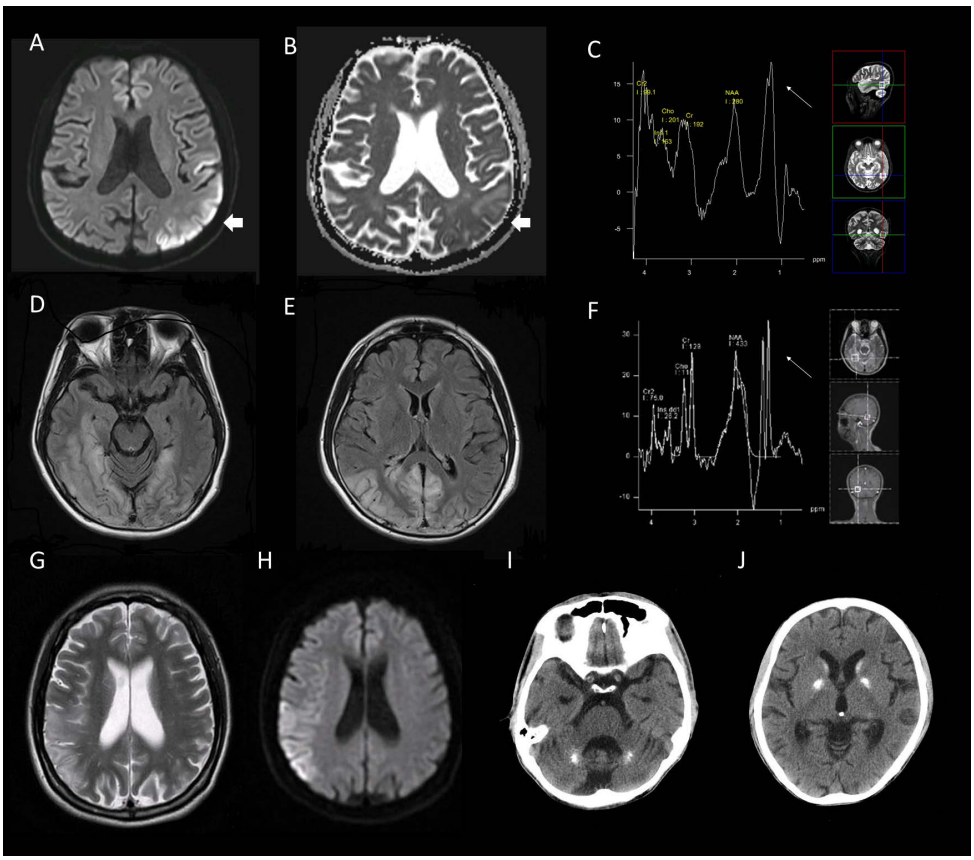

Figure 1. MRI of Mr A (case 1, A-C) showed restricted diffusion over left parietal and occpital cortex (arrow, A), without significant reduction of ADC map (arrow, B); MRS revealed a high lactate double peak at 1.33 ppm (small arrow, C). MRI FLAIR of Mr C (case 3, D-F) showed gyral edema over bilateral occipital and temporal region, the edema was restricted to subcortical white matter (D & E). MRS showed a high lactate double peak at 1.33 ppm (small arrow, F). G & H: MRI of Miss E (case 5) during her second stroke-like episode showed hyperintense T2 lesion at right parietal cortex (G) with restricted diffusion (H). I & J: Brain CT of Mr G (case 7) found cerebral and cerebellar atrophy with bilateral basal ganglia calcifications.

(**Figure 1(C)**). The molecular genetics confirmed m.3243A>G, the commonest mutation for MELAS. Mr A had residual aphasia and cognitive impairment after the stroke-like episode, but remained ambulatory unaided and outdoor going. Metformin was switched to acarbose for his DM. He later developed simple partial seizure which was well controlled with lamotrigine. It has been two years since his stroke-like episode and he remained stable. The family history was also tale telling, with one of his six siblings died at young age from an unknown brain disease, and his mother, who was deceased many years ago, had long standing deafness.

2.2. Case 2. Recurrent Syncope for More Than 10 Years—Time Will Tell

Mr B was a chronic smoker. He had sensorineural deafness since his 30 s, chronic hepatitis B and DM. Started from 40 s he developed recurrent syncope with or without injury, and had repeated hospitalization up to four or five times a year for this problem. These syncope episodes were usually brief, with or without prodrome, exclusively at daytime, but lack of typical syndromic pattern for vasovagal syncope. He underwent very comprehensive diagnostic evaluation for a possible cardiac arrhythmia: multiple holter monitor, echocardiogram, treadmill, diagnostic coronary angiogram, cardiac electrophysiology study and finally implantable loop recorder, all were uneventful. He had been given empirical sodium valproate for suspected seizure related syncope without success, his electroencephalogram was normal. Having followed up his syncope problem for almost 10 years, he was found to have cardiomegaly and symptoms of heart failure. The repeated echocardiogram found dilated cardiomyopathy with poor ejection fraction of 24% only. That probably did not explain his long standing recurrent syncope. Further investigation noticed an abnormal autonomic function test with impairment mainly in sudomotor and cardiovagal pathway, and an inadequate cortisol response from the synacthen test. This was the time, at the age of 57, a genetic test for common mitochondrial mutations was requested, which confirmed m.3243A>G. The "MELAS" phenotype of Mr B consisted of sensorineural deafness, DM, adrenal insufficiency, autonomic neuropathy and cardiomyopathy. The reason for his recurrent syncope was not completely clear, but believed to be a combination of autonomic neuropathy and adrenal insufficiency in the early days, and was aggravated by cardiomyopathy in recent years.

2.3. Case 3. A Fatal Stroke-Like Episode in a Young Man

Mr C, a 29-year-old man, presented with acute left sided homonymous hemianopia, which rapidly progressed to total cortical blindness a day later. MRI brain showed bilateral parietal and occipital gyriform swelling (**Figures 1(D)-(F)**). Blood test found diabetes mellitus, a high random glucose 18 mmol/L and an elevated HbA1C 7; his serum lactate was 4.8 mmol/L. His only significant past medical condition was pulmonary tuberculosis which he had a complete recovery five years ago; he did not have any symptoms of mitochondrial disease before. The clue for a possible mitochondrial disease in his family was traced to his mother, who had long standing deafness and died at the age of 50 s from a suspected cardiac condition. This unfortunate young man deteriorated rapidly despite intravenous L-arginine infusion, developed status epilepticus and deceased. The molecular genetics study identified m.3243 A>G. This is MELAS presented with a fatal stroke-like episode.

2.4. Case 4. Multiple Somatic Complaints Did Not Equate Psychogenic

Ms D was known to carry the m.3243A>G mutation having her son diagnosed MELAS at childhood. She started to feel unwell in her 40 s. She had deafness and dyspepsia symptoms with pain and distension, for which she paid frequent visits to general outpatient, almost weekly. The family clinic physician marked down "multiple complaints!!" in the notes and believed a strong psychological component underlie her symptoms. At age 55 she developed first stroke-like episode with left sided hemi-neglect, ideomotor apraxia and weakness. CT brain revealed right parietal hypodensity. She was treated with L-arginine infusion. This attack was complicated by myoclonic seizure which was controlled with levetiracetam. She recovered from this episode with only mild residual cognitive impairment. One year later she had another stroke-like episode over left parietal region with aphasia. Her third stroke-like episode was stormy; she had a new lesion over left temporal region, and a prolonged refractory status epilepticus which was eventually controlled with phenobarbitone, lacosamide and levetiracetam. Her cognitive impairment worsened after these three stroke-like episodes but she remained ambulatory and independent in her basic self-care. She still complained of abdominal discomfort, but that appeared to be a lesser concern now. We believed it was mitochondrial enteropathy. With a correct diagnosis, things make perfect sense.

2.5. Case 5. Birth Asphyxia or MELAS to Be Blamed for Developmental Delay?

Miss E was believed to have developmental delay and learning disability from birth asphyxia. She presented initially at age 33 with gradual onset of hearing loss and aphasia. Together with these she also developed simple partial seizure with twitching of right-sided face and limbs. MRI brain revealed left temporal and parietal gyraloedema. Serum lactate was high at 4.5 mmol/L. A muscle biopsy was performed but there was no diagnostic feature for mitochondrial cytopathy. She improved and was able to be weaned off from anticonvulsant. Three years later, she suffered another similar attack, presented with involuntary limb movements. The second MRI brain showed new right temporal and parietal gyraloedema (**Figure 1(G)** and **Figure 1(H)**). The molecular genetics again confirmed m.3243A>G. Subsequently, she developed DM, and became insulin dependent shortly afterwards. Migraine was another frequent complaint. These evolving signs and symptoms down the years summarized a typical MELAS phenotype. MELAS should also be accountable for the learning disability in this lady since there was obvious gradual cognitive decline over time.

2.6. Case 6. Severe Insulin Resistance, Liver Derangement, and Psychosis

Miss F came from a broken family. Her mother died of carcinoma of pancreas, and she had a very poor relationship with her father and the step mother. She left the family since teenage, and addicted to multiple substance abuse. She noticed progressive hearing loss and tinnitus when she reached early 20 s, and she wore hearing aid few years later. At 25 she had psychotic symptoms of delusion and auditory hallucination, which was attributed to her substance abuse, and antipsychotics were given. Three years later she had a period of intermittent abdominal cramps, and blood test found persistent elevated liver enzymes ranging from 120 to 300 (ref. < 35) U/L. The usual medical work up for hepatitis was uneventful, and the liver ultrasound only showed fatty changes. A few months later, blood test found hyperglycemia, her HbA1C level was elevated to 15. Gliclazide and metformin were added for the newly diagnosed DM. Miss F was short and slim, her BMI was 17 only; she did not resemble a typical type II DM patient. Within the same year, she started to have muscle weakness and unsteadiness. The electromyography revealed myopathic changes, her CK level was normal, but lactate was elevated at 4.3 mmol/L. The muscle biopsy confirmed mitochondrial myopathy, and the genetic study was positive for m.3243A>G. The most striking management issue in this lady was the high insulin requirement that signified the degree of insulin resistance. Insulin was started about one year after her diagnosis of DM because of the persistent high HbA1C ranging from 9 - 12. Within one year, the daily insulin dosage raised to 132 units, which was equivalent to 3.7 unit/kg/day. Together with pioglitazone and acarbose, her latest HbA1C level was only marginally improved to 9.9. The myopathy also deteriorated, she could barely walk for short distance with a frame three years after the initial presentation of weakness. Her cardiac function was normal. The liver enzyme (ALT) still fluctuated between 100 and 500 IU/L, it might well be a form of mitochondrial hepatopathy, though not commonly reported in MELAS. We do not undercount substance abuse in her psychosis because of their well-known association, though MELAS with schizophrenia-like illness has also been reported.

2.7. Case 7. MELAS with Mild Lactate Elevation

Mr G had hearing loss since teenage. He was diagnosed to have DM in his early 30 s. His blood pressure was all along low with SBP ranging 80 - 90 mmHg only. The echocardiogram revealed normal cardiac function, and the cortisol level was adequate. He developed frequent abdominal pain at around 40, and was admitted many times with repeated vomiting, dehydration, and intestinal pseudo-obstruction. During these admissions his glycemic control fluctuated and he had acute kidney injury with raised creatinine up to 300 μmol/L. In one of these admissions he developed hypoglycemia and persistent metabolic acidosis, with a mildly elevated serum lactate at 2.7 mmol/L. Both of his hypoglycemia and high lactate level were corrected with glucose and fluid replacement, but his metabolic acidosis persisted with pH 7.18, HCO3 14 mmol/L and BE −12.8 mmol/L. His urine pH was 6.2, the anion gap was normal, and his chloride level was 114 (101 - 109) mmol/L. This biochemical profile suggested renal tubular acidosis. His brain CT, at a young age of 45, had already showed marked cerebral and cerebellar atrophy with bilateral basal ganglia calcifications (**Figure 1(I)** and **Figure 1(J)**). The molecular genetics confirmed m. 3243A>G. Mr G has this 'MELAS' phenotype of DM, deafness, enteropathy, and renal tubular disease, and possibly autonomic neuropathy to account for his hypotension. MELAS, but not lactic acidosis, is the lesson to learn.

3. Diagnosis

The above cases demonstrated the diversity of disease presentations in this m.3243A>G mutation. Patients could started with mild symptoms at childhood and gradually accumulate new symptoms, or present acutely at older age. The diagnosis may not be suspected as many of the symptoms are also commonly seen in acquired diseases. The long latency in reaching the correct diagnosis, often in term of decades, are not uncommon. It is the combination of symptoms & signs from multiple organ system, together with a compatible family history of maternal inheritance, that raise the index of suspicion. Deafness is a common symptom at early phase, attentive to this "deafness plus syndrome" provides clue to m.3243A>G.

Good biomarkers for mitochondrial disease is lacking. An elevated blood lactate helps, the yield increases with post-prandial blood sampling, but some patients still have normal lactate level. Serum fibroblast growth factor 21 (FGF-21) has recently be developed as a biomarker for mitochondrial disease with muscle weakness, to distinguish mitochondrial myopathy from other neuromuscular conditions [8]. Its use is only limited to patients with myopathy. It correlates poorly with disease severity and it is not a prognostic marker [9]. Molecular genetics study, from blood, urine or tissue samples, confirms the diagnosis. Blood samples usually have lower level of heteroplasmy compared to urinary epithelial cell and muscle tissue, and its level also decreases with age [10]. Therefore, in older adults it is preferable to use urine or tissue samples for the genetic study.

4. Organ Specific Manifestations

4.1. Stroke-Like Episodes

The most important thing is to recognize the characteristic radiological change, which is best appreciated from MRI. Typically, the acute lesion locates at parietal and occipital region, involve predominantly cortical and subcortical white matter, and spares the deep white matter [11] [12]. There is no clot occluding the vessels despite having large cortical lesions, and the lesion distributions do not conform to vascular territory. The acute lesion shows restricted diffusion (appears bright on DWI), but without significant reduction in apparent diffusion coefficient (ADC) maps [13]. This suggests that most of the swelling seen on MRI is from vasogenic rather than cytotoxic oedema. Migration of lesions may be appreciated with serial monitoring. MR spectroscopy usually demonstrates a high lactate peak in acute lesions, and, with an acute infarction excluded from the lack of darkening on ADC map, points to MELAS [14]. This elevated lactate, if being detected in brain regions spared from acute lesion, also supports the diagnosis.

4.2. Epilepsy

The seizure in MELAS patients is frequently associated with stroke-like episode, just as described in our patients, and then recurs intermittently. Simple motor seizure is the most frequent type. During stroke-like events the seizure could be prolonged, evolving into convulsive or non-convulsive status epilepticus, or epilepsia partialis continua [15].

4.3. Muscle and Heart

Weakness and poor exercise tolerance are prevalent among m.3243A>G carriers. Cardiomyopathy, both dilated and hypertrophic, have been reported [16]. Arrhythmia, such as Wolff-Parkinson-White syndrome, could be another cardiac manifestation [17].

4.4. Diabetes Mellitus

MIDD is a recognized entity and affects about 1% of DM patients [18]. Phenotypically they are young onset DM with a low BMI [19]. Many of them require insulin therapy two years after their diagnosis. Recent studies suggested insulin resistance and relative insulin deficiency is the main reason for MIDD, although the insulin secretion from pancreatic β-cell is dependent on mitochondrial function [20] [21].

4.5. Hepatopathy and Enteropathy

MELAS patients frequently complain of anorexia and poor weight gain. All sorts of gastrointestinal symptoms,

from dyspepsia, vomiting, abdominal cramp, constipation, diarrhoea, to intestinal pseudo-obstruction, have all been described [22] [23]. Hepatopathy, usually in childhood, has been reported in other mitochondrial diseases, whether m.3243A>G mutation causes hepatopathy is unclear. Recurrent pancreatitis is another recognized visceral organ presentation.

4.6. Nephropathy

Proteinuria and impaired kidney function could be a feature in this spectrum. Focal segmental glomerulosclerosis, proximal tubular defects and tubulointerstitial nephropathy have been documented [24] [25].

5. Management

5.1. Acute Treatment in Stroke-Like Episodes

Arginine supplement is the only evidence-based specific treatment for MELAS in acute stroke-like episode for a quick recovery, and to prevent subsequent similar events [26]. MELAS patients in acute stroke-like episode have arginine deficiency, that is believed to further compromise the nitric oxide (NO) dependent endothelial function and vasodilatation [27]. In their early studies, Koga & Co found replacement of arginine through intravenous infusion improved neurological symptoms rapidly within 24 hours, and that was accompanied by improved perfusion in SPECT [28] [29]. Our own experience in intravenous L-arginine is not encouraging, and we believe that discrepancy is because of treatment delay, since the study patients were treated within one hour of symptoms onset, but none of our patient was treated within 24 hours. In order to narrow the gap, a letter or remark in the electronic record system is necessary to alert the in-charge physician for urgent prescription. The regime is L-arginine 0.5 g/kg in normal saline making up a 10% solution, infused over 15 minutes, followed by oral L-arginine 0.3 g/kg/day in three or four divided doses.

5.2. Management of Co-Morbidities

Drug treatments are required for the management of multiple co-morbidities in these patients. In choosing the appropriate agents caution should be taken to avoid those drugs with potential harmful effect on mitochondrial function or oxidative phosphorylation. Valproate, with reports documenting hepatic failure and worsening of MELAS, is the most important agent to avoid [30]. Phenobarbitone and phenytoin should also be used with caution. Metformin is another agent to avoid in the fear of lactic acidosis although there is little evidence in this. Thiazolidinediones impair cell respiration through their effect on complex I, they should also be used with caution [31]. Other potentially harmful agents include statins, fibrate, β-blocker, amiodarone and neuroleptics such as chlorpromazine, haloperidol, risperidone and quetiapine.

5.3. Exercise

It is well known that exercise improves mitochondrial function. Exercise has become another evidence-based treatment in mitochondrial myopathy. Consistently, endurance exercise improves oxidative capacity and quality of life, while resistance exercise increases muscle strength, and may decrease the % heteroplasmy in the muscle [32]-[35]. The latter is more prominent in single large mitochondrial DNA deletions, whether point mutations like m.3243A>G could have the similar benefit is unclear. This gain is thought to be derived from a “genetic drift” phenomenon, where the satellite cells within the muscle could be activated through resistance exercise and fusing their wild type mitochondrial DNA to the muscle cell and dilute the heteroplamy [36]. Therefore, every mitochondrial disease patient should has an exercise program starts at a lower intensity level according his tolerance, and builds up gradually. This should be a long term strategy.

5.4. Genetic Counselling and Prenatal Diagnosis

Genetic counselling is important for the patient and family to understand the disease, mode of inheritance, possible future outcome, and for reproductive planning [37]. With improving technologies in mitochondrial DNA heteroplasmy analyses, it has been advocated for prenatal testing for mitochondrial disease in some countries [38]. Unfortunately, in m.3243A>G mutation, the % heteroplasmy correlates poorly with phenotype and prognosis, this would significantly limit the interpretation of prenatal testing result, especially in those with interme-

diate heteroplasmy level [39]. Besides, affected mother would invariably pass on the mutation to all of her offsprings. The latest mitochondrial donation technology could provide women with another option to stop passing the mutation to their offspring.

6. Conclusion

m.3243A>G is a true big mimicker, the full picture of an affected patient would only be understood through long term follow up. With a high index of suspicion, diagnosis could be reached earlier and appropriate treatment administered. Genetic counselling, reproductive planning and prenatal diagnosis would help to prevent the disease in the family.

Conflicts of Interest

None.

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Macrophage TGF-β1 and the Proapoptotic Extracellular Matrix Protein BIGH3 Induce Renal Cell Apoptosis in Prediabetic and Diabetic Conditions

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Abstract

Metabolically stressed kidney is in part characterized by infiltrating macrophages and macrophage-derived TGF-β1 that promote the synthesis of various ECM molecules. TGF-β1 strongly enhances the expression of the gene *TGFBI* that encodes a cell-adhesion class, proapoptotic ECM protein called BIGH3. We hypothesized that in a diabetic environment a relationship between infiltrating macrophages, macrophage-derived TGF-β1, and BIGH3 protein promotes renal cell death. To investigate this hypothesis, we used our mouse model of diabetic complications. Mice on a high-fat diet developed hypercholesterolemia, and exposure to streptozotocin rendered hypercholesterolemic mice diabetic. Immunohistochemical images show increased macrophage infiltration and BIGH3 protein in the kidney cortices of hypercholesterolemic and diabetic mice. Macrophages induced a two-fold increase in BIGH3 expression and an 86% increase in renal proximal tubule epithelial cell apoptosis. TGF-β1 antibody and TGF-β1 receptor chemical antagonist blocked macrophage-induced apoptosis. BIGH3 antibody completely blocked apoptosis that was induced by TGF-β1, and blocked apoptosis induced by exogenous recombinant BIGH3. These results uncover a distinctive interplay of macrophage-derived TGF-β1, BIGH3 protein, and apoptosis, and indicate that BIGH3 is central in a novel pathway that promotes diabetic nephropathy. Macrophage TGF-β1 and BIGH3 are identified as prediabetic biomarkers, and potential therapeutic targets for intervention in prediabetic and diabetic individuals.

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Keywords

TGF, BIGH3, Macrophages, Diabetes, Extracellular Matrix

1. Introduction

Advances in clinical treatments and strong emphasis on diabetes education have played significant roles in pre-diabetic and diabetic health care management. However, a continued increase in the number of clinical cases of diabetic complications has increased in recent years. Moreover, a greater percentage of minority individuals experience clinical level diabetic diseases of the renal, vascular, and ocular systems when compared to individuals in the non-minority population, highlighting a health disparity element in diabetes [1]. When poorly controlled, diabetes mellitus types I and II promote harmful complications in targeted organs and tissues, including the renal system. Even with modern therapeutic interventions, dysregulated cell signaling, changes in ECM turnover, and apoptosis promote kidney damage and end-stage renal disease, highlighting a need for a more complete understanding of the mechanisms underlying diabetic nephropathy. Development of diabetic nephropathy generally involves monocyte/macrophage infiltration, an increase in the local production of cytokines and reactive oxygen species (ROS), increased apoptosis, and accumulation of ECM molecules. The latter is explained, in part, by cytokine-induced changes in the expression of genes that encode for the ECM molecules fibronectin, collagen types I and IV, laminin and proteoglycans [2]-[4]. TGF-β1 activates the gene *TGFBI*, which encodes the ECM molecule called BIGH3 (Transforming Growth Factor BIInduced Gene Human Clone 3), also known as beta-ig, TGFBI, and kerato-epithelin. BIGH3 is a cell adhesion-class protein that comprises a cysteine-rich domain, four fasciclin-1 (FAS1)-like repeats, and in the C-terminal portion EPDIM and RGD integrin-binding sequences [5] [6]. In its secreted full-length form (minus the secretory sequence) SDS PAGE analysis estimates a mass of 69 kDa. The C-terminal portion of the 69-kDa BIGH3 becomes cleaved, yielding a stable 60-kDa BIGH3 protein, and generating C-terminally derived integrin-ligand peptides that appear to act as competitive inhibitors of the pro-survival ECM-integrin interactions [7]-[9]. These BIGH3-derived C-terminal peptides induce apoptosis, giving rise to the term BMA (BIGH3-mediated apoptosis), which we use in this study. Several different laboratories have reported BMA on retinal pericytes [10], retinal endothelial cells [11] the osteosarcoma cell lines MG-63 and Saos-2 [9], transformed corneal epithelial cells [12], Chinese hamster ovary cells, and other cell types [8], thus the rationale to classify BIGH3 as a proapoptotic ECM protein.

Although macrophages play important roles in tissue homeostasis, they are also major contributors to diabetic progression, promoting metabolic stress and interstitial fibrosis, leading to loss of renal function [13] [14]. In rodents, blocking macrophage infiltration attenuated kidney tubular epithelial cell apoptosis [15]. Similarly, deleting *CCL*2, which encodes monocyte chemoattractant protein-1, attenuated renal tubule cell damage [16], and suppressed development of diabetic nephropathy in streptozotocin (STZ)-treated mice [17]. Macrophage-derived soluble molecules, *i.e.* NO, ROS, have been implicated in rodent glomerular mesangial cell apoptosis [18]. Macrophage ingestion of apoptotic bodies *in vitro* induce macrophages to secrete TGF-β1 [19] [20], accounting for at least some of the TGF-β1 in tubulointerstitium and glomeruli of diabetic patients [21]. These same loci, *i.e.*, tubulointerstitium and glomeruli, in adult diabetic rat show an increase in BIGH3 protein [22] [23], suggesting that in diabetic humans and animals, macrophage-derived TGF-β1 stimulates BIGH3 protein synthesis. Here we document a previously unrecognized relationship involving macrophages, macrophage-derived TGF-β1, an increase in BIGH3 synthesis, and an increase in BMA of renal cells. Discussed is a potential positive feedback mechanism that promotes BMA and diabetic nephropathy.

2. Methods

Animals. Female LDL-R$^{-/-}$ mice (B6.129S7-LDLR^{tmlHer}/J, stock no. 002207) on a C57BL/6J background and C57BL/6J donor mice were obtained from The Jackson Laboratory (Bar Harbor, ME). To render mice diabetic, STZ dissolved in 50 mM citrate buffer (pH = 4.5), was used for intraperitoneal injection at a dose of 50 mg·kg^{-1}·day^{-1} for five consecutive days and, after two days rest, again for two consecutive days [24] [25]. Non-diabetic mice received a comparable volume of citrate buffer. To induce hypercholesterolemia, diabetic mice were fed a high fat diet (HFD), BioServ AIN-76A, fat: 21% wt/wt; cholesterol: 0.15% wt/wt (Frenchtown,

NJ) plus STZ for a total of 12 weeks beginning 3 weeks after the first STZ injection. Non-diabetic mice received either a MD (low-fat maintenance diet, BioServ, AIN-93G) or a HFD. All mice were 17 weeks of age and 18.4 ± 0.2 g at the beginning of the study.

Survival rates of STZ treated female mice significantly exceeded that of corresponding STZ treated male mice, female mice were selected for this study. All studies were performed with the approval of the University of Texas Health Science Center at San Antonio Institutional Animal Care and Use Committee.

Renal Cell Culture. Human renal proximal tubule epithelial cells (RPTEC), renal epithelial basal medium supplements (human epidermal growth factor, hydrocortisone, epinephrine, insulin, triiodothyronine), and the antibiotic and anti-fungal agents (gentamicin sulfate and amphotericin B) were purchased from Clonetics/Lonza (Allendale, NJ), and ATCC. These supplements combined with 10% FBS constituted renal epithelial growth medium (REGM). RPTEC monolayers that were 70% confluent were used to initiate subcultures at 5×10^4 cells per ml medium. All incubations of live cells, for maintenance and experiments, occurred in a humidified 37˚C incubator saturated with 5% CO_2 in 95% ambient air. All experiments were conducted using RPTEC at or below passage eight.

Macrophage-conditioned Media. Mononuclear cells were isolated from blood obtained from healthy human donors through the South Texas Blood and Tissue Center (San Antonio, TX). Mature human monocyte-derived macrophages (HMDM) were prepared as described previously [26]. Two different conditioned media were generated for this study. To mimic normal "healthy" conditions, mature HMDMs were cultured for 24 hours in standard RPMI medium, followed by rinsing and a 24-hour incubation in serum-free RPMI medium. This serum-free conditioned medium was designated macrophage-conditioned medium (MCM). To generate a "diabetic" environment, we cultured mature HMDMs in RPMI supplemented with 20 mM glucose (25 mM final glucose concentration) and 100 μg/ml freshly isolated human LDL. After 24 hours the medium was removed, macrophage monolayers were rinsed and given serum-free RPMI for a 24-hour incubation period. This medium was designated diabetic macrophage-conditioned medium (dMCM). To remove any floating cells the media were centrifuged. Supernatants were kept at −20˚C until use. TGF-β1 in the MCMs was quantified using Quantikine ELISA reagents following the manufacturer's recommendations (R&D Systems). Briefly, 0.1 ml from each batch of MCMs with and without acid activation of latent TGF-β1 was used to quantify active and total TGF-β1. A standard active TGF-β1 curve was generated at the time of assessment.

Antibodies. New Zealand white rabbits immunized with full-length recombinant BIGH3 provided antiserum that we have previously characterized [27]. Preimmunized rabbit serum was used as negative controls where indicated in the individual experiments. Anti-CD68 antibody, clone FA-11, and anti-TGF-β1 antibody, clone 9016, were from AbDSerotech (Raleigh, NC) and R&D Systems (Minneapolis, MN) respectively. Heating serum to 52˚C for 10 min inactivated complement before use in experiments.

Immunohistochemistry. Kidneys from adult MD, HFD and diabetic mice were harvested, immediately frozen in optimal cutting temperature compound [24] and stored at −80˚C until use. From kidney cortex, 10-μm thick sections were fixed for 30 min in 10% fresh paraformaldehyde in PBS. Fixed sections were rinsed with 20 mM glycine in PBS (Buffer A), blocked for 1 hour in 3% BSA in PBS, and incubated 12 hours in Buffer A plus anti-CD68 antibody (1:300) and anti-BIGH3 antiserum (1:200), or with control serums. After rinsing, sections were incubated for 1 hour in blocking buffer with anti-rabbit or anti-mouse antibodies conjugated to DyLight488 and DyLight594 fluorescent dyes, respectively, then rinsed with Buffer A and sealed in Vectashield (Vector Laboratories, Burlingame, CA). Unless indicated otherwise, all incubations were at ambient temperature, and all rinses were 3 × 15 min in Buffer A.

*Recombinant BIGH*3. Spodopterafrugiperda (Sf9) insect cells, GeneJuice transfection reagent and pIEX-3 Ek/LIC were from Novagen (Darmstadt, Germany). Sf9 cells were propagated in 30 ml of 28˚C BacVector insect cell medium in 250 ml flasks in 140-rev/min motion. Sf9 cells were transfected with plasmid encoding a 6His-tagged human BIGH3 cDNA. Two days after transfection, the conditioned medium was exchanged to 10 mM imidazole in 0.3 M NaCl, 50 mM sodium phosphate buffer, pH 8 (Buffer B) using a 30-kDa cutoff membrane in a flow-cell apparatus. The retentate was applied over a 0.3 ml bed volume of Ni-NTA affinity resin that was subsequently washed with Buffer B. Increasing imidazole from 10 mM to 250 mM in Buffer B eluted BIGH3. Western blots identified the fractions containing BIGH3, which were pooled, and Buffer B exchanged for PBS using a 30-kDa cutoff Centricon concentrator. BIGH3 protein was quantified using SDS-PAGE gels, Western blots and bicinchoninic acid protein assays.

Apoptosis Assays. Wells of an 8-well chamber slide, each seeded with 10^4 RPTEC in REGM, were incubated

24 hours. Following REGM aspiration the wells received a mixture of REGM plus 25% dMCM, REGM plus 25% MCM, REGM plus BIGH3, or REGM only. After another 24-hour incubation, media were aspirated and the cells fixed in 4% paraformaldehyde in PBS, washed, and treated with 0.1% Triton X-100 before TUNEL assays (Roche Applied Science, Indianapolis, IN). After washing, Vectashield and coverslips were applied. The numbers of stained cells in ten different random fields at 20× magnification were counted using a ZEISS (Jena, Germany) Axioplan II fluorescent microscope. For ssDNA assays, BIGH3 was added to microtiter wells containing 10^4 RPTEC in 0.1 ml 37˚C REGM. After a 24-hour incubation and 5-minute centrifugation, the medium in each well was replaced with 0.2 ml of 80% methanol in PBS. Wells were incubated at 25˚C for 30 min, dried, and 0.05 ml formamide was added to each well before a 20-min incubation at 75˚C. Detection of ssDNA was accomplished using a monoclonal antibody and apoptosis detection reagents (APT225, Millipore, Billerica, MA). Absorbance at 405 nm quantified ssDNA. DAPI-stained nuclei of BIGH3-treated and non-treated cells provided images for nuclear condensation comparison.

Quantitative PCR. Total RNA isolated from RPTEC was used to synthesize BIGH3 cDNA in accordance with the manufacturer's protocol using TaqMan Reverse Transcription Reagents (ThermoFisher Scientific, Waltham MA). The cDNA obtained from total RNA served as template for qPCR amplification using Power SYBR Green (Applied Biosystems/Life Technologies, Grand Island, NY). BIGH3 transcripts were amplified using the forward and reverse primer pair 5'-TGGACAGACCCTGGAAACTC-3' and 5'-GTCTCCCTTCAGGACATCCA-3' respectively. Real-time PCR was performed on an Applied Biosystems 7300 system using 40 cycles of denaturation (95˚C for 15 s) and annealing/extension (60˚C for 60 s). Ct values of measured fluorescence of BIGH3 gene amplicon elevating above a fixed threshold were recorded and normalized to cDNA generated from 18s rRNA transcripts. Relative measurements were quantified using the ΔΔCT method.

Western blots. Proteins resolved on reducing 4% - 10% SDS PAGE gels and transferred to Immobilon-P membrane were incubated with anti-BIGH3 antiserum. BIGH3 antibody was detected using a second antibody conjugated to horseradish peroxidase and the substrate 3,3'-diaminobenzidine. Densitometry analysis was accomplished using Image J (http://imagej.nih.gov/ij/).

Statistical analysis. For statistical analysis Student's t-test, One-Way ANOVA, and Two-Way ANOVA were performed and P values of less than 0.05 were set as statistically significant. Post Hoc statistical analysis methods used Bonferroni multiple comparisons test and Newman-Keuls Multiple Comparison Test. Results are expressed as ±SEM of the number of experiments. Statistical analysis was performed using GraphPad Prism software.

3. Results

Metabolic stress increases macrophage infiltration and BIGH3 protein in kidney cortex. It is known that macrophages infiltrate diabetic kidney cortex, and that macrophage-derived TGF-β1 promotes ECM accumulation in diabetic cortical interstitium and basal lamina [28] [29]. TGF-β1 strongly upregulates expression of the BIGH3 gene, thus a logical expectation is that a greater quantity of macrophages and BIGH3 protein would be evident in kidney cortex of diabetic mice when compared to non-diabetic kidney cortex. To test this hypothesis, we utilized our previously characterized mouse model of diabetic complications [24]. Immunohistochemical analysis detected few, if any macrophages in the kidney cortex of healthy mice fed a MD (**Figure 1(A)**). In distinction, an increase in macrophage number was observed in the kidney cortex of HFD dyslipidemic mice (**Figure 1(B)**). When STZ rendered HFD mice diabetic, hereafter referred to as HFD + diabetic mice, a further increase in macrophage number was evident when compared to kidney cortices of mice on a MD and HFD (**Figure 1(C)**). Anti-BIGH3 antibody revealed little staining of BIGH3 protein in kidney cortex of mice on a MD (**Figure 1(D)**). Unexpectedly, BIGH3 staining was markedly increased throughout the cortex of mice on a HFD (**Figure 1(E)**), suggesting BIGH3 protein is a potential prediabetic biomarker (discussed below). Similarly, broad, extensive BIGH3 protein staining was evident in kidney cortex of HFD + diabetic mice (**Figure 1(F)**). In kidney cortices of mice on a HFD, and in HFD + diabetic mice, BIGH3 was observed at or near pericellular and interstitial matrices (**Figure 1(H)**, **Figure 1(I)**, long arrows) in greater quantities than in mice on a MD (**Figure 1(G)**). Also noted are macrophages at or near BIGH3 protein (**Figure 1(H)**, **Figure 1(I)**, short arrows), raising the question of whether BIGH3 serves as a substratum in macrophage recruitment and adhesion (see discussion). Here we conclude that HFD and diabetic conditions promote macrophage infiltration and BIGH3 protein synthesis in kidney cortices. We next investigated whether macrophage-derived soluble molecules increase BIGH3 gene expression.

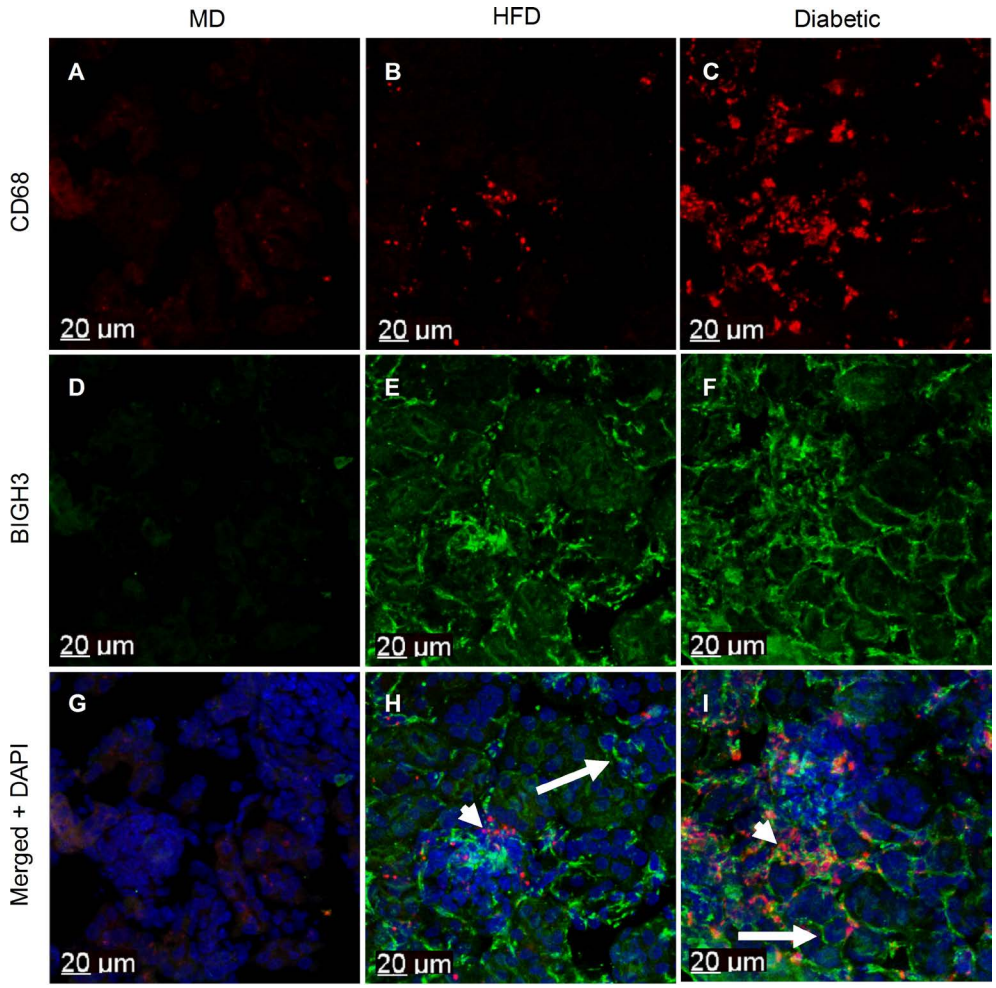

Figure 1. Metabolically-stressed kidney cortex show increased macrophage numbers and BIGH3 protein levels. Macrophages were stained with anti-CD68 antibody (red). BIGH3 antiserum staining and nuclei (DAPI) staining are green and blue, respectively. Images are from kidney cortices of healthy mice on a maintenance diet (MD) (A) (D) (G), a HFD (B) (E) (F) and from diabetic mice on a HFD (C) (F) (I). Short and long arrows indicate macrophages and BIGH3 protein respectively (H) (I). Scale bars (20 µm).

*Macrophage-derived soluble molecules stimulate renal cells to synthesize BIGH*3 *transcripts.* To examine whether macrophages produce factors that promote BIGH3 transcript expression in a diabetic environment, two different media were prepared; macrophage conditioned medium (MCM) and diabetic macrophage conditioned medium (dMCM). Briefly, macrophages were first pre-incubated for 24 hours with RPMI basal medium containing high (25 mM) glucose and high (100 µg/ml) LDL. This high glucose and LDL basal medium was aspirated, and macrophages were washed in RPMI and then used to condition serum-free RPMI for 24 hours to generate dMCM. Therefore, the dMCM used in experiments contained macrophage-derived soluble factors, but not high glucose or LDL. An identical procedure generated MCM, albeit macrophages were pre-incubated in RPMI basal medium without high glucose and LDL. Human RPTEC were maintained in REGM. For experiments, RPTEC were cultured for up to 48 hours in conditions where 25% of REGM was replaced with dMCM, MCM or RPMI. Results in **Figure 2** show that dMCM induced an acute increase in BIGH3 transcript synthesis in RPTEC. Three hours post-exposure to dMCM, BIGH3 mRNA levels had increased 2.5 fold. RPTEC exposed to MCM increased BIGH3 mRNA synthesis initially. At 3 hours post-exposure to MCM, BIGH3 mRNA level decreased and then gradually increased 0.5-fold by 24 hours. In both conditions the increase in BIGH3 mRNA was transient, approaching the REGM/RPMI control baseline throughout the remaining 24 hours of the assay. REGM/RPMI did not significantly change BIGH3 transcript levels.

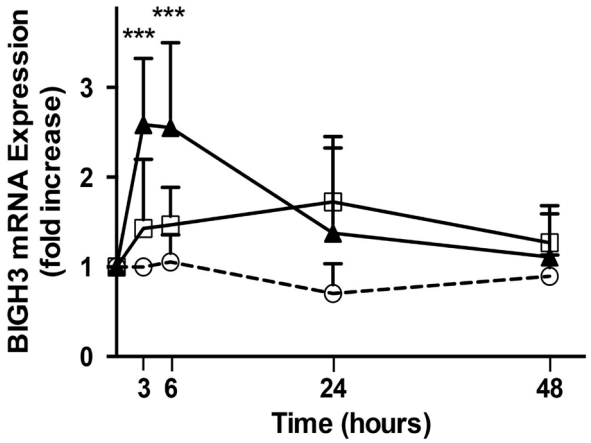

Figure 2. MCMs upregulate BIGH3 transcript expression. RPTEC (10^5) cultured in REGM plus 25% RPMI (white circles), 25% MCM (white squares) or 25% dMCM (black triangles) express BIGH3 transcripts. At times indicated qPCR measured BIGH3 transcripts as described in the methods section. A Two Way ANOVA was performed for treatment and time. There were three treatments, RPMI, MCM, and dMCM; and there were 6 time points, 0, 3, 6, 12, 24, and 48 hours after exposure of RPTEC to the media. There were a total of 9 replicates in each group. Post hoc analysis for significant differences between groups was performed with a Bonferroni multiple comparisons test. Two Way ANOVA was significant [treatment: $F(2, 120) = 26.22$, $p < 0.0001$; time: $F(4, 120) = 10.34$, $p < 0.0001$; and interaction: $F(8, 120) = 6.48$, $p < 0.0001$]. Significance was set at $p < 0.05$, $^{***}p < 0.001$.

RPTEC secrete and cleave BIGH3 protein

Both dMCM and MCM induced greater quantities of secreted BIGH3 protein when compared to the BIGH3 protein in REGM/RPMI control medium (**Figure 3(A)**, **Figure 3(B)**). BIGH3 protein increased with active TGF-β1 in MCM (41 - 53 pg/ml TGF-β1) and dMCM (60 - 76 pg/ml TGF-β1). Albeit TGF-β1 levels in dMCM were higher than levels in MCM, a significant increase was not apparent when comparing BIGH3 protein levels in MCM and dMCM (**Figure 3(B)**). This result suggests TGF-β1 levels in MCM saturated TGF-β1 receptor signaling. If true, then a higher TGF-β1 level in dMCM would not equate with additional BIGH3 synthesis. This suggests that in a prediabetic environment macrophage TGF-β1 increases BIGH3 levels close to BIGH3 levels in a diabetic environment, consistent with the idea that in a prediabetic environment BIGH3 protein in kidney cortex is already accumulating in the interstitial space (**Figure 1(E)**). Additional experiments are necessary to quantify the extent of differences in BIGH3 protein in prediabetic and diabetic kidney cortex. BIGH3 in MCM and dMCM, when compared to BIGH3 in control medium, were significant. Although fresh control medium did not contain detectable levels of TGF-β1, modest levels of BIGH3 transcripts (**Figure 2**) and BIGH3 protein (**Figure 3**), in the control medium indicates that RPTEC synthesize some of the BIGH3 in MCM and dMCM.

On SDS PAGE the relative mobility of secreted BIGH3 was calculated to be 69 kDa [9], which is the estimated size of the upper BIGH3 band detected with polyclonal anti-BIGH3 antibody. The antibody also detected BIGH3 protein at approximately 60 kDa (**Figure 3(A)**). These results agree with previous mass spectrometry analysis showing that BIGH3 protein is cleaved within its C-terminus, generating 62- and 60-kDa BIGH3 proteins, and Western blots showing the 62- and 60-kDa proteins as closely-spaced bands [7]-[9] [30]. We conclude that 1) macrophages in a HFD or diabetic environment provide soluble molecules that increase BIGH3 gene transcription and translation and 2) RPTEC cleave the C-terminus of BIGH3 to generate a 60-kDa mature protein and C-terminally-derived peptides. A logical hypothesis is that in MCM and dMCM, TGF-β1 is the soluble factor that increases BIGH3 gene transcription and translation, followed by BIGH3 secretion and BIGH3 C-terminal cleavage (see discussion).

Blocking TGF-β1 receptor signaling inhibits BIGH3 transcript expression. To test whether macrophage-derived TGF-β1 in dMCM and MCM induce BIGH3 gene transcription, we used the pharmaceutical small chemical inhibitor SB-431542 that selectively blocks TGF-β type I receptor kinase signaling. Results show that 13 nM SB-431542 blocked BIGH3 gene transcription by 50% and 53% respectively in REGM plus 25% dMCM, and REGM plus 25% MCM, when compared to vehicle only controls (**Figure 4**). These data show that TGF-β1

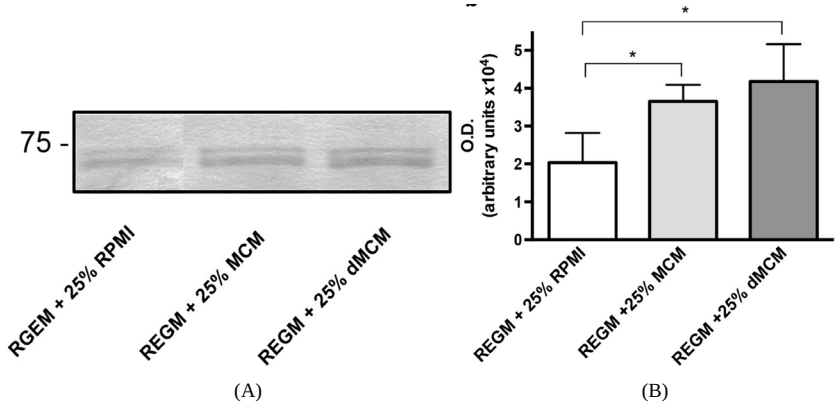

Figure 3. MCMs upregulate BIGH3 protein expression. (A) The differential mRNA levels agree with the quantity of BIGH3 protein in conditioned media. RPTEC (10^5) were cultured in REGM plus 25% RPMI, MCM, or dMCM. After 48 hours incubation Western blots resolved proteins that were then stained with BIGH3 antibody. The upper bands are 69 kDa BIGH3 that has the intact C-terminus. The lower bands are C-terminally cleaved BIGH3. Protein loaded on SDS PAGE was normalized to total cellular protein. The position of the 75-kDa protein standard is indicated. (B) Densitometry quantified BIGH3 protein in each of the three culture conditions. One-Way ANOVA indicates that there is significantly more BIGH3 in MCM and dMCM compared to BIGH3 in RPMI ($p < 0.05$), but no significant differences were evident when comparing BIGH3 protein levels in MCM to dMCM.

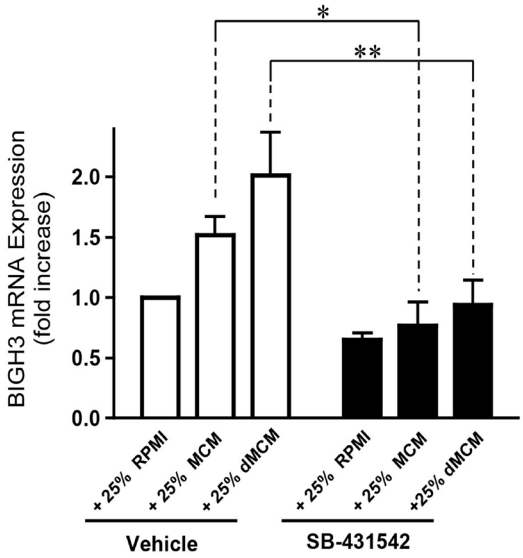

Figure 4. Macrophage-derived TGF-β1 upregulates BIGH3 transcript expression. Cells were cultured in REGM + 25% RPMI, REGM + 25% MCM and REGM + 25% dMCM, each with the TGF-β1 receptor inhibitor SB-431542 or DMSO vehicle. After a 24-hour incubation period qPCR measured BIGH3 transcripts. A Two Way ANOVA was performed with a Bonferroni Multiple Comparison post hoc test for significant differences. The Two Way ANOVA was significant for SB-431542, $p < 0.0001$, and for medium, $p < 0.05$. The effect of SB-431542 on MCM was significant at $^{*}p < 0.05$ and on dMCM at $^{**}p < 0.01$.

signaling in RPTEC is a strong transcriptional stimulator of the BIGH3 gene. In the control medium (no MCM/dMCM added), SB-431542 blocked BIGH3 expression by 30% (**Figure 4**). This result indicates that RPTEC themselves synthesize low-levels of TGF-β1 that induce some BIGH3 expression, as predicted in the previous results (**Figure 2** and **Figure 3**). We conclude that macrophage-derived TGF-β1 and TGF-β1 receptor signaling induces BIGH3 gene transcription.

TGF-β1 upregulates RPTEC BIGH3 protein synthesis and secretion. Treating RPTEC with 42 pM TGF-β1 for 24 hours more than doubled BIGH3 protein quantity in conditioned medium (**Figure 5(A)**, **Figure 5(B)**).

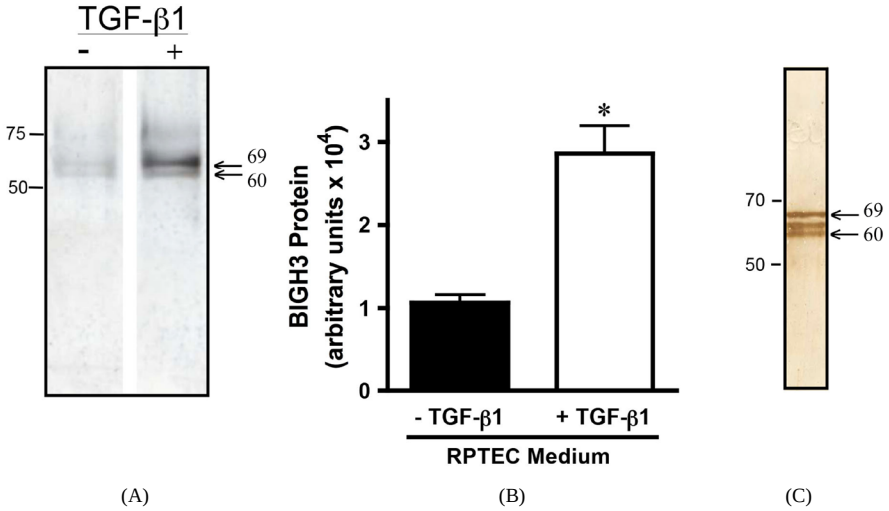

Figure 5. TGF-β1 upregulates BIGH3 protein expression in RPTEC. (A) Western blot of BIGH3 in the culture medium of RPTEC treated for 24 hours with vehicle only (−) or 42 pM TGF-β1 (+). (B) Densitometry of bands from 3 separate experiments quantified BIGH3 protein in (A), n = 3. Results are shown as mean ± S.D. The effect of TGF-β1 on increasing BIGH3 protein in the cells' medium was significant, t-test ($p < 0.05$). (C) Western blot showing BIGH3 in the culture medium of a recombinant expression system (no TGF-β1 present). Arrows in (A) and (C) indicate BIGH3 protein bands. The 50-, 70- and 75-kDa protein standards are indicated. In each blot the lower band is consistent with the 60-kDa form of BIGH3 after C-terminal cleavage. The center protein band in (C) is the 62-kDa intermediate BIGH3 protein.

The TGF-*β*1-induced increase on renal cell BIGH3 synthesis is consistent with the MCM- and dMCM-induced increase on BIGH3 expression (**Figure 3(A)**, **Figure 3(B)**). BIGH3 isolated from RPTEC conditioned medium was cleaved (**Figure 5(A)**). Interestingly, BIGH3 isolated from our Sf9 recombinant protein expression system was also cleaved (**Figure 5(C)**). Western blot staining resolved a 69-kDa protein, a 62 kDa C-terminus truncated intermediate BIGH3 [9], and a 60-kDa C-terminal truncated BIGH3 protein (**Figure 5(C)**). The three BIGH3 proteins coincide with mass spectrometry analysis, documenting BIGH3 C-terminal cleavage yields an intermediate 62-kDa BIGH3 protein and a relatively stable mature 60-kDa BIGH3 protein [7] [9] [31] and suggest that renal cells and other cell types cleave BIGH3 (see discussion). We conclude that TGF-*β*1 stimulates RPTEC to synthesize and secrete BIGH3, and that RPTEC cleave BIGH3 protein.

BIGH3 promotes RPTEC apoptosis. Cleavage of BIGH3 C-terminus yields integrin ligand peptides that induce BMA in various cell types [8]-[12] [32]. To test for renal cell BMA, recombinant BIGH3 protein was added directly to REGM. After a 24-hour incubation period BMA was quantified using TUNEL assays, nuclei condensation analysis, and quantitation of single-stranded DNA. TUNEL and DAPI staining revealed an increase in the number of condensed nuclei in BIGH3-treated cells when compared to non-treated control cells (**Figures 6(a)-(i)**). The number of BIGH3-treated TUNEL-labeled cells was greater (**Figure 6(b)**) when compared to non-treated cells (**Figure 6(g)**). Non-apoptotic and apoptotic nuclei (**Figure 6(c)**, arrows) were magnified to show nuclear condensation in cells in control REGM (**Figure 6(d)**, **Figure 6(e)**). An apoptotic cell nucleus is compared to neighboring non-apoptotic cell nuclei (**Figure 6(h)**, boxed area magnified in **Figure 6(i)**).

The extent of RPTEC BMA was dependent on the concentration of BIGH3 added to the growth medium. TUNEL and ssDNA assays quantified BMA of cells that were treated with 5 μg/ml BIGH3 (**Figure 6(j)**, **Figure 6(k)**, respectively). Increasing BIGH3 concentration to 10 μg/ml increased BMA, but there was no statistically significant change in the number of apoptotic cells when comparing effects of 10 and 20 μg/ml BIGH3. These results show that 5 μg/ml BIGH3 is sufficient to induce a significant increase in renal cell BMA. A 24-hour exposure to high glucose (25 mM) and LDL (100 μg/ml) (without exogenous dMCM, MCM and BIGH3) did not increase BMA of RPTEC when compared to untreated cells (**Figure 6(l)**) indicating that *in vitro* the signal promoting BMA is independent of glucose and LDL *per se*. We conclude that in addition to macrophage-derived injurious molecules (e.g., NO, ROS), macrophage-derived TGF-*β*1 and BIGH3 account for at least some of the renal cell damage and death in DN.

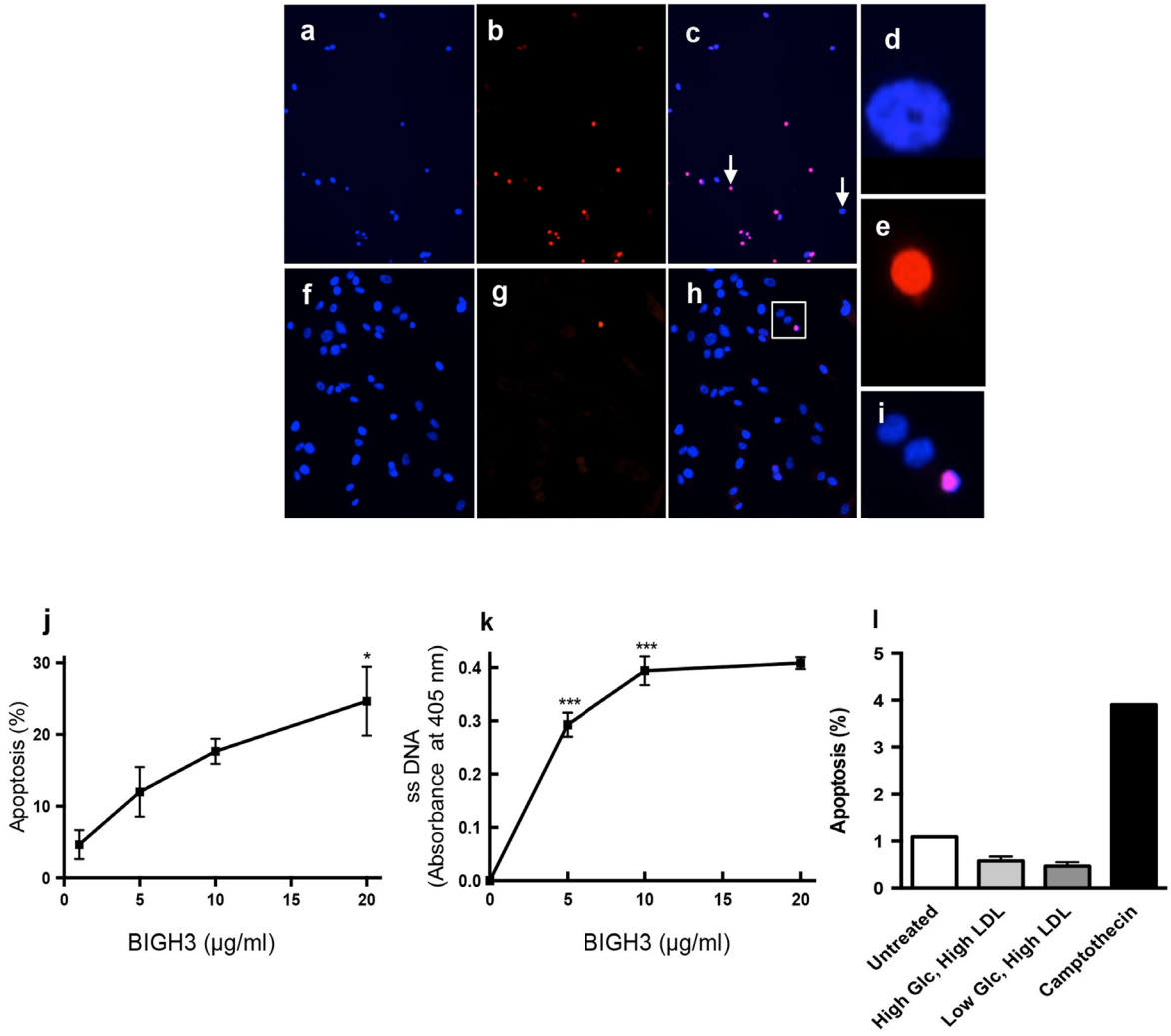

Figure 6. BIGH3 promotes renal cell apoptosis. RPTEC were treated with 5 μg/ml BIGH3 for 24 hours. (a) Cells stained with DAPI. (b) TUNEL labeled cells. (c) a and b merged. Images (a and b) were recorded using a 20× objective. Cell nuclei denoted by arrows in (c) were magnified using an identical digital command (no other parameters changed) to show non-apoptotic and apoptotic nuclei (d, e, respectively). Controls are cells treated with vehicle only, shown with (f) DAPI staining and (g) TUNEL labeling. (h) d and e merged. Images (g-h) were recorded using a 40× objective to better show nuclear condensation. (i) The boxed area in (h) is magnified to show apoptotic and non-apoptotic nuclei. (j) Cultured RPTEC were treated with increasing concentrations of rBIGH3 added directly to growth medium. After 24 hours, TUNEL labeling revealed a significant increase in BMA. Significance when comparing 20 μg/mL with 1 μg/mL ($^{*}p < 0.05$) was observed by One Way ANOVA with a Newman-Keuls Multiple Comparison Test for significance between groups [$F(3, 11) = 6.806$; $p < 0.05$]. (k) ssDNA staining in a concentration response curve similarly show a significant increase in BMA of renal cells. The percent apoptosis and absorbance recorded in negative control wells (PBS-treated and non-treated wells) was subtracted from values shown in j and k. The One Way ANOVA for dose was significant [$F(3, 35) = 105.1$; $p < 0.0001$] ($^{***}p < 0.001$). (l) TUNEL analysis of RPTEC cultured with 100 μg LDL in high and low glucose media show that, under conditions here, glucose and LDL did not increase cell apoptosis when compared to untreated cells in REGM.

BIGH3 is a key mediator of MCM and dMCM proapoptotic activity. RPTEC cultured in REGM plus 25% dMCM showed an 86% increase in BMA when compared to cells cultured in REGM plus 25% RPMI. To examine the percent apoptosis that TGF-β1 and BIGH3 induce, RPTEC were cultured in dMCM in the presence of TGF-β1-blocking and BIGH3-blocking agents (**Figure 7(A)**). A pharmacological inhibitor of TGF-β receptor activation (SB-431542), and anti-TGF-β1 antibody significantly blocked dMCM-induced BMA when compared to DMSO vehicle and serum controls. BIGH3 antiserum effectively blocked BMA when compared to pre-immune serum. A significant increase in BMA was also evident in cells in MCM, in which BIGH3 antiserum,

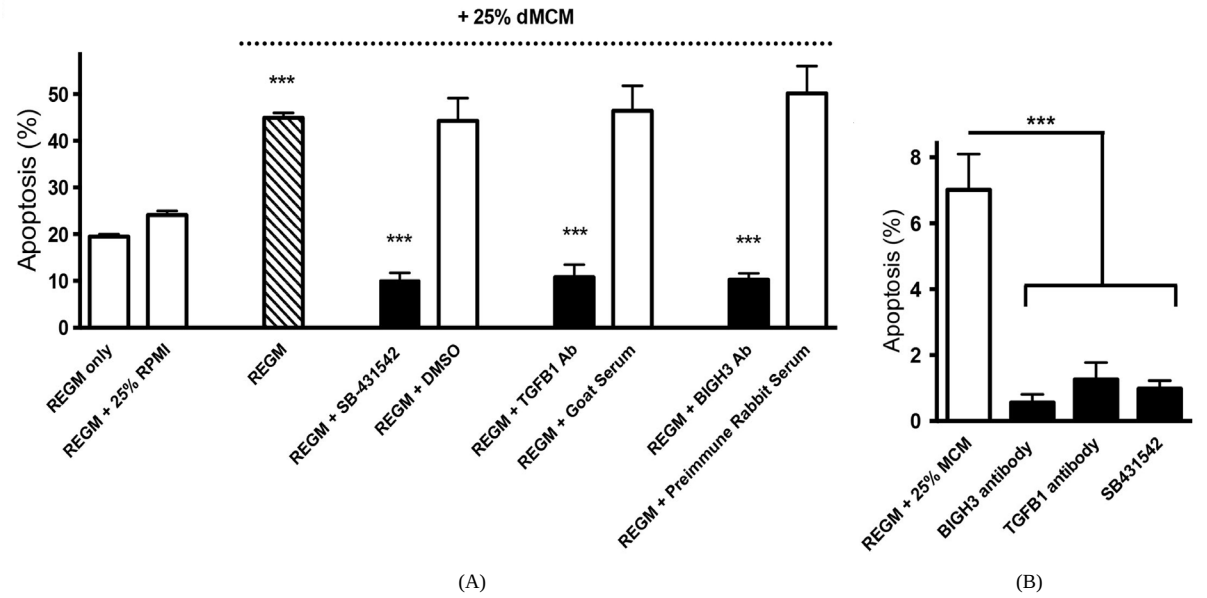

Figure 7. TGF-β1 inhibitors and BIGH3 antiserum block BMA. (A) Shown is BMA of RPTEC cultured in REGM + 25% dMCM with and without SB-431542, TGF-β1 Ab (goat anti-TGF-β1 antibody) and BIGH3 Ab (rabbit polyclonal anti-BIGH3 serum). Controls are vehicle only (DMSO), normal goat serum and preimmune rabbit serum. Three One Way ANOVAs were performed that included the three treatments and then each other treatment with its corresponding control. The effect of SB-431542 was significant [$F(4, 14) = 4.31$; $p < 0.0001$]. REGM + 25% dMCM was significantly different from either baseline controls (REGM only and REGM + 25% RPMI) at $p < 0.001$. REGM + SB-431542 was significantly different from REGM + 25% dMCM at $p < 0.001$. Vehicle DMSO had no effect. The effect of TGF-β1 antibody was significant [$F(4, 14) = 32.7$; $p < 0.0001$]. REGM + TGF-β1 Ab was significantly different from REGM + 25% dMCM at $p < 0.001$. Goat serum had no effect. The effect of BIGH3 antibody was significant [$F(4, 14) = 38.77$; $p < 0.0001$]. The REGM + BIGH3 Ab was significantly different from REGM + 25% dMCM at $p < 0.001$. Preimmune serum had no effect. Each comparison of REGM + SB-431542, REGM + TGF-β1 Ab, and REGM + BIGH3 Ab to REGM only was significant ($p < 0.001$). For each condition $n \geq 3$ ($^{***}p < 0.001$). (B) MCM induced BMA, which was blocked by BIGH3 antiserum, TGF-β1 antibody, and SB-431542. In REGM + 25% MCM the One Way ANOVA for SB-431542, TGF-β1 and BIGH3 Abs was significant $F(3, 23) = 4.986$, $p \leq 0.0001$. For each condition $n \geq 3$. Significance was set at $p < 0.05$.

TGF-β1 antibody, and SB-431542 effectively and significantly blocked BMA (**Figure 7(B)**). We conclude that both MCM and dMCM promote apoptosis through a TGF-β1 and BIGH3-mediated mechanism.

4. Discussion

The results of this study agree with the principle that a hyperglycemic environment promotes macrophage infiltration and kidney damage. This report extends this principle, showing that macrophage-derived TGF-β1 promotes renal cell apoptosis by stimulating expression of the gene *TGFBI*, which encodes the extracellular matrix protein BIGH3. In the diabetic kidney cortex RPTEC are a probable source of BIGH3 [33]. BIGH3 in the cortical interstitial matrix is likely derived from resident mesenchymal cells. Macrophages and BIGH3 protein were broadly distributed in diabetic kidney cortices of our mouse model of diabetic complications [24]. However, immunological analysis unexpectedly revealed an increase in macrophage number, and BIGH3 protein, in the HFD dyslipidemic kidney when compared to non-diabetic kidney cortex. This result indicates a metabolically-stressed renal environment itself stimulates macrophage infiltration and BIGH3 protein expression, supporting the prospect that macrophage TGF-β1 and BIGH3 protein are prediabetic biomarkers. Indeed, others and we have reported that TGF-β1, and BIGH3, are at significantly higher levels in the urine of diabetic patients when compared to urine of non-diabetic individuals [34]-[36].

RPTEC in REGM control medium (without exogenous TGF-β1, BIGH3, or MCMs) expressed relatively low-levels of BIGH3 and exhibited BMA. BIGH3 antiserum and SB-431542 blocked the BMA observed in control medium, raising the possibility that in a healthy normoglycemic environment BIGH3 protein is involved in apoptosis in physiological cell turnover. In this perspective, healthy kidney cells synthesize a low level of new

BIGH3 protein that induces modest, low-level BMA, which sustains cell turnover. Along this line of reasoning, this study supports the hypothesis that increased and accumulating BIGH3 protein in kidney cortex is an indicator of a prediabetic state [37]. Extending this view, a prediabetic environment promotes TGF-β1 signaling [38] BIGH3 synthesis, and BMA, and continues as disease progression develops DN.

It is well established that under physiological conditions BIGH3's C-terminus is cleaved, generating C-terminal fragments less than 3 kDa that induce BMA [7]-[9] [39]. In contrast, a recombinant BIGH3 protein that did not undergo C-terminal cleavage failed to induce apoptosis [8], indicating that C-terminal cleavage is a requisite for BMA. C-terminally cleaved BIGH3 protein has been found *in vivo* in cornea, skeletal muscle and tendon [7] [27]. The peptidases serine protease high-temperature requirement A1 [40], plasmin [31], and matrix metalloproteinase 9 [41] have been implicated in BIGH3 cleavage. However, the extent of cleavage, and which proteases cleave kidney cortical BIGH3 *in vivo*, in healthy tissue, and in metabolically stressed conditions, remains unclear.

We show here that TGF-β1-treated and untreated RPTEC cleave endogenous BIGH3, and thus these cells would be expected to cleave exogenous recombinant BIGH3, explaining the increase in BMA in BIGH3 protein add-back experiments. However we also note that some BIGH3 is cleaved when isolated from Sf9 medium, indicating Sf9 cells cleave BIGH3. Therefore the apoptosis quantified in add-back experiments may have been induced from BIGH3 already cleaved by Sf9 cells (recombinant BIGH3 containing uncleaved and cleaved BIGH3 that was used in add back experiments) and also by RPTEC cleaving the uncleaved BIGH3 recombinant protein that was added back. Mass spectrometry and biochemical analysis revealed C-terminal cleavage accounts for lower mass BIGH3 proteins [7] [9] [31], which we have previously shown to migrate on Western blots as a 62-kDa intermediate band and a stable 60-kDa lower band [9]. C-terminal cleavage generates peptides that likely comprise the integrin-binding sequences EPDIM (residues 615 - 619) and RGD (642 - 644). Both of these integrin-binding sequences have been implicated in BMA, and introduced point mutations in EPDIM and RGD have blocked BMA in various different cell types [8]-[10] [12].

The data presented in this study frame a potential feedback mechanism. Firstly, injured kidney cortex recruits monocyte-derived macrophages. These macrophages provide TGF-β1 that stimulates RPTEC to synthesize and secrete BIGH3. Secondly, C-terminal cleavage generates integrin ligand peptides. In a paracrine or autocrine mechanism the peptides induce BMA, presumably involving integrins. Thirdly, an increase in the number of apoptotic cells promote phagocytic cell infiltration, increasing macrophage number, macrophage-derived TGF-β1, and BMA. Macrophage ingestion of apoptotic bodies induce macrophages to release additional TGF-β1 [19] and moreover, stimulates macrophages themselves to synthesize and secrete BIGH3 protein [42]. RNA-Seq data from TGF-β1 stimulated human kidney epithelial cells compared with microarray data from human DN renal biopsies revealed 179 genes presumed to be upregulated by TGF-β1 signaling. The BIGH3 gene was the most significantly upregulated gene in a TGF-β1 induced transcriptional profile [43]. In addition to RPTEC BMA shown here, evidence suggests that BIGH3 negatively regulates E-cadherin transcription and translation in human renal epithelial cells [43] and dissociate VE-cadherin junctions between endothelial cells [43] [44], thereby promoting epithelial myofibroblast transdifferentiation (EMT) and providing myofibroblast-derived TGF-β1 [45] [46]. Interestingly, integrins αvβ3, αvβ5, αMβ2, and α3β1 bind sequence in the FAS1-like domains of the relatively stable 60-kDa BIGH3 protein [5] [47]-[49] raising the possibility that *in vivo* the 60-kDa BIGH3 protein is a macrophage adhesion substrate, potentiating a robust, self-propagating positive feedback stimulus of a mechanism propelled by a metabolically-stressed environment, macrophage-derived TGF-β1, BIGH3 synthesis, EMT and BMA.

5. Conclusion

This study describes a novel mechanism underlying TGF-β1-induced apoptosis *i.e.* BIGH3 synthesis and cleavage. The results distinguish macrophage-derived TGF-β1 and BIGH3 as potential biomarkers, and targets for prediabetic and diabetic therapeutic interventions. We have recently reported that macrophages infiltrate diabetic human retina, and that our MCMs induced BMA of retinal endothelial cells, implicating BMA in retinal completions in patients with poorly-controlled diabetes [11]. Others have shown that BMA targets retinal pericytes [10], which we have confirmed and show involvement of a similar mechanism leading to an increase in BMA (manuscript in preparation). These findings substantiate the probability that BMA plays a significant role promoting microvascular and macrovascular diseases, underlining the importance of regulating genes encoding

ECM molecules.

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Compliance with Ethical Standards

All applicable institutional guidelines for the care and use of animals were followed.

Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Role of Community Health Practitioners in National Development: The Nigeria Situation

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Abstract

This is a review paper that brings to focus, concepts of Community Health Practice that connect Community Health Practitioners' Roles to National development in view of its composite index improvement measure of social welfare services provision among others for the citizens of a country over time, with particular emphasis on medical care component of such index aimed at reduction in diseases and poverty in the population. The objective of the review work is to determine the extent to which Community Health Practice, particularly by Community Health Practitioners is capable of ensuring National Development in democratic governance or otherwise, in the context of our country, Nigeria. The methodology applied was traditional review of published literatures concerning the subject and findings of operational research of programme implemented by Community Health Practitioners at the Primary Health Care facilities and household level in the communities. This paper emphasizes on Primary Health Care services delivery contribution to National Development, since it is the level where Community Health Practitioners are mainly commissioned to render their services. Home-Based Care Strategy for Integrated Maternal, Newborn and Child Health piloted in three (3) local government areas (Ahoada West, Etche and Oyigbo) in Rivers State, Nigeria, in 2012 and implemented by Community Health Practitioners, aimed at reducing maternal, newborn and child morbidity and mortality by 20% by 2015 in line with the United Nations (UN) Millennium Development Goals 4 and 5, had been shown to achieve an average of 26% improvement in utilization of maternal and newborn health services, an average of 27% overall reduction in maternal malnutrition status, an average of 14% overall improvement in under 5 years malnutrition status among others in 2013 on comparing with baseline indicators. Nigeria also attained 80% coverage in routine immunization in most vaccine preventable diseases except Tetanus Toxiod (TT) 2 (54%) in 2013 to achieve herd immunity of the community to prevent transmission of disease pathogen to cause a disease. Community Health Practitioners are the frontline Primary Health Care Professionals charged with the responsibility of implementation of immunization programmes in Nigeria and therefore contributing significantly to

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the prevention and control of targeted vaccine preventable diseases in Nigeria Health System. Our findings on factors militating against Community Health Practitioners' Roles in National Development as elicited in this paper may form basis for empirical studies to determine the level of significance of each of these factors. In conclusion, it is when the Community Health parameters are adequately addressed that we can ensure sustainable National Development and we can say we have succeeded in our various strategic agenda of government at whatever level that makes up the complex whole. This brings to fore, the importance of the roles of Community Health Practitioners in health care delivery to National Development in the context of our country, Nigeria.

Keywords

National, Development, National Development, Community, Community Health Practitioners, Roles, Primary Health Care, Promotive, Preventive, Curative, Rehabilitative, Accessibility, Acceptability, Affordability, Rural, Nigeria Health System

1. Introduction

Community Health and National Development are inextricably tied together, in which the evaluation of National Development cannot be complete without the Community Health component. This review paper seeks to look at the extent to which Community Health Practice, particularly by Community Health Practitioners is capable of ensuring National Development in democratic governance or otherwise, in the context of our country, Nigeria. For us to do this to the reasonable understanding of what the subject entails, we shall look at the separate key words or concepts implied, then we bring to focus specific roles of Community Health Practitioners in National Development, factors militating against such roles and to draw conclusion in these perspectives.

1.1. What is National Development?

The term National Development is framed from two entities—National and Development. The Longman dictionary of contemporary English, viewed National as a phenomenon embracing a whole nation. On the other hand, Development as a concept is difficult to have a universally accepted definition. According to [1], development is taken to involve not only economic growth, but also notion of equitable distribution, provision of health care, education, housing and other essential services all intended to improve the individual and collective quality of life. While in the view of [2], development is an idea that seeks in all ramifications to improve the conditions of human existence. Furthermore, it implies improvement in material well being of all citizens, not the most powerful and rich alone, in a sustainable way such that today's consumption does not imperil the future, it also demands that poverty and inequality of access to the good things of life be removed or drastically reduced. It seeks to improve personal physical security and livelihoods and expansion of life chances.

It is therefore, unequivocally clears that development as a concept is not just an economic exercise alone, but reaches out to involve both socio-economic and political issues and transcends all aspects of societal life.

National development therefore can be described as the overall development or collective socio-economic, political as well as religious advancement of a country or nation. This is best achieved through development planning, which can be described as the country's collection of strategies mapped out by the government [3].

National development is also seen as the ability of a country or countries to improve the social welfare of the people for example by providing social amenities like quality education, potable water, transportation infrastructure, medical care, etc., with the aim of achieving increase in real per capita income as well as reduction in inequality, poverty, illiteracy and diseases. However, our emphasis in this paper is health care delivery aspect, more so the primary health care component within the frame works of its contribution to national development.

1.2. What Is Health?

Health they say is Wealth and wealth is created and/or measured by factors of productivity. Productivity; in the present context means a measure of the health care needs of the public so provided in comparison to resources

put in place to do so.

Effective service delivery in the health sector entails several factors and/or components that must be harnessed adequately in a synergistic manner to achieve the aims and aspiration of health care as encapsulated in its variable terms of Promotive, Preventive, Curative and Rehabilitative health care services.

The World Health Organization (WHO) defines health in the year 1948 as a "complete state of physical, mental and social well-being and not merely the absence of disease or infirmity". Whilst criticized as too utopian and unachievable by some, [4] [5], it aptly presents the broad nature of health in its many meanings, influences, and outcomes, guiding its conception away from the purely biomedical perspective. This clearly shows the complexity involved in the provision of health care needs of the public and hence its measurement in terms of productivity as earlier defined which are bound to vary depending on the aspect that is being viewed and the associated pattern of interpretation at the circumstance, because health is dynamic in nature. It is probably in realization of this, that the Executive Board of the World Health Organization (WHO) considered redefining "health" by inclusion of the fourth dimension of health (*spiritual health*) as thus: "A dynamic state of complete physical, mental, social and spiritual well being, and not merely the absence of disease or infirmity" [6].

1.3. What are Community and Community Health?

Community is the hub of Community Health Practice, anything short of that is not considered as Community Health Practice. It is the essential laboratory for practice of teaching, training and research in the subject of community medicine/health [7].

The definition of community has been varied because of its diversity and complexity, such that no common or universally acceptable definition is attempted. Community is also seen as a group of people living within a common geographical boundary that may not necessarily be of the same origin as in language, culture and practices, but are often of the spirit of joint ownership of issues of common interest and advancement. According to [8], a community is a whole entity that functions because of the interdependence of its parts or subsystems. Eight subsystems plus the community core are identified. The community core is; history, socio-demographic characteristics, vital statistics, values/beliefs/religions, while the eight subsystems are; Physical environment, Education, Safety and transportation, Politics and government, Health and social services, Communication, Economics and recreation.

The idea of the community as the centre of health services delivery was advocated as far back in 1960s. From the concept of Basic Health Services, Primary Health Care emerged. In this regard, the principle of health services in relation to availability, accessibility, acceptability and appropriateness became important considerations in WHO health policy from the late 1960s and into the 1970s [9].

In the works of [10], Community Health is defined in the following perspective:

1) Part of medicine which is concerned with the health of the whole population and the prevention of diseases from which the population suffers.

2) It identifies the root causes of diseases and health problems not only from the individual but also from family, the community and the environment.

3) The community resources are utilized principally in solving their problems. The resources from government and private sector can also be used.

4) It aims at giving the highest level of health for all people in the community and such level includes that of physical, mental, moral, social and spiritual health.

In the reasoning of [11], Community Health consists of principles and practices aimed at achieving prevention of premature death, disabilities and diseases through organized Community efforts with a view to assuring the promotion of optimal health of members of a Community in the context of their environment. Optimal health is said to mean a balance of physical, emotional, social, spiritual and intellectual health.

Community Health could also be seen as the application of simple but scientifically sound and culturally acceptable methods and skills in the prevention, promotion, rehabilitation and or treatment of health conditions in the population or community in reference.

"Community Health" parameters are different from health parameters of an individual. Community health can be measured through indicators of economics such as Gross National Product, Gross National Income and Per Capita Income, as well as life expectancy, under five mortality, infant mortality, literacy level, composite index like human development index, and maternal mortality rate [12]-[14]. The other indicators of community health are environmental indicators, demographic, health services, health care utilization and health policy indicators [7].

A community is seen to be healthy if it enjoys sound health where disease and death rate are considerably low, it is not threatened with bad environments and its economy is sound and the health practices are sound and based on scientific evidences. It is also, seen to be healthy if it records high literacy level and having a balanced demographic sex ratio and the people live long, quality of life is good and human development index is high.

A village is equally seen to be healthy when it has; safe source of improved water supply, safe method of waste water disposal, paved streets, disposal of garbage, refuse and animal excreta by manure pits, people use sanitary latrines, female literacy is high, girls enrolment is universal, deliveries are conducted by trained persons, birth rate and death rate are within acceptable limits, immunization coverage is high and housing condition is good [7].

1.4. Who Are Community Health Practitioners?

Community Health Practitioners are Primary Health Care Professionals who had undertaken a standard training programme and passed the examinations set by the training institution and national regulatory body meant for the cadre and licensed [15]. They were created in 1978 by the then Military administration to work at the Primary Health Care system, with the aim of correcting the short-fall observed during third National Development Plan (1975-1980) period of our country, Nigeria. According to [16], Community Health Practitioners are "core" polyvalent workers and these have remained the core Primary Health Care Workers in Nigerian Primary Health Care system. It is a family comprising:

Primary Health Care Tutors,
Community Health Officers,
Community Health Supervisors which training was stopped in 1990,
Community Health Assistants (*now Community Health Extension Workers* (*CHEWs*), *and*
Community Health Aides (*now Junior Community Health Extension Workers* (*JCHEWs*).

The CHEWs and JCHEWs, the most important members of the Primary Health Care, are intended to be based in the community (50% and 80% of the time respectively), particularly, in the villages where they will motivate the community members to action in the provision of health services. In this regards, they are seen as architects of Community participation—a prerequisite for transforming a community from its traditional past to the age of science.

1.5. What Is Primary Health Care?

The concept of Primary Health Care started when the World Health Assembly at a meeting of health professionals from all over the world at Alma-Ata in U.S.S.R in September, 1978, wherein they propounded a new concept of health care delivery-Primary Health Care. Nigeria launched a national health policy in October 1988, the bedrock of the policy was primary health care which form the integral part of the national health care system.

The conference defined *Primary Health Care as essential health care based on practical, scientifically sound and socially acceptable methods and technology, made universally accessible to individuals and families in the community through their full participation at a cost the community and country can afford to maintain at every stage of their development in the spirit of self reliance and self determination.*

As an integral part of the country's health system, it remained the central function and main focus, and of the overall social and economic development of the community. It is the first level of contact of individuals, the family and community with the national health system bringing health care as close as possible to where people live and work and constitutes the first element of continuing health care process.

The concept of Primary Health Care is therefore explained in the following perspective:

1) It integrates preventive, promotive and curative services using the type of technology the community will accept at the level it can afford with an efficient and effective system of supervision and referral.

2) It involves in addition all health sections, all health related sectors. Any aspect of National and Community development in particular, the agriculture, animal husbandry, food and industry, Education, Housing, Public utility and works, Communications and other sectors and demand the coordinated efforts of all these sectors.

3) It also involves a close partnership between the community and government in the development of resources and health care.

The import of the primary health care system is that:

1) Health care should trickle down to the grass-root. This means that there should be better coverage of the

population with health care services.

2) There should be more emphasis on preventive as well as basic curative services to the majority of the population.

3) Appropriate technology is being used thereby reducing cost and therefore making health care affordable.

4) Appropriate and essential health care is being provided since community diagnosis as a major component of the primary health care is carried out in the local government areas and communities to ensure solving specific prevalent health problems in the context of such communities.

5) The primary health care system is being co-managed by various health development committees which are made up mainly of the local population, therefore, encouraging community participation which pave way for self-reliance and self-determination.

6) Emphasis is laid on inter-sectoral collaboration, therefore, avoiding duplication of efforts that enabled fund to be reserved.

2. Community Health Practitioners' Roles in National Development

Report showed that healthcare costs continue to rise as medical care becomes more complex and the burden of disease shifts toward chronic illnesses [17]. Focus on racial and ethnic disparities in health outcomes had also motivated novel methods of serving disadvantaged populations [18].

Community health through the application of primary health care principles and concepts focuses more on the well-being of an entire population rather than that of the individual. Investment in human health had been a powerful means to encourage economic growth, protect the environment, and reduce poverty [19]. Most public health investment-for instance, immunization or safe water-bring with them benefits larger than their costs.

Community Health Practitioners, particularly, the CHEWs and JCHEWs having constant touch with the households in their community-based duties and "while diagnosing and treating common conditions with simple but scientifically sound measures, identifying pregnant women and ensuring that they deliver safely, or identifying malnourished children and providing health education in the community, the Community Health Extension Workers mobilizes the community for preventive action as in the building of latrines, wells and roads. This is no mean task and to call them "aides" is therefore misleading and belittles their important role" [20].

Community health practitioners essentially try to prevent problems from happening or re-occurring through implementation of educational programs, administration of health care services, and conduct of research, in contrast to clinical professionals, such as doctors and nurses, who focus primarily on treating individuals after they become sick or injured. They are also concerned with limiting health disparities and a large part of Community health practice by Community Health Practitioners is the fight for health care equity, quality, and accessibility through taking health care services to the door steps of the citizenry in the rural area in particular.

Poor geographical and economic access to health care services had been a bane to effective disease control efforts in Nigeria.

According to [21] official documents, as graphically presented in **Figure 1**, only an estimated 54% of Nigerians have access to modern health services. The document also recognizes that "rural communities and the urban poor were not well served". The issue in question is access to available care, what happens to the 46% of the population without access to modern health, probably medical care [22].

In this regards Community Health Practitioners can contribute significantly to improvements in community members' access to, adherence to and continuity of care, as well as reducing health care costs. This is so because, Community health practice emphasizes coordinated primary and preventive services that promote reductions in health disparities for low-income individuals, racial and ethnic minorities, rural communities, and other underserved populations.

Community health practice also emphasizes reduction in costs to health systems; in this regards, the community health practitioner model of care ensures reduction in the use of costlier providers of care, such as emergency departments and hospitals. What more can we say, the outcome of these services or duties by Community Health Practitioners form the essential ingredient of National Development where ever primary health care is sincerely practiced.

For instance, Home-Based Care Strategy for Integrated Maternal, Newborn and Child Health piloted in three (3) local government areas (Ahoada West, Etche and Oyigbo) in Rivers State, Nigeria, in 2012, targeting about 189,913 population and implemented by Community Health Practitioners, aimed at reducing maternal, newborn

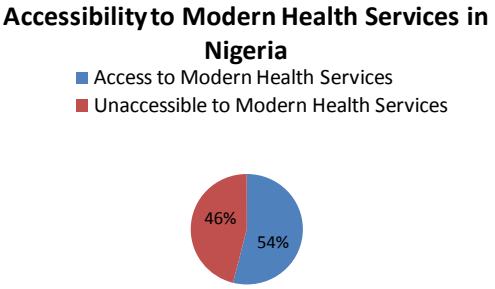

Figure 1. Accessibility to modern health services in Nigeria. Source: [21].

and child morbidity and mortality by 20% by 2015 in line with the United Nations (UN) Millennium Development Goals 4 and 5, had been shown to achieve an average of 26% improvement in utilization of maternal and newborn health services, an average of 27% overall reduction in maternal malnutrition status, an average of 14% overall improvement in under 5 years malnutrition status among others in 2013 on comparing with baseline indicators, etc. [23]. These variables had been shown from statistics as conditions that contribute to the maternal, newborn and child morbidity and mortality in sub-Saharan Africa, where Nigeria is located.

It is also worthy of note that Nigeria attained 80% coverage in routine immunization in most vaccine preventable diseases except Tetanus Toxiod (TT) 2 (54%) in 2013 to achieve herd immunity of the community [24]. Herd immunity is the total immunity level of a community capable of preventing transmission of disease pathogen to cause a disease. It is equally on record that Community Health Practitioners are the frontline Primary Health Care Professionals charged with the responsibility of implementation of immunization programmes in Nigeria and therefore contributing significantly to the prevention and control of targeted vaccine preventable diseases in Nigeria Health System.

In the overall analysis, when a community remains relatively healthy through simple but scientifically sound and culturally accepted methods which are basically from within the community, it is bound to be sustainable and it is only a sustainably healthy community that can venture in other development activities. It is for this reason, quality and affordable health care services is viewed as the foundation of National Development if it were not so "Health" cannot be "Wealth" again. It is a healthy mind in healthy body that brings in several other components to complex whole and in the present context the contribution of Community Health Practitioners by virtue of their roles in health care services delivery to ensure equitable, quality, accessible and affordable primary health care services toward National Development.

3. Factors Militating against Community Health Practitioners' Roles in National Development

1) It is true that Primary Health Centres were established in both rural and urban areas in Nigeria with the aim to ensuring equity and easy access to health care; however, the rural populations in Nigeria are seriously underserved when compared with their urban counterparts. What we mean is that, the distribution of Primary Health Care (PHC) facilities is skewed in favour of urban areas, whereas the populations of the rural communities where Community Health Practitioners are commissioned to serve constitute about 70% of the general population, therefore making coverage a challenge and perhaps the attainment of sustainable National Development in view of our presentation difficult.

2) Most PHC facilities, for Community Health Practitioners to perform their roles are in various stages of disrepair, with equipment and infrastructure being either absent or obsolete, the referral system almost non-existent, non-functional or facing serious criticism and rejection by the higher level care providers. These had the capacity to affect their morale and motivational spirit as well as to endanger continuity of care, which outcome had never been different from poor utilization of available health care services occasioned by dissatisfaction of services by clients/patients. In such situation, sustainable National Development through Primary Health Care services delivery may be far from expectation.

3) Poor political will by successive governments in funding community health programmes, leading to donor driven health programmes in Nigeria: This also had the capacity to affect sustainability of progress and or

successes recorded over time, once donors' contributions are withdrawn and so may reduce the efforts put in by Community Health Practitioners in Primary Health Care services delivery to attain National Development.

4) Inadequate number of Community Health Practitioners in the public service as well as their uneven distribution: This equally had the capacity to exert excessive pressure on available manpower, so much so that health care services may be limited to populations that had the advantage to access such services and such had been a challenge to adequate coverage of targeted population to translate to what we can say sustainable National Development, through Primary Health Care services.

5) Poor logistic system in reaching out to difficult-to-reach communities/settlements: Since it is practically impossible to provide functional health facilities in all communities/settlements by government, it behoves that functional logistic system be put in place to carry out planned outreach health care delivery services to make health care services more accessible, to come in line with the concept of National Development. However, this had not been done smoothly, thereby limiting a major role of the Community Health Practitioners and so considered counterproductive to National Development.

6) Lack of understanding of Primary Health Care among health professionals and decision-makers resulting in poor quality services: Primary Health Care is the first level of contact with the National Health System, for preventive and promotive health care services as well as early detection and prompt treatment of cases and referral of more serious cases to the secondary and tertiary levels health care. Rather, what had been observed is that, these preventive and promotive health care services such as immunization and primary infant welfare clinic just to mention but few are carried out even at tertiary level health care (Teaching Hospitals), whose management are necessarily part of the decision making body in Nigeria Health System. This in our consideration exerts negative influence on the decisions of policy makers in making the working environment for Community Health Practitioners conducive and devoid of professional wrangling and role conflict. Obviously, the resultant of this is poor quality health care services that negate sustainable National Development.

7) Inadequate training and retraining programme for Community Health Practitioners commensurate with their responsibilities and roles: One of the cardinal strengths in health care delivery at whatever level is training and retraining, but it had been difficult for Community Health Practitioners to secure approval and sponsorship for in-service training and professional continuing education for proficiency and enhancement of their performance. This in no doubt had been a source of discouragement to Community Health Practitioners to render their all important roles in the health care industry towards National Development.

8) Poor remuneration to Community Health Practitioners that dampens their zeal to render their all important roles towards National Development: The joy of every worker is adequate and regular remuneration in its diverse forms. This had not been easy to come by, as salary, even as not being adequate, had not been so regular; promotion had also not been regular, adequate funding for running health facilities' operations and programme had been no go area. Such situations are inimical to quality health care delivery to attain National Development in the context of this paper.

These factors, as elicited above were findings from interactive sessions of review meetings of Home-Based Care for Integrated Maternal, Newborn and Child Health programme, piloted in three (3) Local Government Areas, namely Ahoada West, Etche and Oyigbo in Rivers State, Nigeria from 2012 to 2014, implemented by Community Health Practitioners in these Local Government Areas, coordinated and supervised by the corresponding author of this paper among other team of supervisors through the Rivers State Primary Health Care Management Board.

4. Recommendations

No doubt, these findings may form the basis for empirical studies to determine the level of significance of each of these factors to guide policy formulation and implementation in Primary Health Care services delivery by Community Health Practitioners and indeed other Primary Health Care professionals to achieve sustainable National Development.

Successive governments should address these factors with appropriate policies, legislations and enforcement to sustain the roles of Community Health Practitioners toward National Development.

5. Conclusion

The definition of National Development, as presented in this paper, portrays its composite index requirement

towards achieving economic, socio-demographic and health outcome of a country, state, local government or community, where in community health parameters are fundamental. It is when the Community health parameters are adequately addressed that we can ensure sustainable National Development and we can say we have succeeded in our various strategic agenda of government at whatever level that makes up the complex whole. This brings to fore, the importance of the roles of Community Health Practitioners in health care delivery to National Development in the context of our country, Nigeria.

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