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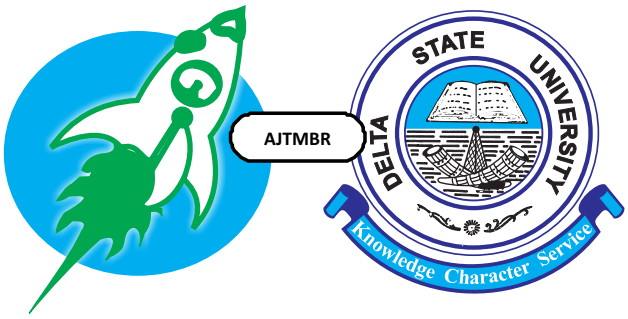

The Journal is the Official Publication of the College of Health Sciences, Delta State University, Abraka, Nigeria.

ISSN: 2141-6397

Focus and Scope

The African Journal of Tropical Medicine and Biomedical Research is a multidisciplinary and international journal published by the College of Health Sciences, Delta State University of Abraka, Nigeria. It provides a forum for Authors working in Africa to share their research findings on all aspects of Tropical Medicine and Biomedical Sciences and to disseminate innovative, relevant and useful information on tropical medicine and biomedical sciences throughout the continent. The journal will publish original research articles, reviews, editorials, commentaries, short reports, case reports and letters to the editor. Articles are welcome in all branches of medicine and dentistry including basic sciences (Anatomy, Biochemistry, Physiology, Pharmacology, Psychology, Nursing etc) and clinical sciences (Internal Medicine, Surgery, Obstetrics and Gynaecology, Dental surgery, Child Health, Laboratory Sciences, Radiology, Community Medicine, etc). Articles are also welcome from social science researchers that document the intermediating and background social factors influencing health in countries of Africa. Priority will be given to publication of articles that describe the application of the principles of primary health care in the prevention and treatment of diseases.

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Editorial

Quantification of Unsafe Abortion in Nigeria and *Possible Panacea*

Omo-Aghoja LO

(Largely culled from an earlier publication by the author: Omo-Aghoja LO. Unsafe Abortion and miscarriages: Quantification and public health related perspectives. Port Harcourt Medical Journal 2013; 7:219-231).

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Introduction

Induced abortion continues to be a major public health issue that evokes social, political, legal, ethical, cultural, religious sentiments and debates in all societies.[1] And existing data indicates that unsafe abortion is a leading cause of maternal morbidity and mortality in developing countries.[1]

Discussion

About 53 million pregnancies are estimated to be terminated each year worldwide, over 20 million of these are unsafe.[2] Worldwide, 38% of the estimated 210 million pregnancies yearly are unplanned and 22% of these end up aborted, while 36% of the 182 million pregnancies occurring in developing countries including Nigeria are unplanned and 20% of these end up aborted. Many of these abortions are unsafe and Nigeria accounts for 20% of global estimates of abortion related deaths.[2] Of the 67,800 women that die from abortion each year, only 300 of these occur in developed countries and others in developing countries.[3] In developing countries, there are 330/100,000 abortion related deaths and 0.7/100,000 in developed countries.[4] Africa has the highest mortality ratio of 680/100,000. Indeed, the risk of dying from unsafe abortion in Africa is 1 in 150 and 1 in 1,900 in Europe.[4] These deaths occur in young adolescents, poor women and largely rural women with unmet contraceptive needs which is largely responsible for why they undertake abortion.[1-5] These abortions are rendered unsafe because of the restrictive abortion laws in Nigeria that have driven the practice underground and undertaken by backstreet professionals.

It is instructive to note that not only do large numbers of women require medical care because of unsafe abortion, but some of these women are likely to suffer long-term health consequences, while others will die as a result. In 1996, an estimated 610,000 abortions occurred (25 per 1,000 women of childbearing age), of which 142,000 resulted in complications severe enough to require hospitalizations.[1-5] The number of abortions was estimated to have risen to 760,000 in

2006. In 2012, an estimated 1.25 million induced abortions occurred in Nigeria, equivalent to a rate of 33 abortions per 1,000 women aged 15–49.[6] The estimated unintended pregnancy rate was 59 per 1,000 women aged 15–49. Fifty-six percent of unintended pregnancies were resolved by abortion. About 212,000 women were treated for complications of unsafe abortion, representing a treatment rate of 5.6 per 1,000 women of reproductive age, and an additional 285,000 experienced serious health consequences but did not receive the treatment they needed. Unsafe abortions are major reason Nigeria's maternal mortality rate is one of the world's highest. According to conservative estimates, more than 3,000 women die annually in Nigeria because of unsafe abortion.[1]

The World Health Organization estimates that each year, 12,000 deaths in West Africa result from unsafe abortion.[2] Henshaw et al in 1998 revealed that the rate of abortion is much lower in the poor, rural regions of northern Nigeria than in the more economically developed southern regions.[2] Regional differences in the level of abortion are considerable. Based on the best estimates from the work, the abortion rate is highest in the Southwest (46 abortions per 1,000 women), somewhat lower in the Southeast (32 abortions per 1,000) and much lower in the two northern regions (10-13 per 1,000). In the Southwest, the ratio of treatment for complications from abortions to that for miscarriages is higher than in any other region about 65,000 complications compared with nearly 46,000 miscarriages; in the Northwest, some 12,000 cases of abortion complications are treated annually, compared with about 28,000 miscarriages (not shown). Additionally, an estimated 40% of abortions were reported to be performed by physicians in established health facilities, while the rest are performed by nonphysician providers.

Of all hospitals and clinics that provide abortions, 87% are privately owned, and abortions are provided by non-specialist general practitioners at 73%. Three-quarters of physician providers use manual vacuum aspiration to perform abortions, and 51% of providers who treat abortion complications use this method. Physician respondents believe that the main methods used by nurses, midwives and other nonphysicians to induce abortions are dilation and curettage, hormonal or synthetic drugs and insertion of solid or sharp objects. Finally, the proportion of abortions performed by nonphysicians is highest in the Northeast (72% of procedures, compared with a national average of 60%).[2]

Possible panacea

Clearly unsafe abortion remains a major challenge and significant contributor to maternal morbidity and mortality. If the set sustainable development goal of maternal mortality reduction is to be achieved and the ICPD programme of action realizable in Nigeria, then concerted efforts must be made and geared towards addressing the key reasons and all intermediating factors why women undertake unsafe abortion. It is against this backdrop that the following recommendations are proffered as relevant interventions that will help.

Firstly, it is necessary to advocate for a review of the existing restrictive laws in Nigeria and other developing countries in order to reduce the high morbidity and mortality from unsafe abortion.[7] Advocacy and public health education that would increase the women's and provider's knowledge of the revised law,

help deal with the issue of religious and socio-cultural stigmatization of abortion, would certainly increase the benefits of liberalization in reducing mortality associated with unsafe abortion and this is advocated for priority attention. Secondly, is making available and creating access to comprehensivee contraceptive services. The fact that contraception is a necessary step to reducing the incidence of unwanted pregnancy (the real reason women will procure abortion) has been very well captured in the consensus statement by the International Federation of Gynecology and Obstetrics (FIGO), International Confederation of Midwives (ICM), International Council of Nurses (ICN), and the United States Agency for International Development (USAID) on 25 September 2009*: "If the woman we treat for post abortion complications is there because she could not get contraception, we have failed her. If she leaves without family planning, we have failed her twice."* (1994, Postabortion Care (PAC) Consortium, International Conference on Population and Development (ICPD), Cairo). Additionally, a comprehensive sexual and reproductive health education must be put in place in our schools and in the community. Extensive advocacy activities and programs should be instituted to ensure wide coverage and dissemination of the facts. Barriers to obtaining a safe abortion by a trained provider could be reduced by publicizing the availability of such services and by making abortion available at low cost in more facilities, including public hospitals and clinics. More training in the safest abortion methods could be provided to physicians and others who perform abortions, and more physicians could be encouraged to offer the service. Women empowerment and gender equity is also advocated for.

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Common Precipitants of Acute Decompensated Heart Failure

Ogbemudia, EJ, Umuerri, EM

Abstract

Introduction: Acute decompensated heart failure (ADHF) is a common acute heart failure syndrome, and it is often caused by certain factors called precipitants. However, the common precipitants of ADHF in our locale have not been well documented.
Aim: To determine the common factors that precipitate acute decompensated heart failure in our locale.
Materials and Method: This was a retrospective study of acute heart failure patients hospitalized from January 2019 to June 2020 in a university teaching hospital. The age, gender, blood pressures were extracted from the records. Others included the cause of heart failure, precipitant of acute decompensation and left ventricular ejection fraction. The data were managed as appropriate, and p values less than 0.05 were statistically significant.
Results: There were 165 cases of ADHF and 86 (52.1%) were males with a median age of 57 years. Precipitants of ADHF were identified in 128(77.6%) of cases. The prevalence of the precipitants were pneumonia (PMN) 66 (51.5%), poor drug adherence (PDA) 47(36.7%), arrhythmia 38 (29.7%), urinary tract infections (UTI) 16.4% and renal dysfunction (10.2%). The others were acute exacerbation of chronic obstructive pulmonary disease (COPD) (6.3%), severe hypertension (4.7%). The association of PMN, PDA and arrhythmias among age groups yielded p values of 0.019, 0.010 and 0.016, respectively.
Conclusion: Most cases of ADHF (77.6%) are caused by precipitants. Pneumonia, poor drug adherence and arrhythmias are the common precipitants of ADHF, and they are associated with the elderly. Therefore, these factors should be actively sought for during initial evaluation, and measures for prevention initiated.
Keywords: Acute decompensated heart failure, precipitant, common

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Introduction

Acute decompensated heart failure (ADHF) is the sudden or gradual worsening of heart failure symptoms in a previously stable HF patient.[1] It is one of the acute heart failure (AHF) syndromes, a common medical cause of hospitalization. Hospitalizations for ADHF contribute significantly (70%) to the economic burden of its management.[2]

The precipitant of ADHF is usually an acute illness not related to the evolution of the primary cardiac disease. It worsens cardiac function and has prognostic implications.[3,4] Fortunately, some precipitants such as poor drug adherence (PDA) are preventable.[5,6]

Early identification and adequate management of the precipitant optimizes the treatment of ADHF, which positively

influences outcomes. However, the common factors that precipitate ADHF have not been well documented in our locale. Indeed, the prevalence of the different precipitants of ADHF has not been extensively investigated.

In a study of the pattern, precipitants, and short-term outcomes of heart failure, Baba et al. [7] reported chest infections, poor drug adherence and urinary tract infections as the common precipitants of ADHF, but the associated factors were not determined. Furthermore, the study was conducted in North-eastern Nigeria, a region with significant socio-cultural differences from the South. Ogah et al., [8] also documented factors that precipitate AHF in a study of the contemporary profile and clinical characteristics of HF patients, but they were not highlighted because it was not the study's primary objective. The common factors that precipitate ADHF in our locale therefore need to be further investigated.

This study's information should expedite the initial evaluation of patients with ADHF in the emergency room in terms of early identification of the precipitant of exacerbation and institution of appropriate therapy. It should also inform stakeholders on appropriate measures to initiate to forestall repeated exacerbations of HF.

Therefore, this study aims to determine the common factors that precipitate ADHF in our practice.

Materials and Methods

This retrospective cross-sectional study of patients hospitalized for acute decompensated heart failure was conducted in the medical wards of a tertiary health centre. The hospital's research and ethics committee reviewed and approved the protocol, and the principles of the Helsinki declaration guided the conduct of the study.

The minimum sample size was determined with the Fisher statistical formula: $z^2p\ (1 - p)/d.^2$The prevalence of AHF applied was 11% [9] with a confidence interval of 95% (1.96) and degree of accuracy set at 0.05. This gave a sample size of 150; an attrition rate of 10% was applied, which gave a final number of 165. Data of patients with ADHF hospitalized from January 2019 to June 2020 were retrieved from the records. They included age, gender, New York Heart Association (NYHA) functional class and blood pressure. Others were the aetiology of HF, the precipitants and left ventricular ejection fraction.

Definition of Terms

Acute decompensated heart failure: Worsening dyspnoea in a previously stable heart failure patient (NYHA class 3 or 4).

Pneumonia: A history of cough and fever with abnormal chest signs and infiltrates on chest x-ray.

Poor drug adherence: Was determined by patents' self-reported failure to take medications daily as prescribed.

Atrial fibrillation: Absent P waves, irregular narrow QRS complexes with a fibrillar baseline.

Ventricular tachycardia: Regular broad complex tachycardia with fusion or capture beats.

Urinary Tract Infection: Clinical features of cystitis (dysuria, frequency) or pyelonephritis (fever and flank pain) and abnormal urine microscopy with or without a positive urine culture.

Renal dysfunction: Glomerular filtration rate < 60mls/min in the setting of concomitant acute or chronic renal disease (cardiorenal syndrome type 3 and 4)

Acute Exacerbation of chronic obstructive pulmonary disease (COPD): Cough, dyspnoea and wheeze in a previously stable COPD patient.

Severe Hypertension: Features of acute pulmonary oedema with blood pressure greater than 160/100mmHg

Acute myocardial infarction (AMI): The diagnosis of AMI was made based on one or more of the following: Symptoms of myocardial ischaemia, significant ST-segment / T wave changes, and new left bundle branch block (LBBB) and development of pathological Q waves in the presence of elevated cardiac troponin T.

Acute pulmonary embolism (APE): Symptoms suggestive of PE (dyspnoea, chest pain) with D-dimers' elevation and confirmed on CT pulmonary angiography.

Data Analysis:
Data analysis was with the Statistical Product and Service Solutions (SPSS) version 20 Inc. Chicago, Il, USA software. Continuous variables such as the age, blood pressure and ejection fraction were expressed as median and interquartile ranges. The gender, age group, blood pressure category and cause of heart failure were expressed as frequencies. Comparisons were made with the chi-square test, and p values < 0.05 were considered statistically significant.

The cases were grouped into three age groups, the young (18 – 39), middle-aged (40 – 64) and the elderly (65 and above).[10] Systolic blood pressures < 100mmHg were categorized as low blood pressure, while 100 - 139mmHg and ≥ 140mm Hg were grouped as normal and high blood pressure groups, respectively. Ejection fraction ≤ 40%, 41% to 49% and ≥ 50% were described as HF with reduced, mid-range and preserved ejection fractions, respectively.

Results:
One hundred and sixty – fifty (165) cases of ADHF were studied with a median age of 57 years. Nineteen (11.5%) had no formal education, while 65 (39.4%) ,39 (23.6%), and 42 (25.4%) had primary, secondary and tertiary levels of education respectively. Precipitants of ADHF were identified in 128 (77.6%) of cases. but no precipitant was identified in 37 (22.4%). Sixty - five (50.8%) of those cases with precipitant had only one precipitant, while 63 (49.2%) had more than one precipitant of ADHF.

TABLE 1: BASELINE DEMOGRAPHIC AND CLINICAL VARIABLES OF ALL CASES

Clinical characteristics	Median	IQR
AGE (yrs)	57.0	49.5-70.5
SBP (mmHg)	120.0	110.0-150.0
DBP (mmHg)	80.0	70.0-100.0
MAP (mmHg)	97.0	27 – 173.0
LVEF (%)	38.0	25.2-45.0

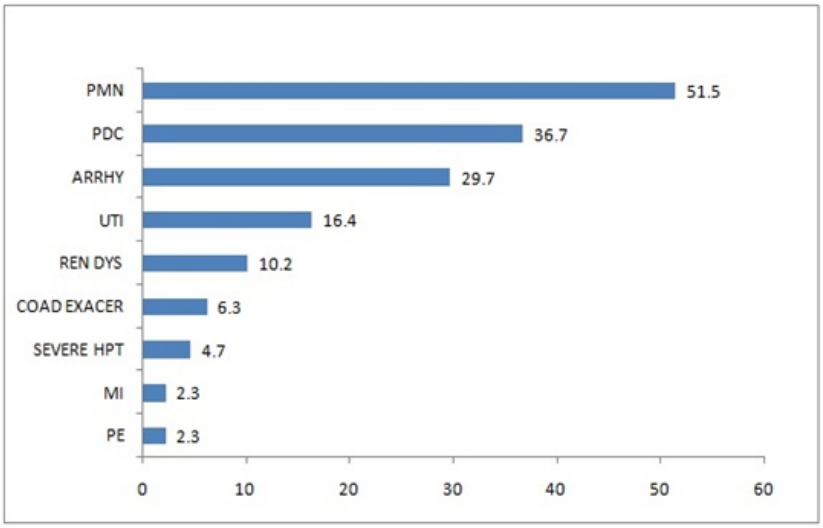
SBP - Systolic blood pressure, **DBP -** Diastolic blood pressure, **LVEF -** Left ventricular ejection fraction, **IQR –** Inter quartile range, **MAP** – Mean arterial pressure

TABLE 2: DISTRIBUTION OF CASES AMONG DEMOGRAPHIC AND CLINICAL VARIABLES

Clinical characteristics	Categories	No (%)
Sex	Male	86 (52.1)
	Female	79 (47.9)
Age group	Young	23 (13.9)
	Middle	81 (49.1)
	Elderly	61(37.0)
NYHA class	111	41 (24.8%)
	1V	124 (75.2%)
Blood pressure group	Low	25 (15.2)
	Normal	85 (51.5)
	High	55 (33.3)
Cause of heart failure	CMP	26 (15.8)
	CONG	5 (3.0)
	COPUL	12 (7.3)
	HHD	82 (49.7)
	RHD	40 (24.2)
Left ventricular ejection fraction	HFmrEF	43 (26.0)
	HFpEF	30 (18.2)
	HFrEF	92 (55.8)

CMP: Cardiomyopathy, CONG: Congenital heart disease, COPUL: Cor pulmonale, HHD: Hypertensive heart disease, RHD: Rheumatic heart disease, HFpEF: Heart failure with preserved ejection fraction, HFmrEF: Heart failure with mid-range ejection fraction, HFrEF: Heart failure with reduced ejection. NYHA – New York Heart Association

FIGURE 2: FREQUENCY OF PRECIPITANTS OF ACUTE DECOMPENSATED HEART FAILURE



PMN– Pneumonia, **PDC** – Poor Drug Compliance, **ARRYH**– Arrhythmia, **UTI** – Urinary Tract Infection, **RENAL DYS** – Renal Dysfunction, **COAD EXACER** - Acute Exacerbation of Chronic obstructive airway disease, **HPT**-SevereHypertensive, **MI** – Myocardial infarction, **PE** – Pulmonary embolism

TABLE 3: ASSOCIATION BETWEEN COMMON PRECIPITANTS OF ACUTE DECOMPENSATED HEART FAILURE AND CLINICO - DEMOGTRAPHIC VARIABLES

VARIABLE	PMN	P	PDA	P	ARRHY	P
SEX						
Male	30(50.0)	0.215	30(50.0	0.515	12(20.0)	0.217
Female	40(58.8)		27(39.7)		12(17.6)	
AGEGROUP						
Young	7(50.0)	0.019	4(28.6)	0.010	2(14.3)	0.016
Middle	23(40.4)		13(22.8)		8(14.0)	
Elderly	40(70.2)		40(70.2)		14(24.6)	
CAUSE OF HF						
CMP	8(40.0)	0.572	9(45.0)	0.823	3(15.0)	0.273
CONG	1(33.3)		2(66.7)		0(0.0)	
COPUL	4(40.0)		4(40.0)		0(0.0)	
HHD	43(63.2)		35(51.5)		16(23.5)	
RHD	14(51.9)		7(25.9)		5(18.5)	

PMN: Pneumonia, **PDA:** Poor drug adherence, **ARRHY:** Arrhythmia, **HF;** Heart Failure, **CMP:** Cardiomyopathy, **CONG:** Congenital heart disease, **COPUL:** Cor pulmonale, **HHD:** Hypertensive heart disease, **RHD**: Rheumatic heart disease

Discussion

This study has revealed that pneumonia is the most common precipitant of ADHF 66 (51.5%) in our practice. This is not surprising, because HF patients are susceptible to chest infections which further worsens cardiac function.[11, 12] Pneumonia increases circulatory levels of inflammatory cytokines and induces hypoxia via ventilation/perfusion mismatch. These factors (cytokines and hypoxia) suppress ventricular function and trigger arrhythmias, further undermining cardiac function.[13] Baba et al.[7] and Ogah et al.[8] reported likewise. The similarity in the populations studied can explain this concordance. However, this result differs from that of Foranow et al.,[14] who reported acute coronary syndrome (ACS) as the most common precipitant of ADHF in the OPTIMIZE - HF study. This difference is most probably due to the high prevalence of coronary artery disease (CAD) in the developed countries where the study was conducted.[15]

Poor drug adherence (PDA) is another common precipitant 47 (36.7%) of ADHF. This is a significant proportion, but fortunately, it is preventable if patients are adequately counseled and motivated. PDC cause fluid retention and increases after load, both of which reduce myocardial performance. Improvement in symptoms and the burden of taking multiple pills daily are possible reasons for this observation. Financial constraints in the purchase of medications could also be a factor, particularly in a low resource setting like Nigeria.

Arrhythmias are also common precipitants of ADHF 38 (29.7%). This is not unexpected because of the interrelationship between arrhythmias and HF. HF is a cause of arrhythmias and arrhythmias (particularly

new onset) also worsens HF. Therefore, it may be a challenge to ascertain which started first; both conditions should be treated simultaneously as recommended.[16] Tachycardia, irregular rhythm and atrioventricular dissociation are mechanisms by which arrhythmias cause dysfunction and induce hemodynamic derangement in stable HF patients. Others include loss of atrial contribution to ventricular filling. Ventricular arrhythmias also trigger ADHF, but they are less commonly encountered, probably because they cause cardiac arrest and sudden cardiac death when sustained.

It is pertinent to note that although HHD was the most common aetiology of HF(49.7%) as shown in table 2, only 4.7% of the precipitants were due to severe hypertension (figure 1). This is not surprising, because severe hypertension typically precipitates HF in the setting of hypertensive emergencies such as the classical acute left ventricular failure, which usually presents as denovo (new onset) HF. Only cases of decompensated chronic HF were enrolled in this study. The absence of infective endocarditis within the period studied reflects the ongoing improvement in healthcare notably better availability of antibiotics.

There was no significant association between the aetiology of heart failure and the common precipitants of ADHF. (Table 3) This agrees with the results of a study by Ogbemudia and Obasohan.[17] They were, however, significantly associated with the elderly (Table 3). The elderly are susceptible to infections, particularly pneumonia, because of reduced cellular and humoral mediated immunity, impaired mucociliary clearance and cough reflex. The presence of heart disease alongside other comorbidities further increases this risk.[18, 19] Arrhythmias are also more common in the elderly. The prevalence of arrhythmias, particularly atrial fibrillation, increases with age, due to age-related structural and electrical remodelling, which results in fibrosis.[20] This study also shows that the elderly are associated with poor drug adherence. Polypharmacy due to multiple comorbidities, forgetfulness, and cost-related issues are some barriers to good drug adherence in the elderly.

Precipitants of HF exacerbations were identified in 77.6% of cases (see results). This confirms the fact that ADHF is usually triggered by precipitants which are identifiable in most cases. However, precipitants may not be detected in some cases even after an exhaustive search as in 22.4% in this study. Progressive ventricular dysfunction is the most likely cause of deterioration in these cases. Adhikari et al.[21] reported a higher prevalence of precipitants in their study (95% of cases) because; they identified other precipitants such as dietary salt, fluid indiscretion, and usage of non-prescription medications with adverse cardiac effect such as non-steroidal anti-inflammatory drugs and others.

Implications for future research include the need to follow up these patients with common precipitants and monitor outcomes (rehospitalisation and mortality). A comparison of the distribution of precipitants of ADHF among acute heart failure syndromes and assessment of possible barriers to good drug adherence is also necessary. The retrospective study design was a limitation in this study. Patient education and adherence could not be objectively assessed, and it was a single-centre study which limits its generalisation.

In conclusion, ADHF is a common AHF syndrome that is usually precipitated by factors that can be identified in most cases

(77.6%). Besides, pneumonia, PDC and arrhythmias are the common factors that precipitate ADHF in our locale, and they were associated with the elderly age group. Therefore, an active search for these factors is necessary during the initial evaluation of patients with ADHF to optimise management and improve outcomes. Interventions such as vaccination against pneumonia, health education/counseling on drug adherence and other self-care practices will help prevent recurrence, reduce repeated exacerbations and hospitalization for ADHF, and the associated economic burden.

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Citation: This article should be cited as: Ogbemudia EJ, Umuerri EM. Common Precipitants of Acute Decompensated Heart Failure. Afr. J. Trop. Med. & Biomed. Res. 2021; 5(1): 10-17

Chronic Venous Leg Ulcers: A Narrative Review.

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ABSTRACT

Background: Chronic venous leg ulcers are known to be very common and debilitating. Treatment is arduous and recurrence rates are high. The prevalence of chronic venous disease (CVD), especially leg ulcers, rises with age. Slow healing and recurrence continue to weigh down the patients. There is a great need to understand the aetio-pathogenesis and eliminate the recurrence of the pathological processes leading to chronic venous leg ulcers.
This review therefore, aims at enlightening the medical community by harnessing available literature and knowledge of chronic venous disease with a view to improving prognosis and decreasing recurrence especially of chronic venous leg ulcers.
Methods: Materials were sourced from available publications and internet search of Google scholar, Pubmed and Hinari. Only full articles were included.
Results: The prevalence of chronic venous leg ulcers increases with age, even though it is not restricted to the elderly and it is commoner in women. Chronic venous leg ulcers are most commonly caused by venous hypertension and valvular incompetence. Results improve drastically with early presentation and recurrence rates decrease with better compliance with treatment modalities.
Conclusion: Chronic venous leg ulcers remain a great source of concern to clinicians and patients. To improve treatment outcomes and reduce recurrence rates, appropriate diagnosis and a combination of measures to prevent or reduce recurrence should be instituted. In spite of all options for the management of chronic venous leg ulcer, the age long method of graduated compression bandaging still appears to be a very effective and reliable method and so should be maintained.
Key Words – Chronic, Venous leg Ulcer, Recurrence, Review

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Introduction

Venous ulcers, also called stasis ulcers, make up 80% of ulcerations of the lower extremity.[1] Chronic leg ulcer is a chronic wound of the leg which shows no tendency to heal after 3 months of appropriate treatment or is still not fully healed at 12 months.[2] The prevalence of Chronic venous disease (CVD) was found to increase with age, especially chronic leg ulcers, but this is not restricted to the elderly.[3-5] Active or healed venous leg ulcers occur in approximately 1

percent of the general population.[3,4]

Even though the difference between sexes was small, majority of other studies show that the prevalence is more among women.[6]

Risk factors for CVD and chronic leg ulcers include heredity, age, female sex, obesity (especially in women), pregnancy, prolonged standing, and greater height.[4,7,8-10]

Chronic venous leg ulcer (CVLU) following chronic venous insufficiency (CVI) is most commonly caused by valvular incompetence and venous hypertension. It is a disease attributed to many factors, the exact pathogenesis remains unclear, though a potential genetic contribution has been suggested by various studies.[11,12]This condition may be primary (abnormalities of vein walls or valves) or secondary (after venous thrombosis, i.e. post-thrombotic syndrome).[12] Clinical manifestations include leg pain, lower extremity edema, skin changes, varicose veins, and venous ulceration.[13]

Many signs are manifested in CVD of the lower limbs, the most obvious signs are varicose veins and venous ulcers. Other signs include oedema, hyperpigmentation around the ankle, venous eczema, atrophie blanche (white scar tissue), and induration caused by fibrosis of the subcutaneous fat called lipodermatosclerosis.[14] The severity of chronic venous leg ulcers and symptoms of other venous disease of the lower limbs, increases with number of systems affected.[15]

This paper reviews the pathology and management of chronic venous leg ulcers with a view to updating knowledge on current concepts in the care of this disease.

Methodology

Materials were sourced from available publications and internet search of Google scholar, Hinari and Pubmed using chronic venous leg ulcer and venous leg ulcer in humans between January 13, 2019 and April 31, 2021.

Pubmed; 230, Hinari; 33. From both Pubmed and Hinari, 38 papers met the selection criteria. For Google scholar, 97 out of which 91 met the selection criteria. Only full articles were included.

Aetio-Pathogenesis

Risk factors identified to be associated with CVD include, age, female gender, pregnancy, family history, obesity, and prolonged orthostasis[13] and these are especially for chronic venous leg ulcers. Other identified risk factors also include previous leg injury, phlebitis and deep vein thrombosis.[21,22,23]

Tissue damage in CVI results from perivascular inflammation caused by a variety of cytokine mechanisms[14] that weaken the usual dermal barrier against pathogens and allergens.[16]Lymphatic dysfunction is present in up to one third of cases of CVI. This is detected by means of nucleotide lymphangiography, and may resolve with correction of abnormalities in the vein.[17]

Multiple studies have also suggested genetic contributions to the aetio-pathogenesis of CVD and CVLU. Grzela et al[18] reviewed 4 genes that may play a role in venous ulceration: tumor necrosis factor (TNF), fibroblast growth factor-R (FGF-R), estrogen receptor (ER), and hemochromatosis (HFE) gene. Compared with normal acute wounds, levels of TNF-α and interleukin-1 (IL-1) are higher in venous leg ulcers, with certain single nucleotide polymorphisms (SNPs) (such as the −308A variant in TNF-α) conferring a higher risk of venous ulceration compared with wild-type.[13,18,19] Along with demonstrating the previously mentioned association with TNF-

α, Wallace et al[19] also identified that polymorphism in intron 10 of the BAT1 gene (human leukocyte antigen B–associated transcript-1) is a significant risk factor for venous ulceration.

Estrogen is a known contributor to extracellular matrix (ECM) metabolism; CVI is prevented by hormone replacement therapy and by decreasing inflammatory response topical estrogen promotes wound healing in the elderly.[20]

Venous hypertension is usually present in majority of patients with CVD as most symptoms and signs can be traced to it. It is mostly caused by reflux through incompetent valves.[6,21]

It has been documented that after standing for a long time, venous pressure in the foot is approximately 90 mm Hg in both patients with incompetent venous valves and those with normal veins. During walking, the musculovenous pump rapidly lowers the venous pressure in the normal leg but this is ineffective in the leg with valvular incompetence.[24]

Structural changes in the wall of the vein also contribute to the aetio-pathogenesis of CVLU. Histologic and ultrastructural studies of varicose saphenous veins have found hypertrophy of the vein wall with increased collagen content,[25] together with disruption of the orderly arrangements of smooth-muscle cells and elastin fibers.[26,27] Impaired wound healing and ulcer development are contributed to by leukocyte activation, endothelial damage, platelet aggregation, and intracellular edema.[28,29]

Clinical Features

Patients suffering from chronic venous ulcers often present with a number of features in addition to the ulcers. In a project to explore the lived experiences of patients with leg ulcers to ascertain impact on their quality of life, done in the UK,[30] to develop a new Leg Ulcer Consultation Template (LUCT), observations revealed that pain dominated the lives of participants while other symptoms included exudate and odour as well as poor self-image, severe anxiety and depression, and fear of people's reactions. Other effects on daily lives observed included restrictions in daily life activities, effects on usual mobility, difficulties with maintaining hygiene, inability to use regular clothes and shoes, sleep disturbances and effects on social and family relationships.[30]

Traditionally, certain symptoms are attributed to CVD and they include heaviness, aching, a feeling of swelling, itching, tingling, cramps and restless legs.[14] Similarly, CVD is known to negatively affect quality of life especially as it relates to pain, physical function, and mobility. Depression and social isolation are also associated.[31] Venous leg ulcers, the most severe manifestation of CVD, are usually painful[32] and affect the quality of life.[33] Measures that lower venous pressures such as elevation of the leg, use of support stockings, and walking all lead to relief of venous leg pain which is characteristically worse when the leg is dependent.[34]

An ulcer from venous stasis has an indolent appearance and is usually located superior to the medial malleolus, with granulation tissue at its base which does not look ischaemic. Chronic and recurrent ulcers are usually surrounded by scarring of variable extent.[34] Lipodermatosclerosis, hyperpigmentation, and stasis dermatitis are variably present in the leg especially at the lower third which is called the "gaiter" area.[34]

Investigations

Aetiology of venous insufficiency could be

via reflux or obstruction and diagnostic testing serves to confirm the diagnosis, to localize the anatomic site as well as level of disease.[35]Duplex ultrasonography is taken as method of choice out of the variety of functional and imaging tests available, because it is accurate, reproducible, and noninvasive.[36,37] The constituents include real-time, B-mode imaging of the superficial and deep veins combined with directional pulsed Doppler assessment of blood flow. A real-time scanner in B-mode imaging, rapidly and automatically sweeps the ultrasound beam over the area to be imaged and an image is constructed from the returned signals and allows for detection of movement in the structures imaged.[38] Whereas, relative motion between the source of the signal and the reflector of the signal is detected by directional pulsed Doppler transducers.[35] The accuracy of B-mode ultrasonography or duplex scanning DVT diagnosis has been demonstrated by various studies.[22,23,39–41]

The diagnosis of CVI may be determined by the use of Photoplethysmography (PPG).[46] On the other hand air plethysmography (APG) has the ability to measure each potential component of the pathophysiological mechanisms of CVI— reflux, obstruction, and muscle pump dysfunction.[47,48]

Phlebography or venography which are invasive imaging techniques may be either ascending ordescending.[45] In ascending phlebography contrast is injected in the dorsum of the foot with visualization of contrast traveling up the lower extremity in the deep venous system. However, ascending phlebography despite being considered the gold standard to determine the patency of veins, has been largely replaced by noninvasive imaging.[46] Descending phlebography involves injection of contrast proximally in a semi-vertical posture on a tilt table with the use of the Valsalva maneuver and it is most useful to identify reflux in the common femoral vein and at the saphenofemoral junction, but it may also be used to evaluate some other locations.[46]

Ambulatory venous pressure (AVP) monitoring is the hemodynamic gold standard in assessing CVI.[47, 48] AVP has also been shown to be valuable in assessing the severity and clinical outcomes in CVI.[49]

In patients with post-thrombotic disease the iliac veins should be assessed, since these veins are commonly involved,[50] and should also be considered in patients with non-thrombotic disease, if the clinical presentation is more severe than would be expected from the abnormalities detected in other veins of the lower limb.[51]Trans-femoral venography can detect extensive iliac vein lesions but it is unreliable for focal obstructions with a post-thrombotic or non-thrombotic cause.[52] High-resolution magnetic resonance venography or computed tomography appears to be sensitive for focal iliac-vein lesions,[53] but experience with these techniques is limited and their role in practice is uncertain.[34]

Other investigative modalities such as ankle brachial pressure index (ABPI), toe brachial pressure index (TBPI) and pulse oximetry, which are useful in detecting limb ischemia can also be useful in ruling out other aetiologies.[54]

Treatment and Measures to Reduce Recurrence

Since the time of Hippocrates, leg elevation and compression have been advocated, in chronic venous leg ulcers, as the primary treatment modalities.[35] In recalcitrant cases,

leg pumping with intermittent pneumatic compression may be helpful.[35] No clear advantage among the various ulcer dressings, although patients may prefer hydrocolloidal occlusive dressings because of their convenience.[35]

Treatment of CVI and CVLU have been divided into different components namely: conservative treatment, Interventional treatment and Surgical treatment. Pharmacological therapy, wound and skin care, compressive leg garments and exercise make up the conservative treatment while Interventional treatment includes sclerotherapy, ablative therapy, as well as endovascular therapy; and surgeries which include, ligation, stripping and venous phlebectomy, subfascial endoscopic perforator surgery and valve reconstruction.[46]

Graded Compression Therapy

In treating venous leg ulcerations, compression therapy has the following goals namely; ulcer healing, reduction of pain, reduction of edema, and prevention of recurrence.[55]

Compression is the most widely used therapy for venous leg ulcers and has been in use for more than 400 years.[56] The mechanism of action is not completely understood. Numerous studies point to the fact that external pressure to the calf muscle raises the interstitial pressure leading to improved venous return and reduction in the venous hypertension.[14,46] Other animal and clinical studies have demonstrated that compression also improves the cutaneous microcirculation,[57 - 60] as well as lymphatic flow.[61,62]

Compression therapy has also been shown to enhance fibrinolysis,[63-65] and it may be an important mechanism in reducing fibrosis and promoting ulcer healing. Elastic bandages , for example, Profore, may be used in place of compression stockings. A recent meta-analysis showed that elastic compression therapy is more effective than inelastic therapy.[66]

The failure of venous leg ulcers to heal with compression therapy has been found to be consistent with a number of risk factors which include; large surface area, longer ulcer duration, fibrinous deposition present on greater than 50% of the wound surface, and an Ankle Brachial Pressure Index [ABPI] of less than 0.85.[67]

Several compression garments such as; graded elastic compressive stockings, layered bandaging, paste gauze boots, and adjustable layered compression garments are available.[46] The use of compression stockings at 30 to 40 mm Hg results in significant improvement in pain, swelling, activity, skin pigmentation, and well-being if patients can be 70 to 80% compliant during treatment.[68] Graded compression and other compressive bandaging modalities are effective in both healing and prevention of recurrences of ulceration in patients with venous ulcers. With a structured regimen of compression therapy 93% of patients with venous ulcers can achieve complete healing at a mean of 5.3 months.[69] When CVI is severe, treatment of venous ulcers may last for as long as 6 months before complete healing is achieved, and when compression therapy is not maintained recurrence is frequent.[46]

Care of the Skin and Ulcer

Appropriate and adequate care of the ulcer and skin are very important in the overall care of patients with chronic venous disease especially chronic venous leg ulcers. A variety of hydrocolloids and foam dressings are available to control wound fluid drainage and

resultant maceration of the adjacent skin.[70] In the presence of an infected ulcer bed, silver-impregnated dressings have been effective in controlling infection and restoring tissue integrity.[71,72]

Pharmacological Therapy

Four groups of drugs, with venoactive properties, have been assessed in the treatment of CVI: they are, flavonoids (benzopyrones), coumarins (benzopyrones), saponosides (horse chestnut extracts), and other plant extracts.[46]Even though the exact mechanism of action of these drugs is unknown,the principle for the use of venoactive drugs in CVI is to improve venous tone and capillary permeability.[46]

It is thought that the flavonoids affect leukocytes and the endothelium by modifying the degree of inflammation and reducing edema. A micronized purified flavonoid fraction, Daflon, reduces edema-related symptoms as either primary treatment or in conjunction with surgical therapy.[73] Other agents have been used in the treatment of advanced venous disease with ulceration.[46]A number of trials have shown that pentoxifylline may improve venous ulcer healing rates, however, the magnitude of the effect appears small and its role in patient management is not clear.[74,75]

Routine administrations of systemic antibiotics failed to improve the healing rates of ulcers and should be reserved for ulcers that are obviously infected, or are complicated by clinically apparent cellulitis.[76]

Exercise

Exercise is noted to improve calf muscle function and so in conjunction with other methods of treatment of CVI, improve patients' conditions. In a small controlled study by Padberg et al,[77]duplex ultrasound and air plethysmography were used to assess venous hemodynamics, while a dynamometer was used to assess muscle strength. Patients receiving the calf muscle exercise regimen had, after 6 months, normalized their calf muscle pump function parameters but there was no change in the amount of reflux or severity scores. The conclusion of the researchers was therefore that structured exercise to reestablish calf muscle pump function in CVI may prove beneficial as a supplemental therapy to medical and surgical treatment in advanced disease.[77]

Sclerotherapy

Venous sclerotherapy is a treatment modality for obliterating telangiectases, varicose veins, and venous segments with reflux.[46] Sclerotherapy may be used as a primary treatment or in conjunction with surgical procedures in the correction of CVI.[46] There are several sclerosing agents and they include; hypertonic solution of sodium chloride (23.4%), detergents such as sodium tetradecyl sulfate, polidocanol, and sodium morrhuate, and other compounds such as sodium iodide and chromated glycerin.[46]Polidocanol and similar agents are superior to normal saline in obliteration of incompetent varicose veins and enhancing hemodynamics at 12 weeks.[78]

Ablative Therapy (with endovenous radiofrequency and laser)

Thermal energy technique in this form is often used for great saphenous vein reflux as an alternative to stripping. Local thermal injury wall follows heat generated, leading to thrombosis and eventual fibrosis.[46]Complete obliteration in most patients after 2 years with recanalization in 11% with the use of ablation of the great saphenous vein from radio frequency, however, most patients are free from reflux while 95% are satisfied with improved symptoms.[79]

Endovascular Therapy

In CVI, to relieve obstruction and restore outflow this method has gained prominence.[46] In a large single-center series, iliac vein stenting led to clinical improvement: one half of the patients were completely relieved of pain, 33% had complete resolution of edema and 55% had complete healing of their ulcer.[80]

Surgical Therapy

Invasive and surgical methods are options in patients who are unable to comply with use of compression or experience recurrent varicose veins.[46]

Such surgical therapy includes the following: Ligation, Stripping and Venous Phlebectomy

The saphenous vein when removed with high ligation of the saphenofemoral junction is considered durable and the standard for many patients with CVI.[81] Similarly, stab phlebectomy technique can be used to avulse large venous varicose clusters that communicate with the incompetent saphenous vein at the same setting. There is also the use of transilluminated power phlebectomy (or TriVex) to remove varicosities with reduced operation time as well as fewer incisions.[82]Furthermore, evaluation of 500 patients with venous ulcer and reflux of superficial and deep venous systems, randomization to surgery (only to the superficial venous segments) plus compression demonstrated a significant reduction in ulcer recurrence at 12 months as compared with compression alone (12% versus 28%).[83]

Subfascial Endoscopic Perforator Surgery(SEPS)

SEPS is used to ligate incompetent perforator veins via a remote site thereby avoiding area of lipodermatosclerosis or ulcers.[46]Accumulative ulcer healing of 88% at 1 year and ulcer recurrence of 28% at 2 years were demonstrated in a multicenter study.[84]

Valve Reconstruction

In some advanced CVI patients who have recurrent ulceration with disabling symptoms, reconstruction of the deep vein valves has been performed.[46]

An open technique for repairing the femoral vein valve that renders the valve leaflets competent has been described.[85] This technique of open valvuloplasty has been refined, and closed techniques for venous repair developed with transcommissural valvuloplasty.[86] Other procedures for the reconstruction of non-functioning venous valves resulting from post-thrombotic valve destruction (not amenable to valvuloplasty) include transposition of the profunda femoris vein or saphenous vein valve and axillary vein valve transplantation to the popliteal or femoral vein segments.[46]

Skin Grafting

The ulcers may also be debrided and by the use of negative pressure wound therapy (NPWT) formation of healthy granulation tissue is encouraged and closed with a skin graft.[87]

Poor prognostic factors[88]

a. Larger ulcers
b. Ulcers longer than 1 year - these ulcers usually have a recurrence rate greater than 70%
c. Fibrin in >50% of wound surface
d. Ankle-brachial pressure index (ABPI) <0.8
e. A positive history of venous ligation/stripping

Conclusion

Chronic venous leg ulcers and chronic venous

diseases in general have continued to be great sources of concern to clinicians and patients especially because of the difficulty in treatment and the high rate of recurrence. To improve treatment outcomes and reduce recurrence rates painstaking and appropriate diagnoses as well as adequate combination of measures to prevent or reduce recurrence to the barest minimum have to be in place. Inspite of all options for the management of Chronic venous leg ulcer, the age long method of graduated compression bandaging still appears to be a very effective and reliable method and so should be maintained, However, further research is required to develop more modern interventions to complement present methods to aid quick treatment and prevent recurrence.

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Citation: This article should be cited as: Otene CI, Akpo EE, Uchendu JO, Odion-Obomhense HK, Sefia ET, Ikubor JE, Oriahki SN, Orugbo VP, Odatuwa-Omagbemi DO, Obanovwe CE. Chronic Venous Leg Ulcers: A Narrative Review. Afr. J. Trop. Med. & Biomed. Res. 2021; 5(1): 18-30

Blood Glucose and Hepato-Renal Alterations Following Administration of *Gongronema latifolium* and *Allium sativum* in Diabetic Wistar Rats

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Abstract

Background: *Gongronema latifolium* (GL) and *Allium sativum* (AS) are reported to possess anti-diabetic properties, and preference to its single or concomitant use varies widely.
Objective: The effect of concomitant use of (GL) leaves and (AS) bulb extracts, on the hepato-renal indices of Streptozotocin (STZ) induced hyperglycemic rats was studied.
Materials and methods: Diabetes mellitus was induced by single intraperitoneal dose of (STZ) at 65 mg per kg body weight (bwt) of rats. Thirty female Wistar rats (160 –180 g) were randomly divided into 6 groups of 5 animals each. Groups I and II received 10 mL distilled water per kg bwt and served as normal and diabetic controls [NC and DC] respectively. Group III received Metformin 150 mg per kg bwt of rat, while groups IV, V and VI received 400 mg of AS, GL, and AS + GL extracts per kg body weight respectively. Biochemical analyses were performed after the experimental period of 14 days.
Results: Body weight significantly ($p < 0.05$) increased in animals treated with the extracts compared to DC. Blood glucose levels, aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase concentrations significantly ($p < 0.05$) decreased in the treatment groups, compared to DC. The concentrations of total protein, albumin, sodium, potassium and chloride were significantly increased while urea and creatinine concentrations were significantly decreased when compared to DC.
Conclusion: Extracts of AS and GL singly and in concomitantly use exhibited antihyperglycemic and hepato-renal protective properties, however combined doses outperformed single administration.

Keywords: Diabetes mellitus, *Gongronema latifolium, Allium sativum,* hypoglycaemia

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Introduction

Diabetes mellitus (DM) is a metabolic disorder of several etiology characterized by chronic hyperglycemia, resulting from insulin deficiency, malfunction or even both.[1] Diabetes is a complex, chronic ailment requiring continuous medical care with multifactorial risk-reduction approaches beyond glycemic control.[2] Chronic hyperglycemia of diabetes is accompanied with complications like cardiovascular disorder, neurological complications, hepato-renal disorders, muscular system disorder and eventually premature death.[2] The number of people living with diabetes is expected to surge to 300 million or more in the year 2025.[3] Presently, DM is one of the greatest obvious health threats and its incidence is rising swiftly.[4] This has led to the unremitting concern and investigation for various treatment alternatives available to the repertoire of orthodox medications like Insulin, Glibenclamide, Metformin and many others.[5]

Natural medicine involves the use of organic

product/materials with likely less toxic implications sourced from roots, seeds, pulps, stems, barks, leaves in the control, treatment or management of different ailments and diseases with successes.[6] Polyherbal therapy is the mishmash of two or more plant products in the treatment of a particular ailment.[7] Studies have reported that polyherbal therapy produce enhanced therapeutic efficacy with least side effects.[8] The combination of various types of agents from different plant source could have synergistic, antagonistic, potentiative, pharmacological and therapeutic effects.[8] *G. latifolium* and *A. sativum* have been proven to be extremely nutritional and medicinal.[9-10] They are both antidiabetic plants that have been used traditionally as mixture for the management of the disease. Researches have shown that these plants possess pharmacological and therapeutic effects with numerous bioactive compounds.[11-12]

The hypothesis for this study is that combined ethanol extracts of *G. latifolium* and *A. sativum* moderates/attenuates hepatorenal dysfunction of Streptozotocin-induced diabetic Wistar rats, than single extract components.

Materials and Methods

Collection and Identification of Plant Materials

The leaves of *G. latifolium* and bulbs of *A. sativum* were obtained from Akpan Andem Market, Uyo, Akwa Ibom State in July 2020, and were duly authenticated at the Department of Botany and Ecological study, University of Uyo, Uyo, and specimen voucher numbers UUPH 9(a) and UUPH 44(b) obtained for *G. latifolium* and *A. sativum* samples respectively.

Drug Acquisition

Streptozotocin (300 mg) was obtained from Santa Cruz Biotechnology, Inc., U.S.A. Metformin (Glucophage) was obtained from Merck S. L. Poligono Merck Ltd., Barcelona, Spain. Citrate buffer was obtained from Nanjing Shuguang Silane Chemical Co., Ltd., 5611EH Eindhoven, Netherlands. Normal saline and distilled water were obtained from the laboratory of the Department of Biochemistry, University of Uyo, Nigeria.

Preparation of Plant Extract

Matured leaves of *G. latifolium* and *A. sativum* bulbs were washed with clean tap water. The garlic bulbs were peeled and chopped into smaller pieces. These plants were air dried at room temperature for one week to constant weight. The dried plant materials were ground into powder. Each of the powdered samples (500 g) were macerated in 6000 mL of 90 % ethanol for 24 hours, after which the extracts were filtered through a whatman filter paper (No. 1) and crude extract obtained by evaporation in a water bath (Thermo Fisher Scientific, Germany) at 40 ºC. Crude extracts of *G. latifolium* (78.9 g) and *A. sativum* (58.40 g) were obtained as yields and stored in a refrigerator at about 8 ºC.

Experimental Animals

Thirty healthy female Wistar rats weighing between 160 – 180 g were obtained from the Animal House, Faculty of Basic Medical Sciences, University of Uyo, Uyo, Nigeria. The animals were allowed to acclimatize for 2 weeks, before the commencement of the research.

Experimental condition:

They animals were kept in spacious wooden caged under 12 hour light and dark cycle 6:30 am to 6:30 pm, 5 rats were allotted in 6 cages of size 30 cm length, 25 cm width and 15 cm height with clean beddings changed daily. The rats were provided with normal rat feed (Vital® feed, Oyo state, Nigeria) and clean water *ad*

libitum. All experimental protocol were assessed and approved by the Faculty of Basic Medical Sciences Ethical/Research Committee, University of Uyo, Nigeria and followed the Guide for the Care and Use of Laboratory Animals. [13]

Induction of Diabetes and inclusion Criteria

Diabetes was induced by single intraperitoneal dose of Streptozotocin (STZ) (Sigma Aldrich, Germany) at 65 mg/kg b.w of rats, dissolved in 0.1 mL fresh cold citrate buffer pH 4.5 into 12h fasted rats. On the 3rd day post-induction, the rats were fasted for 6 h and blood glucose determined using an On-call-plus glucometer® (Viva Check Laboratories, USA).[12] They rats were alloted selected into 6 groups of 5 rats each and grouped as shown.

Group I: Normal control, (NC) received normal rat diet and 10 mL distilled water per kg bwt.

Group II: Negative control, (DC) received normal rat diet and 10 mL distilled water per kg bwt.

Group III: Diabetic + Metformin 150 mg per kg bwt of rats.

Group IV: Diabetic + 400mg *A. Sativum* (AS) extract per kg bwt of rats

Group V: Diabetic + 400 mg*G. latifolium* (GL) extract per kg bwt of rats

Group VI: Diabetic + 200 mg AS + 200 mg GL extracts per kg bwt of rats Administration were performed via oral route using an oral-gauge cannula, and lasted for 14 days.

Phytochemical Screening

The method as described by Trease GE, Evans WC [14] was used in the qualitative screening of the extracts of *G. latifolium* and *A. sativum*

Acute Toxicity Studies

The modified Lorke D.A[15] method was used in the oral toxicity studies of the extracts of GL and AS respectively. Increasing doses of extracts 10 to 5000 mg per kg bwt of swiss mice was investigated for behavioural changes such as writhing, motor dysfunction, a version to feed and water, and mortality within 24 hours.

Body and Organ Weights

The body weights of rats were recorded on a 3 days interval using a digital balance (Reptech, India), while the organ weight was recorded at the end of the study, using an electronic balance (Reptech, India).

Determination of Blood Glucose Concentration

The concentrations of blood glucose in the Wistar rats were determined with On-call-plus glucometer® (Viva Check Laboratories, USA) using strip method.[16] A drop of blood was collected from the tip of the tail of the rats after cutting it with a pair of scissors. The blood was then dropped at one end of the strip on the glucometer. After ten seconds the reading was taken.

Biochemical assays

Alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, albumin, urea, creatinine, Na^+, K^+ and Cl^- concentrations in serum of rats were evaluated using assay kits (Randox Laboratories LTD. United Kingdom).

Statistical Analysis

The data were analysed by one-way ANOVA, using SPSS statistical package. All data were expressed as Mean ± SEM and difference between groups considered significant at ($p < 0.05$.

Results

Phytochemical Analysis of Ethanol extracts of *G. latifolium* **Leaves and** *A. sativum* **Bulb**

A total of 11 phytochemical components were screened for in the leaves of *G. latifolium* and *A. sativum* bulb. Alkaloids and saponins concentrations were higher in *G. latifolium* compared to *A. sativum*. While glycoside was present in *A. sativum* and absent in *G. latifolium*. Similarly, carbohydrate and terpenoids concentrations in *G. latifolium* were higher when compared to *A. sativum*. Protein and steroid concentrations were higher in *A. sativum* when compared to *G. latifolium*. Finally anthraquinones was higher in *G. latifolium* and absent in *A. sativum,* while flavonoids and cardiac glycosides had similar concentrations in both *G. latifolium* and *A. sativum* (Table 1).

Effect of *G. latifolium* **and** *A. sativum* **on Median Lethal Dose Determination**

No behavioral changes such as alertness, breathlessness, restlessness, diarrhoea, convulsion and coma were observed at the administered doses during the acute toxicity testing. The Swiss Mice were physically active and no death was recorded upon the oral administration of extracts up to a dose of 5000 mg/kg body weight. At this point, the process was discontinued and the median lethal dose of the ethanol leaf extract of *G. latifolium* and *A. sativum* was estimated to be over 5000 mg/kg body weight (Table 2).

Effect of *G. latifolium, A. sativum* **and their Combination on Body, Liver and Kidney weight of Diabetic and Non-diabetic Rats**

Induction of diabetes mellitus led to drastic loss of body weight of rats during 14 days of experiment. There was no significant ($p > 0.05$) difference between the body weights of animals in all groups at the beginning of the experiment (170.40 ± 0.51 to 186.80 ± 1.62 g). Following treatment, groups on Metformin, extracts (AS and GL) and normal control gained weight significantly ($p < 0.05$) compared to DC group. Initial body weight of treatment groups range from (170.40 ± 0.51 to 180.20 ± 0.49 g), final weight on day 14 of experiment was (179.60 ± 1.44 to188.20 ± 0.58 g) (Table 3).

Liver weight of DC (8.97 ± 0.26 g) increased significantly ($p < 0.05$) compared to the NC (7.32 ± 0.13 g). Liver weight of all diabetic treatments were significantly lower (6.83 ± 0.48, 7.23 ± 0.07, 7.29 ± 0.21 and 6.87 ± 0.31 g) compared to DC (8.97 ± 0.26 g) (Table 3).There was a significant ($p<0.05$) increase in the kidney weights of DC (0.79 ± 0.07) compared to the normal control (0.66 ± 0.03), and the treatment groups (0.65 ± 0.05, 0.69 ± 0.04, 0.67 ± 0.03, and 0.63 ± 0.04) respectively.

Effect of *G. latifolium, A. Sativum* **and their Combination on Blood Glucose Concentration of Diabetic and Non-diabetic Rats**

Blood glucose concentrations of rats were monitored every 3 days following daily treatment with extracts (AS and GL) and Metformin. Induction of diabetes led to significant ($p < 0.05$) increase in blood glucose concentration (325.40to 339.60 mg/dL) in diabetic groups compared to the non-diabetic rats (71.80mg/dL). The blood glucose concentrations of the untreated rats

were high (325.40to 398.20mg/dL) throughout the duration of the experiment compared to the NC and extracts treated groups. Diabetic treatment with Metformin and the different extract groups led to a significant ($p < 0.05$) decrease in blood glucose concentration (331.40 - 155.40 mg/dL), (330.00- 171.00 mg/dL), (328.40-168.40 mg/dL) respectively. Group VI, shows a significant decrease in the blood glucose concentration (339.60- 146.00 mg/dL) when compared to other treatment groups (Table 4).

Effect of G. latifolium, A. Sativum and Their Combination on Liver Enzymes of Diabetic and Non-diabetic Rats

Serum AST, ALT and ALP concentrations were raised significantly ($p < 0.05$) in the DC group (113.20 ± 3.81, 44.80 ± 3.71 and 74.40 ± 4.95) respectively when compared to NC (79.40 ± 0.51, 29.40 ± 0.68 and 45.20 ± 1.39). Singly administered extracts significantly ($p < 0.05$) decreased the activities of AST, ALT and ALP when compared to DC group. However, combined extract treated group improved the activities of AST, ALT and ALP more significantly ($p < 0.05$) compared to groups III, IV and V (Table 5).

Table 1: Phytochemical Constituents of Ethanol Extracts of *G. latifolium* leaves and *A. sativum* bulb

Chemical constituents	*Gongronema latifolium*	*Allium sativum*
Alkaloids	+++	++
Flavonoids	+	+
Saponins	++	+
Glycosides	-	+
Carbohydrates	++	+
Protein	++	+++
Steroids	-	++
Anthraquinones	++	-
Tannins	+	+
Terpenoids	+++	++
Cardiac glycosides	++	++

-, not present;
+, present in small concentration;
++, present in moderately high concentration;
+++, present in high concentration;

Table 2: Median lethal dose of ethanol extracts of *G. latifolium, A. sativum* and combined administered orally

Groups (n=3)	Dose of AS (mg/kg)	Dose of GL (mg/kg)	Dose of AS+GL (mg/kg)	Mice mortality
1	10	10	10	None
2	100	100	100	None
3	1000	1000	1000	None
4	1600	1600	1600	None
5	2900	2900	2900	None
6	5000	5000	5000	None

Table 3: Effect of *G. latifolium, A. Sativum* and their combination on body weights of diabetic and non-diabetic rats

Groups	Before Induction (g)	Day 0 (g)	Day 3 (g)	Day 6 (g)	Day 9 (g)	Day 12 (g)	Day 14(g)
I (NC)	185.40 ± 1.33	188.20 ± 1.16	190.00 ± 0.45	194.20 ± 1.59	196.80 ± 0.66	200.80 ± 0.58	201.00 ± 1.05
II (DC)	186.80 ± 1.62	186.80 ± 1.07	185.00 ± 0.84	181.00 ± 0.81	179.20 ± 0.58[a]	178.00 ± 1.10[a]	175.60 ± 068[a]
III (Met)	178.00 ± 1.38	176.40 ± 0.93	177.80 ± 1.36	180.00 ± 1.14	181.00 ± 1.05	182.40 ± 1.03	183.80 ± 0.92[b]
IV (AS)	180.20 ± 0.49	178.00 ± 1.26	181.00 ± 0.63	183.40 ± 1.20	184.60 ± 0.81	188.40 ± 1.21b	188.20 ± 0.58[b]
V (GL)	170.40 ± 0.51	168.40 ± 1.03	169.80 ± 0.49	172.60 ± 0.81	174.80 ± 0.80	179.20 ± 1.24	183.00 ± 1.26[b]
VI (AS+GL)	172.40 ± 1.33	170.40 ± 0.81	171.60 ± 1.21	174.40 ± 0.51	178.40 ± 0.24	177.20 ± 0.86	179.60 ± 1.44[b]

Table 3b: Liver and Kidney weights of diabetic and non-diabetic rats

Groups	Liver (g)	Kidney (g)
I (NC)	7.32 ± 0.13	0.66 ± 0.03
II (DC)	8.97 ± 0.26[a]	0.79 ± 0.07[a]
III (Met)	6.83 ± 0.48[b]	0.65 ± 0.05[b]
IV (AS)	7.23 ± 0.07[b]	0.69 ± 0.04[b]
V (GL)	7.29 ± 0.21[b]	0.67 ± 0.03[b]
VI (AS+GL)	6.87 ± 0.31[bde]	0.63 ± 0.04[bde]

[a] = significantly different from group I ($p < 0.05$)
[b] = significantly different from group II ($p < 0.05$)
[c] = significantly different from group III ($p < 0.05$)
[d] = significantly different from group IV ($p < 0.05$)
[e] = significantly different from group V ($p < 0.05$)

Table 4: Effects of *G. latifolium, A. sativum* and their combination on blood glucose concentrations of diabetic and non-diabetic rats

Group	Before Induction (mg/dL)	Day 0 (mg/dL)	Day 3 (mg/dL)	Day 6 (mg/dL)	Day 9 (mg/dL)	Day 12 (mg/dL)	Day 14 (mg/dL)
I (NC)	70.40 ± 0.81	71.80 ± 0.93	70.40 ± 1.08	88.80 ± 1.07	74.20 ± 1.16	76.80 ± 0.97	71.60 ± 1.75
II (DC)	75.60 ± 1.21	325.40 ± 3.36[a]	325.20 ± 2.24[a]	335.40 ± 0.68[a]	333.80 ± 1.24[a]	351.20 ± 0.58[a]	398.20 ± 1.36[a]
III (Met)	73.60 ± 1.47	331.40 ± 3.67[a]	321.40 ± 1.75[a]	297.40 ± 1.91[a,b]	266.40 ± 1.03[a,b]	200.20 ± 2.63[a,b]	155.40 ± 0.51[a,b]
IV (AS)	76.80 ± 1.07	330.00 ± 2.44[a]	312.60 ± 1.47[a]	277.00 ± 0.77[a,b]	251.60 ± 1.69[a,b]	187.08 ± 1.39[a,b]	171.00 ± 3.69[a,b]
V (GL)	71.40 ± 0.51	328.40 ± 3.25[a]	321.20 ± 0.97[a]	296.80 ± 0.80[a,b,d]	269.20 ± 0.97[a,b,d]	172.20 ± 1.32[a,b,c]	168.40 ± 1.47[a,b]
VI (AS+GL)	74.20 ± 2.13	339.60 ± 2.18[a]	327.00 ± 1.34[a]	287.00 ± 1.14[a,b,d,e]	246.20 ± 0.86[a,b,c,d,e]	190.00 ± 2.56[a,b,c,d,e]	146.00 ± 1.26[a,b,d,e]

[a] = significantly different from group I ($p < 0.05$)
[b] = significantly different from group II ($p < 0.05$)
[c] = significantly different from group III ($p < 0.05$)
[d] = significantly different from group IV ($p < 0.05$)
[e] = significantly different from group V ($p < 0.05$)

Table 5: Effects of *G. latifolium, A. sativum* and their combination on liver enzymes of diabetic and non-diabetic rats

Groups	AST(U/L)	ALT (UL)	ALP (U/L)
I (NC)	79.40 ± 0.51	29.40 ± 0.68	45.20 ± 1.39
II (DC)	113.20 ± 3.81[a]	44.80 ± 3.71[a]	74.40 ± 4.95[a]
III (Met)	90.40 ± 4.19[b]	27.20 ± 3.73[b]	53.80 ± 4.81[b]
IV (AS)	99.00 ± 0.84[b]	37.20 ± 1.32[b]	59.60 ± 1.96[b]
V (GL)	93.80 ± 1.69[b]	35.60 ± 1.69[b]	58.00 ± 1.30[b]
VI (AS + GL)	83.67 ± 0.70[b,c,d,e]	29.00 ± 1.00[b,d,e]	45.33 ± 0.33[b,c,d,e]

[a] = significantly different from group I ($p < 0.05$)
[b] = significantly different from group II ($p < 0.05$)
[c] = significantly different from group III ($p < 0.05$)
[d] = significantly different from group IV ($p < 0.05$)
[e] = significantly different from group V ($p < 0.05$)

Table 6: Effect of *G. latifolium, A. sativum* and their combination on renal enzymes of diabetic and non-diabetic rats

Group	Total protein (g/dL)	Albumin (g/dL)	Urea (mmol/L)	Creatinine (mmol/L)	Na^+ (mmol/L)	K^+ (mmol/L)	Cl^- (mmol/L)
I (NC)	64.20 ± 0.73	38.20 ± 0.58	4.38 ± 0.19	68.38 ± 0.19	141.58 ± 1.01	6.64 ± 0.11	95.66 ± 0.45
II (DC)	49.40 ± 0.68[a]	22.00 ± 0.89[a]	7.28 ± 0.34[a]	85.40 ± 4.37[a]	123.70 ± 3.66[a]	4.04 ± 0.25[a]	87.10 ± 1.81
III (Met)	60.60 ± 1.91[b]	37.40 ± 0.75[b]	5.12 ± 0.51[b]	72.00 ± 3.79[b]	145.36 ± 3.11[b]	6.24 ± 0.45[b]	92.30 ± 1.63
IV (AS)	54.20 ± 1.56[b]	34.80 ± 0.80[b]	5.58 ± 0.20[b]	75.00 ± 1.38[b]	135.70 ± 2.91[b]	6.94 ± 0.23[b]	98.16 ± 1.81[b]
V (GL)	58.40 ± 1.14[b]	32.60 ± 0.24[b]	5.71 ± 0.30[b]	74.60 ± 1.08[b]	132.58 ± 0.83[b]	6.66 ± 0.28[b]	95.90 ± 1.86
VI (AS+GL)	61.33 ± 0.50[b]	38.00 ± 0.58[b,e]	4.21 ± 0.54[b,c,d,e]	71.80 ± 0.58[b]	142.43 ± 0.80[b,d,e]	6.43 ± 0.48[b]	94.63 ± 1.39

[a] = significantly different from group I ($p < 0.05$)
[b] = significantly different from group II ($p < 0.05$)
[c] = significantly different from group III ($p < 0.05$)
[d] = significantly different from group IV ($p < 0.05$)
[e] = significantly different from group V ($p < 0.05$)

Discussion

The medicinal potentials of plants lie in its bioactive phytochemical constituents that elicit physiological response in the human body.[17] The Phytochemical analysis of the plant extracts of AS and GL revealed the presence of tannins, flavonoids, saponins, terpenoids, cardiac glycosides and alkaloids, which are known to exhibit pharmacological activities. The therapeutic potentials of plants have been linked with their antioxidant potentials.[18] Flavonoids are potent antioxidants and free radical scavengers that mitigate oxidative cell damage, possess strong anticancer activities, anti-inflammatory activities and defensive against the different degree of carcinogenesis.[19-20] Most plants containing glycosides, alkaloids, terpenoids, flavonoids and carotenoids are also frequently implicated as possessing antidiabetic activities.[21] Tannins is important in the treatment of inflamed or ulcerated tissues, burns, wounds, pneumonia and dysentery, while saponins have antitumor and anti-mutagenic activities by preventing cancer cells from growing.[22] Alkaloids have analgesic and anti-inflammatory effects.[23]

In the acute toxicity study carried out, it was observed that the oral administration of *G. latifolium* and *A. sativum* singly, and in combination did not present any mortality in the test animals even at its highest concentration of 5000 mg/kg that these extracts were safe and non-toxic for use after administering them on the experimental animals up to 5000 mg per kg body weight. They reported on the individual acute toxicity studies of extracts of *G. latifolium* and *A. sativum* respectively.[25] The result of this study indicates that the combined extract is safe and non-toxic, as the acute toxicity test showed an LD_{50} value of greater than 5000 mg per kg body weight of mice, which is also consistent with its popular use.

Streptozotocin induced diabetes is typically characterized by severe loss in body weight, and this reduction is due to degeneration of structural proteins.[26] In this study, the induction of experimental diabetes elicited markedly significant decrease in body weight of rats when compared to NC group. The animals gained weight in the course of treatment with the extract, which may be due to the efficacy of the plant extracts and or benefits from the herb-herb interaction. This result is in agreement with the report of [9] who demonstrated that the combined extracts of *Gongronema latifolium* and *Ocimum gratissimum* were effective in restoring the body weights of experimental animals to normal.

The effects of DM on weight of some internal organs have been reported in many studies. The extracts (GL and AS) and metformin effectively restored the derangement on the organ weight caused by STZ. The result shows that diabetes increases weight of liver and kidney.[9,27] The enlargement of the liver and kidney due to induction of experimental diabetes is due to hepatopathy and nephropathy which causes lesion on the liver and kidney.[28] Treatment with *G. latifolium* and *A. sativum* normalized the weight of liver and kidney. This results support that reduction in the weight of the liver and kidney after treatment with leaf extract as a consequence of the removal of the challenge of hyperglycemia. The result indicates that once hyperglycemia is corrected, there is possibility of subsequent normalization of the weight of the internal organs.

The reduction on the blood sugar concentrations elicited by the combined extract was significantly similar to the reduction in the group treated with Metformin. Though *G. latifolium, A. sativum*

and the combined extracts all proved effective in this study, the combined extract had the maximum capacity to restore blood glucose to near normal concentrations. The hypoglycemic activity of the extracts and composite may be due to its protective action against STZ-mediated damage to the pancreatic ß-cells, and also possibly through regeneration of damaged ß-cells or increased insulin release or secretion.[29] Some of these bioactive compounds (saponins, flavonoids, tannins and alkaloids) are thought to be responsible for the blood glucose lowering activities of these plants.[30] This result is in consonance with reports by [31, 32] who demonstrated the hypoglycemic effect of combined extracts of *Vernonia amygdalina, Ocimum gratissimum* and *Gongronema latifolium*.

The liver is a large, complex organ that plays a central role in biomolecule metabolism.[33] The liver encloses several enzymes within the hepatocytes. Most of the enzymes found in the hepatocytes can be measured in the serum and are used as tests of liver function, such as the aminotransferases.[34] Raised liver enzymes concentration in the blood, may point to inflammation or injury to cells in the liver. Injury to the liver ultimately results in a rise in serum concentrations of aminotransferases.[33] The increase in serum enzyme activities are roughly relative to the degree of tissue harm.[35]

The significant increase in the serum AST, ALT and ALP observed in diabetic rats (Table 5) is consistent with studies by [36], indicating possible liver damage due to STZ mediated action, which may cause leakage of these enzymes from the liver cytosol into the blood.[37] Treatment with *G. latifoium* and *A. sativum* significantly decreased the raised levels of AST, ALT and ALP. The highest reduction was observed in the combined extract treated group, followed by *G. latifoium and A. sativum* treated groups for AST and ALP levels, while *A. sativum* and *G. latifoium* for ALT levels. The decrease in AST, ALT and ALP in rats given the combined extract indicates the possible hepatoprotective effect of the plant extracts. This study confirms reports by[12], who demonstrated the hepatoprotective activity of the extracts on diabetic rats.

The renal system plays a major role in the regulation of electrolyte/fluid balance, the pH buffer system and in the elimination of waste products such as urea and creatinine. When kidney function declines, obviously these processes become impaired.[38] Kidney disease is one of the most common and severe complications of diabetes.[39] Overtime, individuals with diabetes can develop a condition called diabetic nephropathy. Total protein, albumin, creatinine and urea are markers alongside electrolyte balance used in the assessment of kidney functions.[38] One major problem with diabetes is that the amount of glucose in the blood can offset the proportion of serum electrolytes.

Treatment with ethanol extracts of *G. latifoium, A. sativum*, composite and Metformin brought about a significant increase in serum protein and albumin and a decrease in urea concentration of DC. This increase may be as a result of renal dysfunction which results in elevated urea concentration. Decrease of serum protein concentration in diabetic control rats may be due to impaired protein turnover and muscle wasting in diabetic condition. The uncontrolled diabetes is associated with severe muscle wasting.[40] A significant increase in albumin concentration was observed in the composite treated group. This may be due to inhibition of proteolytic activity which enhance insulin secretion and proper

utilization of blood glucose. Similar effect was reported by [41]. Decrease in serum total protein and albumin concentration was also reversed upon the administration of the single and combined extracts as seen in the treatment groups.

Creatinine is a metabolite of muscle creatine, whose amount in serum is proportional to the body's muscle mass. The amount of creatinine is usually constant, as elevated levels indicate diminished renal function, since it is easily excreted by the kidneys. Treatment with combined extracts of G. *latifolium*, A. *sativum*, brought about a significant decrease in the creatinine concentration of diabetic rats to near normal.[38,12]

Sodium, potassium and chloride (Cl-) are essential in maintaining cellular and extracellular homeostasis. They are regulated by the kidney. Most metabolic processes are dependent on, or affected by these electrolytes. Some of the functions of these electrolytes are; maintenance of osmotic pressure and water distribution in various body fluid compartments.[42] Diabetes is characterized by increased volume and metabolites excretions via the kidney, usually in excess of normal thresholds. This usually gives rise to derangement in homeostatic balance with respect to electrolytes.[43] Interestingly the concentrations of these electrolytes were brought to near normal state by treatment with the combined extracts of G. *latifoium* and A. *sativum*. The result of this study shows that the extract treatment has significant improvement in electrolyte imbalance and raised the electrolyte concentrations of diabetic animals to normal compared to the DC group and is in line with the findings.[44]

Conclusion

Oral administration of *A. sativum* and *G. latifolium,* at 400 mg per kg body weight of rats for 14 days, has the potential to restore the altered concentrations of these liver and kidney enzymes and thus modulate diabetic hepatic and renal perturbations. This restoration was observed more in the combined extract than in the single extracts. From the results of this study, it can be concluded that the combined extracts of *A. sativum* and *G. latifolium* possesses better hypoglycemic and hepato-renal protective activities than the individual extracts. Therefore it may be gainful in managing diabetes and its related complications, thus supporting the claim of the local use of the combined extracts of both plants in the treatment of diabetes mellitus.

Acknowledgments

The authors are grateful to Mr. Aniekan U. Akpan of Faculty of Basic Medical Sciences and Dr. Itemobong S. Ekaidem of Faculty of Clinical Sciences, University of Uyo, Uyo, Nigeria for their technical assistance.

Financial Support and Sponsorship

Nil.

Conflicts of Interest

There are no conflicts of interest.

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Citation: This article should be cited as: Ntuenibok NE, Usoh IF, Edagha IA, Akpan HD, Eze CM. Blood Glucose and Hepato-Renal Alterations Following Administration of Gongronema latifolium and Allium sativum in Diabetic Wistar Rats. Afr. J. Trop. Med. & Biomed. Res. 2021; 5(1): 31-45

Fruit Peels of Citrus Tangerina Attenuate the Oxidative Stress and Cell Damage Caused by Acetaminophen on Wistar Rats

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ABSTRACT

Introduction: The regulation of the physiological processes in the body is one of the vital roles of the liver. Hepatic damage or liver dysfunction is a major health concern in the society. The need to explore alternative drugs for the treatment of hepatic diseases necessitated the present study on the effect of fruit peels extract of *Citrus tangerina* on acetaminophen-induced hepatotoxicity in Wistar rats.
Materials and methods: Animals were grouped as follows: group I received normal diet, group II was given acetaminophen 500 mg/kg/day, groups III and IV received fruit peel extracts of *Citrus tangerina* at 200 and 400 mg/kg/day respectively, while group V received silymarin 100 mg/kg/day (standard drug). Groups III-V were simultaneously administered acetaminophen 500 mg/kg/day to induce hepatotoxicity. All drugs were given orally. At the end of a 7-days experimental period, the animals' serum and liver were obtained for biochemical and histopathological analyses.
Results: Results of this study showed that acetaminophen dosing increased serum AST (aspartate transaminase), ALT (alanine transaminase) and ALP (alkaline phosphatase), as well as decreased antioxidant enzymes. Treatment with *C. tangerina* fruit peel extract significantly reversed acetaminophen hepatotoxic effect in a dose-dependent manner.
Conclusion: This study suggests that *C. tangerina* fruit peel extract possesses antioxidant property and attenuates liver damage induced by acetaminophen in Wistar rats.
Keywords: acetaminophen, *Citrus tangerina*, flavonoid, antioxidants

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Introduction

The regulation of the physiological processes in the body is one of the vital roles of the liver. The liver is involved in the metabolism clearance of most chemicals, including drugs, and toxins.The metabolic functions of the liver are important for the removal of waste, the accumulation of which causes complications to the body[1].Hepatic damage or liver dysfunction is a major health concern in the society. Chronic exposure of the liver to certain chemical substances, alcohol, long-term drug therapy, and even commonly prescribed medicines such as acetaminophen and diclofenac, affect hepatic functioning. Some disease conditions have been implicated in liver dysfunction. Overdose of acetaminophen(paracetamol)

can cause acute liver failure and even death[2,3]. Hepatotoxic effect of acetaminophen has been shown to be due to its toxic metabolite, N-acetyl-p-benzoquinineamine which binds to macromolecules of the liver cells resulting in cell necrosis[4].

Treatment of common liver diseases with various synthetic antioxidants like butylated hydroxyanisole and butylatedhydroxytoluene and also conventional drugs like corticosteroids, antiviral and immunosuppressants are quite unsafe and accompanied with serious adverse effects[5]. Hence, the need to explore alternative drugs with lesser side effects for the treatment of hepatic diseases. Herbal medicine involving the use of natural remedies from medicinal plants for medical therapy is now on the rise, particularly in developing regions like Africa, as it is considered to be efficient and safe[6]. Majority of these medicinal plants have been shown to possess pharmacological activities[7-15].

Citrus tangerina (family, Rutaceae) has been used as folk medicine across the African, Asian, and South American continents. Parts of the plant possess biological properties which have been shown to be medicinal[16,17]. Free radical scavenging activity and oxidative stability of *C. tangerina* oils extracted from the seeds of citrus have been reported[18,19]. Little or no research to the best of our knowledge, have been carried out to evaluate the effect of fruit peels extract of *C. tangerina* on antioxidant status of acetaminophen-induced hepatotoxicity in Wistar rats, thus, the aim of this present study.

Materials and Methods

Plant material and preparation of extract

Citrus tangerina fruits were collected from the local market of Abraka, Nigeria and authenticated in the Department of Botany, Faculty of Sciences, Delta State University, Abrakaby a taxonomist (Dr. A.H.Erhenhi). The fruits' peels were rinsed properly with water, air-dried, and powdered. The powdered peel of *Citrus tangerina* (1.67 kg) was extracted exhaustively with 3200 ml of 70% methanol using Soxhlet evaporator at 25-35^{0}C. The filtrate was further concentrated to dryness with the aid of a water bath set at 40 ^{0}C. The weight of the final extract was recorded and stored in the refrigerator prior to the study.

Animals

Wistar rats (150 – 200 g) were procured from Animal House, Faculty of Basic Medical Science, Delta State University, Abraka, Nigeria. The animals were acclimatized for a period of two weeks under standard conditions before starting the study, and were fed rat feed and portable water *ad libitum*. Guidelines followed in the handling of animals were in accordance with the global standard adopted by the Ethical Committee of the Faculty of Basic Medical Science, Delta State University, Abraka, Nigeria.

Experimental design

The rats were randomly placed into five groups, n = 5:

Group I – Normal Control, rats were fed with normal diet for 7 days.

Group II – Acetaminophen Control, rats were given acetaminophen at 500 mg/kg daily for 7 days.

Group III–*C. tangerina* 200, rats were simultaneously given acetaminophen at 500 mg/kg daily + *Citrus tangerina* peel extract at 200 mg/kg daily for 7 days.

Group IV - *C. tangerina* 400, rats were simultaneously given acetaminophen at 500 mg/kg daily + *Citrus tangerina* peel extract at 400 mg/kg daily for 7 days.

Group V– Silymarin (standard drug

treatment), rats were simultaneously given acetaminophen at 500 mg/kg daily + silymarin at 100 mg/kg daily for 7 days.
The experimental animals were orally administered the extracts or silymarin once daily for 7 days. All the animals except the normal control group were administered acetaminophen 500mg/kg/day orally for 7 days[20] before blood samples were collected under chloroform anaesthesia by cardiac thoracic puncture into plain sample bottles and centrifuged at 4000 rpm for 10 min. The serum obtained was used to estimate biochemical paraments. Antioxidants activity via the estimation of serum level of superoxide dismutase (SOD), catalase (CAT) and malondialdehyde (MDA)was analyzed[21-23]. Methods of Reitman and Frankel[24] and Roy[25] were used in determining **a**lkaline phosphatase (ALP), aspartate aminotransefrase (AST), and alanine transaminase (ALT) in serum.

Histopathological studies
The liver was harvested for histopathological studies using haematoxylin-eosin staining method. The tissues were processed andembedded in paraffin wax. Sections of liver tissue were cut and stained with hematoxylinand eosin following standard microtechnique, and were examined under the microscope to analyze the histopathological changes in the liver, with micrographs taken.

Data analysis
Results are presented as the mean ± standard error of the mean (SEM). Data were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. P-values < 0.05 were taken as significant. Data were processed by GraphPad Prism software version 7.

Results

Biochemical assay
There was significant ($P<0.05$) increase in the serum liver enzymes (AST, ALT, and ALP) of rats in the acetaminophen (ACM) control group as compared with those in the normal control group. Administration of 200 mg/kg and 400 mg/kg of *C. tangerina* peel extracts resulted in significant ($P<0.05$) reduction in serum AST. At 400 mg/kg, the extract also significantly ($P<0.05$) reduced serum ALT and ALP levels when compared to the acetaminophen control group. Significant ($P<0.05$) decrease in AST was observed in silymarin-treated rats when compared to the acetaminophen control group. (Table 1)

Non-significant ($P>0.05$) increase in kidney function indices (urea and creatinine) was seen with the acetaminophen control group when compared with the normal control group. Both doses of *C. tangerina* (200 and 400 mg/kg) showed significant ($P<0.05$) decrease on serum urea and creatinine when compared to the acetaminophen control group. Similarly, silymarin significantly ($P<0.05$) decreased urea and creatinine (Table 1).

Comparative significant ($P<0.05$) decrease in serum antioxidant levels (SOD and CAT) and increase in MDA (lipid peroxidation biomarker) were observed in acetaminophen control group as against those in the normal control group. A significant ($P<0.05$) increase in SOD and CAT enzymes with decreased MDA were seen in rats administered *C. tangerina* peel extract at doses of 200 and 400 mg/kg as compared with the acetaminophen control group. (Table 2)

Histopathological analysis
Histopathological analysis of the liver tissues showed massive necrosis of hepatocytes and hepatic congestion, with extensive infiltration by macrophages obviously induced by

acetaminophen administration. Simultaneous treatment with *C. tangerina* peel extracts or silymarin diminished the level of hepatic lesions induced by the hepatotoxin. The observed alterations of the liver architecture coincided with the corresponding changes in the enzyme levels, thus the hepatoprotective effect of *C. tangerina* fruit peel extract was established. (Figure 1)

Table 1: Effect of *Citrus tangerina* fruit peel on liver and kidney parameters in acetaminophen (PCM)-induced hepatoxicity in rats

	AST (IU/L)	**ALT (IU/L)**	**ALP (IU/L)**	**Urea (mg/dL)**	**Creatinine (mg/dL)**
Normal Control	46.41 ± 1.51	11.53 ± 1.79	31.23 ± 3.27	16.30 ± 0.64	2.63 ± 0.05
ACM control	66.71 ± 0.94 *	18.92 ± 3.18 *	48.77 ± 1.18 *	19.43 ± 2.78	3.80 ± 0.34
C. tangerina 200	48.74 ± 0.71 **	13.66 ± 2.13	38.70 ± 3.18	14.76 ± 0.61 **	2.81 ± 0.51 **
C. tangerina 400	48.55 ± 1.17 **	9.64 ± 1.76 **	35.70 ± 2.20 **	10.10 ± 0.80 **	2.25 ± 0.35 **
Silymarin	48.86 ± 0.75 **	13.94 ± 1.85	40.42 ± 2.04	7.26 ± 0.54 **	2.23 ± 0.76 **

All values are expressed as mean ± standard error of mean (SEM); n=5
** = P<0.05 when compared with normal control;** = P<0.05 when compared with acetaminophen control group*

Table 2: Effect of *Citrus tangerina* fruit peel on antioxidative parameters in acetaminophen (PCM)-induced hepatoxicity in rats

	SOD (IU/L)	**CAT(IU/L)**	**MDA(IU/L)**
Normal Control	0.59 ± 0.03	1.02 ± 0.05	0.41 ± 0.06
ACM control	0.37 ± 0.04 *	0.55 ± 0.09 *	0.73 ± 0.07 *
C. tangerina 200	0.65 ± 0.01 **	0.93 ± 0.01 **	0.42 ± 0.04 **
C. tangerina 400	0.77 ± 0.01 **	1.12 ± 0.06 **	0.40 ± 0.02 **
Silymarin	0.99 ± 0.05 **	1.51 ± 0.04 **	0.42 ± 0.04 **

All values are expressed as mean ± standard error of mean (SEM); n=5
** = P<0.05 when compared with normal control;** = P<0.05 when compared with acetaminophen control group*

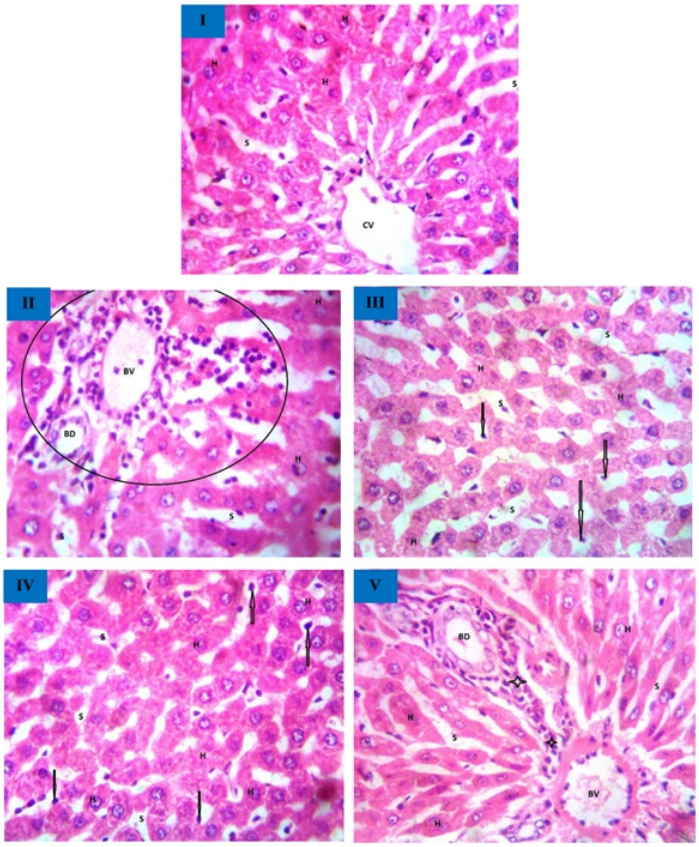

Figure 1: Photomicrograph of liver histology. **I** (normal control) – shows hepatic tissue free from inflammatory cells and congestion; **II** (acetaminophen control) – shows marked periportal hepatitis (circle) infiltrated by inflammatory cells; **III** (*C. tangerina* 200) – shows moderate activation of hepatic macrophage (arrow) within the sinusoids; **IV** (*C. tangerina* 400) – shows mild hepatic macrophage (arrow) within the sinusoids; **V** (silymarin) – shows mild periportal inflammatory cells infiltration (star) with sinusoids free from congestion. *(CV–central vein; H–hepatocytes; s–sinusoids; BV–blood vessel; BD–bile duct) (H&E staining; ×400 magnification).*

Discussion

In recent times, search for newer drug of herbal origin is on the rise as researches continue to attempt discoveries at best therapy for hepatic diseases[26]. The present study evaluated the efficacy of methanol fruit peel extract of *C. tangerina* in preventing hepatic cell damage produced by excessive dose of acetaminophen. Acetaminophen elicits its hepatotoxic effect by its toxic phase I metabolite (N-acetyl-p-benzoquinineamine) binding to cellular components of hepatocytes, consequently leading to cell necrosis[4,27]. Silymarin is a well established drug treatment for liver damage[28]. As an antioxidant compound, silymarin scavenges free radicals that are destructive to cell, increases the level of antioxidant enzymes in the liver, and promotes hepatic cell regeneration by stimulating protein synthesis in the liver[29,30].

Acetaminophen resulted in an increase in the levels of serum AST, ALT, and ALP, which are biomarkers of hepatic cell damage and loss of functional integrity[31]. Results from this study revealed that *C. tangerina* fruit peel extract reduced the acetaminophen-induced elevated serum liver function enzymes,

although this effect was profound at the higher dose of 400 mg/kg. This implies that 400 mg/kg of *C. tangerina* fruit peel will improve health status of hepatocytes. Liver histology revealed that *C. tangerina* fruit peel extract can possiblyattenuate hepatic damage induced by acetaminophen. The observed cellular repair by *C. tangerina* fruit peel extract is much similar to that produced by silymarin in this study.

Daily dosing with acetaminophen 500 mg/kg caused a decrease in the serum levels of superoxide dismutase and catalase, and induced lipid peroxidation by increasing malondialdehyde serum level. This resulted in elevation of oxidative stress on hepatic cell[32]. *Citus tangerina* fruit peel extract co-administration with acetaminophen markedly alleviated the induced oxidative stress in a dose-dependent manner by decreasing the elevated MDA level while increasing SOD and CAT levels. This is an indication that generated reactive oxygen species could be scavenged by the fruit peel extract of *C. tangerina*, hence, its oxidative stability potential. The antioxidant effect of *C. tangerina* fruit peel extract may be implicated in the cell damage repair of liver cells as reported in this study (Figure 1).

The hepatoprotective and antioxidant effects of the fruit peel extract of *C. tangerina* may be attributed to the fact that it is enriched with flavonoids and phenolic compounds which have potent antioxidant actions[17,18]. Absorption and neutralization of free radicals, inhibition of enzymes associated with reactive oxygen species (ROS) pathways, and improvement of antioxidant enzymes activities (SOD, CAT, GSH) are basic mechanisms by which these phytochemicals exhibit antioxidant actions[33-36].

Conclusion

The result of this study evidently reveals that alterations produced by the administration of acetaminophen in the various biochemical parameters, namely AST, ALT, ALP, urea, creatinine, SOD, CAT, and MDA were reversed significantly by the treatment with extracts of *C.tangerina* fruit peels. Histopathological examinations of the rat liver supported this finding as shown from the regeneration of hepatocytes upon treatment with *C. tangerina* fruit peel extract. This study suggests that *C. tangerina* fruit peel extract possess antioxidant property and attenuates cell damage in acetaminophen-induced hepatotoxicity.

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Citation: This article should be cited as: Moke EG, Umukoro EK, Anachuna KK, Daubry TME, Ezedom T, Asiwe JN. Fruit Peels of Citrus Tangerina Attenuate the Oxidative Stress and Cell Damage Caused by Acetaminophen on Wistar Rats. Afr. J. Trop. Med. & Biomed. Res. 2021; 5(1): 46-53

Sociodemographic Characteristics And Outcomes of Teenage Pregnancy at the John. F. Kennedy(JFK) Maternity Center, Monrovia, Liberia.

Odunvbun, W.

Abstract

Background: Teenage Pregnancy is a high-risk condition with adverse maternal and perinatal outcomes. The Literatures suggest an increase in global trend, as a result of sociodemographic variables.
Aim: To determine the sociodemographic characteristics and pregnancy outcomes among teenage mothers at John F. Kennedy Maternity Center.
Methods: A retrospective study involving the evaluation of obstetric records of teenage mothers at the JFK maternity center, Monrovia from October 1, 2018, to September 30, 2019. Data was analyzed using IBM SPSS statistics for windows, version 20.
Results: Total antenatal registration was 5,560. Total delivery was 3,600, made up of 73.0% vaginal deliveries and 27.0% caesarean sections. Teenagers accounted for 11.6% and 4.0% of all pregnancies and deliveries, respectively. Compared to the general obstetric population, teenagers had fewer caesarean sections (21.0% versus 27.0%). The mean age of subjects was 16.0 ± 1.1 years. About 50.0% (63/124) of the subjects were below 17 years, they were all single and mostly (90%) residing with their parents. One-fifth (25/124) of the subjects had no formal education. All the pregnancies were not desired. About a quarter (29/124) had pregnancy-related complications. There were two perinatal deaths from cord prolapse and obstructed labour. Prenatal care was associated with less complication and improved fetal weight. There was no mortality among subjects.
Conclusion: This study established an institutional prevalence of teenage pregnancy of 11.6% and delivery rate among teenage mothers of 4.0%. Low level of education was associated with higher pregnancy complications, while booking status and prenatal care was associated with improved fetal weight.

Keywords: Teenage pregnancy, Prevalence, Pregnancy outcome, Fetal outcome

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Introduction.

Teenage pregnancy remains a global challenge, requiring attention all over the world.[1] Sub-Saharan Africa is reported to have had the highest prevalence of teenage pregnancy in the world in 2013.[1]. The consequences following teenage pregnancy are numerous. These include obstetric, health, economic and social problems. Pregnancy in a teenager is more likely to result in obstetric complications such as incontinence from obstetric fistula, eclampsia, postpartum haemorrhage, sepsis, and a five-fold increased risk of maternal mortality.[2,3]

Teenage pregnancy contributes to lifelong health disparities for both the mother and the child.[4] In contrast to adult women who become pregnant, teenage mothers are more likely to have low educational attainment and

fewer employment opportunities.[5,6] Recent studies on teenage pregnancy in sub-Saharan Africa have looked at individual-level demographic, socio-economic, and reproductive health knowledge and behavior parameters.[7-10]

Many physical, psychological, environmental, and socio-cultural factors, such as peer pressure, lack of knowledge of reproductive health, have been associated with adolescent pregnancy, especially in developing countries, as this is a transition period.[11] Access to pregnancy preventive measures such as contraceptives, sexual health information, and family planning services are not available to adolescents in many societies.[12] Even when contraceptives are widely available, adolescents are less likely to use them, compared with adults.[12]

Between 1989 and 2003, Liberia suffered two civil wars, with significant disruption in family life and human casualty, estimated to be over 500,000, and well over a million people displaced from their homes.[13] About two decades after the end of the second war in 2003, the extent of the social and family disruption is not known. Teenage pregnancy is one of such social and family disruptions that could occur during and after war. Therefore, the objective of this study was to determine the prevalence of teenage pregnancy in post-war Liberia and the pregnancy outcome.

Materials and Methods

This was a cross-sectional retrospective study of teenage mothers who were managed at John. F. Kennedy (JFK) Maternity Center, Monrovia, Liberia, from October 1, 2018, to September 30, 2019. This is a public health facility established in 1971. It provides tertiary health services and training in Obstetrics and Gynaecology, Paediatrics, Surgery, Internal Medicine, among other specialties. Services are paid for by patients, though subsidized by the Liberian government. However, teenage mothers whose education was interrupted by pregnancy and are living with their parents are supported by a program designed by the JFK maternity center management, called " Parenting the parent." It involves cost-free maternity services, while the teenage mother is encouraged to continue her education after childbirth. Most of the other public health facilities in the remaining 14 counties of Liberia provide free maternity services.

This study involved reviewing pregnancies managed at the John .F. Kennedy Maternity Center, from October 1, 2018, to September 30, 2019. Relevant information was obtained from the ANC register, labour ward, and theatre records.

Included in the study were case notes of all pregnancies occurring between the age range of 13 to 19 years. Case notes of patients whose ages were not documented was excluded.

Information on teenage mother's socio-demographic variables and booking status was obtained. Also captured were variables relating to teenage pregnancy outcome, such as complication and mode of delivery. Birth weight and neonatal intensive care unit (NICU) admission were used to assess fetal outcome.

Ethical approval was obtained from the Institutional Review Board (IRB) of John F. Kennedy Medical Center, Liberia.

Data analysis

Data collected were analyzed using IBM SPSS statistics for windows, version 20.0 (IBM Corp, Armonk, NY, USA), and presented in the form of frequency tables and descriptive statistics. Chi-square was used for tests of

statistical differences, for categorical variables. P<0.05 was considered statistically significant.

Results

Case note retrieval from the medical records on teenagers' deliveries was 124/145 (85.5%).

The total antenatal registration during the study period was 5,560. The total delivery was 3,600, made up of 2,640/3,600(73.0%) vaginal deliveries and 960/3600 (27.0%) Caesarean section.

Teenage pregnancies accounted for 645/ 5,560 (11.6%) during the study duration. Mothers whose ages were from 13 to 19 years accounted for145/3600 (4.0%) of the total deliveries. Vaginal deliveries by teenage mothers, accounted for 98/124(79.0%) while Caesarean section was 21.0% (26/124) When compared with total deliveries, there was fewer caesarean sections among the teenage mothers (21.0% versus 27.0%).

About 63/124 (50.0%) of the subjects were below the age of 17 years. The mean age of subjects was 16.0 ±1.1 years. They were all single, with the majority (90%) of the teenagers residing with their parents. Over 80% of the parents of the subjects were cohabitating with their spouses. One-fifth (25/124) of the subjects had no formal education. Eighty-four percent (104/124) were students. [Table 1]

About a quarter (29/124) of the subjects had complications, with pre-eclampsia and anaemia, being the leading two complications [Table 2]

A low level of education was associated with more complications among teenage mothers (P < 0.001). [Table 3

A total of sixteen(12.9%) neonates delivered by the subjects were admitted into NICU due to birth asphyxia. There were two (1.6%) perinatal deaths from cord prolapse and obstructed labour. Both were fresh still birth (FSB) and referrals from the county hospitals, located several kilometers from JFKMC [Table 4].

The mean weight of neonates was 2.85 ±0.51 Kg. Booking status was associated with higher foetal weight (P< 0.001).[Table 5]
There was no maternal death in this study.

Table 1: Socio-demographic characteristics of subjects of teenage pregnancies

	Frequency	Percentage
Age (Years)		
13-16	63	50.8
17-19	61	49.2
Marital Status		
Single	124	100
Married	0	0
Type of parental relationship		
Cohabitation	110	88.7
Married	14	11.3
Place of residence		
With parents	122	98.4
With boyfriend	2	1.6
Educational qualification		
No formal education	25	21.0
Primary	53	42.0
Secondary	45	36.2
Tertiary	1	0.8
Booking Status		
Yes	85	68.5
No	39	31.5

Table 2: Frequency distribution of Booking Status, the desirability of pregnancy, Complications and Type of complications among subjects.

	Frequency	Percentage
Pregnancy Desired		
Yes	0	0
No	124	100.0
Pregnancy complication		
Yes	29	23.4
No	95	76.6
Types of complication		
Pre-eclampsia	8	27.6
Anaemia	6	20.7
Malaria	5	17.2
Intra-uterine growth restriction	4	14.0
Prolonged labour	3	10.3
Obstructed labour	2	7.0
Cord prolapse	1	3.2

Table 3: Relationship between socio-demographic characteristics with pregnancy complications among subjects

	Pregnancy complication at Presentation			
	Yes	**No**	c^2	p
Age Group				
13-16	15(23.8)	48(76.2)	0.013	0.910
17-19	14(23.0)	47(77.0)		
Marital Status				
Single	29(23.8)	93(76.2)	0.621	0.431
Co -habiting	0	2		
Educational qualification				
None	4(16.0)	21(84.0)	17.803	<0.001
Primary	22(41.5)	31(58.5)		
Secondary	3(6.7)	42(93.3)		
Tertiary	0(0.0)	1(100.0)		
Booking Status				
Yes	16(18.8)	69(81.2)	3.141	0.076
No	13(33.3)	26(66.7)		

Table 4: Mode of Delivery and Fetal Outcome among subjects

	Frequency	Percentage
Type Delivery		
Spontaneous Vaginal delivery	98	79.0
Caesarean Section	26	21.0
Fetal Outcome		
NICU Admission	16	12.9
FSB	2	1.6

Table 5: Relationship between Booking Status and Birth weight of Neonate delivered by teenage mothers

	Birth Weight		Chi-square	P
	<2.5kg	≥2.5kg		
Booking Status				
Yes	14(16.5)	71(83.5)	28.5	<0.001
No	20(69.0)	9(31.0)		

Mean Weight of Neonates 2.85 ±0.51

Discussion

The institutional prevalence of teenage pregnancy and birth was 11. 6%, and 4.0% respectively. These rates were lower than the rates quoted in similar studies in Africa.[12,14,17] John F. Kennedy (JFK) Maternity Hospital is the only fully functional, tertiary health facility in Liberia. Services are paid for by patients, except those who meet the selection criteria of the "parenting the parent" program of JFK management. Maternity services in the other 14 county government health facilities are cost free. Therefore, it is likely that the population prevalence of teenage pregnancy may be higher than the 11.6% recorded in this study. Family disruption was reported to be inversely related to teenage Pregnancy in East Africa.[18] Liberia suffered two civil wars in about a decade, resulting in major socio-economic and family disruption, resulting in a loss of half-a-million lives.[13]

The social practice of cohabitation is accepted in Liberian society, which is the rule

rather than the exception. The extent to which the civil war contributed to this practice is not fully known. The combined roles of fractured family life, low level of education, and poverty, as a consequence of the war, may indirectly have a link with teenage pregnancy in any society, including Liberia. All the pregnancies were undesired. This raises some concern about adolescent sexuality and contraception, in Liberia. In a study conducted, it was discovered that 97% of adolescents from 14-17 years among non-students and those with low educational level, have sexual relations at least once a month.[19] The mean age of teenage birth in this study was 16±1.3 years. Education and socio-economic status have been identified consistently as determinants of teenage pregnancy in different studies.[7] A previous study shows that neighborhoods characterized by poverty had higher levels of teenage pregnancy, as teens living in poor communities with fewer opportunities are more likely to engage in sex at earlier ages and eventually become pregnant.[20] Additionally, in localities where poverty is rife, young people may also turn to transactional sex as an economic survival strategy with a pregnancy resulting if contraception fails or the need is unmet.[20] In a descriptive study conducted in Nigeria by Isa and Gani,[8] it was discovered that most 14 to 19-year girls who got pregnant were from low social class.[10] Arguments justifying teenage marriage have often been based on the economic ground and seen as a means of reducing economic burden within the household by marrying off female children and reducing household size with provisions made, through dowry obtained from the groom upon marriage.[18] The situation in Liberia is similar, as opinions and views among citizens suggest that some mothers compel their teenage daughters to contribute financially to the home, through relationship with male partners. In addition, the increasing level of poverty in post war Liberia has increased the economic burden on many families. These could contribute to the prevalence of teenage pregnancy in the country.

The mitigating effect of ANC on the adverse effect of teenage pregnancy was identified in our study. Studies suggest that low education levels and inadequate prenatal care are a contributory factor for the higher incidence of adverse pregnancy outcomes among teenagers.[22,23] Even after adjusting for socio-economic characteristics, de Vinne *et al.* found an association between poor antenatal care and pregnancy outcomes.[22] Our finding of fewer caesarean delivery and higher normal vaginal delivery among teenage mothers is consistent with the findings in a study in Cameroon that suggested that adolescents were likely to have a vaginal delivery and had a lower risk of Caesarean section than adults. These findings contradict reports in the literature.[12] An explanation for this may include the fact that the majority (85/124) of subjects were booked and received prenatal care in the facility, and labour was adequately supervised.

The leading pregnancy complication among teenage mothers in this study was pre-eclampsia and anaemia. Some studies showed that teenage pregnancy was significantly associated with anaemia.[23,2] Underlying poverty and poor nutrition may be the reason for the anaemia in these young mothers. The teenage mothers of the two FSB traveled over several kilometers from the referring county hospitals. There was no death among teenage mothers. The relatively small sample size may be an explanation for the absence of maternal death.

Limitations in our study included the small sample size with a relatively high attrition rate (14.5%) in case note retrieval. The retrospective study design is another limitation. The study site is the only functional tertiary health facility in Liberia, with out-of-pocket services. This contrasts with ANC services in the county health facilities that are free and consequently attract more patronage, consequently, the population prevalence of teenage pregnancy is likely to be higher. Despite these limitations, this study has established the institutional prevalence of teenage pregnancy at the JFK maternity center. A prospective, multi-center study to examine the impact of social and economic factors on teenage pregnancy in Liberia is recommended.

Conclusion

This study established an institutional prevalence of teenage pregnancy of 11.5% and delivery rate among teenage mothers of 4.0%. Low level of education was associated with higher pregnancy complications, while booking status and prenatal care was associated with improved fetal weight.

Acknowledgements

The author would like to appreciate the contributions of the following persons to this study, Drs Numeine E. Enders and Galakpa G. Johnson, resident doctors in the department. Special thanks also to the head of department, medical records and theater.

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Citation: This article should be cited as: Odunvbun W. Sociodemographic Characteristics and Outcomes of Teenage Pregnancy at The John. F. Kennedy (JFK) Maternity Centre, Monrovia, Liberia. Afr. J. Trop. Med. & Biomed. Res. 2021; 5(1): 54-63