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The Dilemma of Exogenous Antioxidant Therapy in Clinical Practice in Nigeria: Insight into Health Implication

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Authors' contributions

This work was carried out in collaboration between all authors. Author BKMM wrote the first draft of the manuscript. Authors SCM and CED managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

The growing interest among health care users in developing countries on antioxidant therapy has led to indiscriminate abuse of highly marketed antioxidant therapy. In a normal cell, there should be a balance of activities between free radicals and antioxidants which are tightly regulated by the homeostatic mechanism of the human body. How does antioxidant therapy effect this balance? This review will be throwing light on the import of exogenous supplementation of antioxidants, especially in a disease state.

Keywords: Antioxidant therapy; exogenous antioxidant; antioxidant supplementation.

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1. INTRODUCTION

Antioxidants are biological substances that decrease or inhibit synthesis, scavenge and neutralise the effects of free radicals. In a normal cell, there tends to be a balance of activities between prooxidants, oxidants and antioxidants. Whereas, prooxidants increase the production and concentration of oxidants and the generation of oxidative stress. Antioxidants suppress the production or mitigate the effect of oxidants. Therefore, antioxidants play a pivotal role in the prevention of oxidative stress. Antioxidant therapy has taken a commonplace in the treatment of various ailments in Nigeria and other developing countries in Africa. These antioxidants are sold in the form of herbal concoctions, nutraceuticals and pharmaceuticals. An antioxidant market is fast growing in these countries. The quest for good health and cure has driven many patients and apparently healthy individuals into the unregulated market of antioxidants which are branded 'blood cleanser, body detoxifiers, healthy supplements etc to attract consumers. This antioxidant supplementation is rampant in patients that have chronic and terminal illnesses such as diabetes mellitus, benign prostate hypertrophy, cancer of the prostate, cancer of the breast, hypertensives etc. The question remains: Antioxidant Therapy; is it beneficial in the management and prevention of these diseases?

2. CLINICAL STUDIES DONE IN NIGERIA

Several works were done in Nigeria to determine the levels of antioxidants in a disease state. In a study, measurement of catalase, superoxide dismutase activities, ascorbic acid (vitamin C) and tocopherol (vitamin E) as an assessment of total antioxidant status indicated that hypertensive subjects had a significantly lower antioxidant status than normotensive subjects. Antioxidant vitamin supplementation for two weeks reduced systolic/diastolic blood pressures of the newly diagnosed hypertensive subjects from 171/104 to 164/95mm Hg, while the hypertensive subjects already on antihypertensive drugs had their blood pressures reduced significantly to 136/85mm Hg [1]. This reduction in blood pressure may not be entirely attributed to antioxidant supplementation, since exercise, diet modification and drugs may also have produced a similar effect. Long-term longitudinal study may be required to ascertain the effect of the anti-oxidant supplementation. In 2014, another study was carried out on 54 hypertensives attending the outpatient clinic of the Usman Dan Fodio University Teaching Hospital, Sokoto, Nigeria and the results were compared with those of apparently healthy non-hypertensives. This study was aimed to estimate blood pressure, vitamins A, C, and E levels in volunteers of comparable age and social status. There were significantly increased levels of blood pressure and significantly decreased levels of antioxidant vitamins A, C, and E in hypertensives. 80% of the hypertensives have deficient serum levels of the vitamins. However, oxidative stress indicators should have been assayed concurrently to ascertain oxidative stress [2].

A study done in 2013, also revealed that *P. falciparum*-infected pre-school children have lower levels of antioxidant vitamins C and E. The low antioxidant vitamin levels observed in this study was attributed to increased utilization of the host's plasma antioxidants by the malaria parasite to counteract the malarial infection-associated oxidative damages [3]. However, anorexia associated with malarial infection as well as age-dependent lipid soluble vitamins depot may also be an essential factor to be considered. In another study, carried out in 2016 to determine levels of trace elements and antioxidant vitamins in Type 2 diabetic patients in Ile-Ife, Nigeria. Reduced Zinc(Zn) and vitamin E level in people with diabetes were found. Those with diabetic nephropathy and retinopathy had lower vitamin E than others [4]. Diabetics mellitus is associated with osmotic polyuria and dyslipidaemia and in part may lead to increased urinary loss and impaired storage of these antioxidant vitamins and co-factors. Similarly, another study carried out on diabetics in 2014 observed in a clinical trial that 88% of the eighty study subjects admitted to relief from "burning pain," and this was noticed 2 weeks following usage of the combination of vitamin E and Eve primrose oil. Vitamin E is an antioxidant vitamin while Eve primrose oil consist of gamma linolenic acid (GLA) [5]. However, subsequent study may consider assessment of glycaemic control at interval in subjects on these therapy in order to rule out improved glycaemic control as a confounding factor. Low Serum Vitamin C Status was observed among fifty-one Pregnant Women Attending Antenatal Care at General Hospital Dawakin Kudu, Northwest Nigeria [6]. Vitamin C deficiency may be accounted partly by the physiological haemodilution of pregnancy, inadequate intake and the use of vitamin C to combat the physiological increase in oxidative

stress associated pregnancy [7]. High nutritional demand of pregnancy may have been a most important cause especially in an environment known for nutritional taboos among pregnant women as well as scarcity of fruits and vegetables [8]. This region is characterized by a relatively hot climate with seasonal rainfall and a marked dry season [8]. Duru et al; 2014 also studied antioxidants in Patients with Prostate Disorders in Enugu, South-East Nigeria. Benign Prostate Hypertrophy(BPH) and Prostate Cancer patients had a significant decrease in glutathione peroxidase (GPx), Superoxide dismutase(SOD), vitamin C and vitamin E concentrations. A significant decrease in SOD and vitamin C levels were observed in Prostate Cancer patients when compared with the BPH group [9]. In another work done by Adaramoye et al .2010, trace elements and Vitamin E status in Nigerian patients with prostate cancer were studied. Superoxide dismutase (SOD), serum Selenium (Se) and zinc(Zn) concentrations were found to be significantly lower in the Prostate Cancer patients [10]. According to work done by Fasola et al.2010 in University College Hospital Ibadan Total Antioxidant Status levels were about 50% lower in the forty Sickle Cell Anaemia(SCA) patients in Steady State compared with control subjects [11]. In 2016, Sabir et al in a study carried out in Sokoto, North-Western Nigeria, found that the subjects with metabolic syndrome had significantly higher malondialdehyde as compared to those without metabolic syndrome. The antioxidant enzymes (superoxide dismutase, glutathione peroxidase and catalase) were significantly lower in subjects with metabolic syndrome than in those without metabolic syndrome respectively. Similarly, the antioxidant Vitamins (A, C, and E) levels were significantly lower in subjects with metabolic syndrome than in those without metabolic syndrome. There was a positive correlation between components of metabolic syndrome and free radicals [12]. In a study carried out in Owerri, Imo state Nigeria, Thiobarbituric reactive substance-Malondialdehyde (TBARS-MDA) and vitamin E concentrations was found to be decreased while vitamin C increased in hypertensive patients. On the contrary, TBARS-MDA level was found to be decreased while vitamin C level still increased in hypertensive diabetic patients compared to normotensive subjects [13].

In another study carried out in Nnewi, Anambra state Nigeria in 2015 among the female diabetic patients. The level of Glutathione Reductase and Total Antioxidant Status(TAS) were significantly lower in hypertensive diabetic patients while vitamin C level increased significantly in both hypertensive and hypertensive diabetic patients which is contrary to the finding by Wali et al [14] which found vitamin C level to be reduced in hypertensive subjects compared to normotensive patients.

Odum et al. 2012 also found that the Total Antioxidant Status, vitamin C and vitamin E of Type 2 Diabetes Mellitus patients to be decreased compared with those of controls. Significant increases in the levels of lipid peroxide (LPO) and 8-hydroxyl-2′-deoxyguanosine (8-OHdG) and glutathione peroxidase (GPx)activity were also found in diabetic foot ulcer(DFU) patients compared to controls [15]. Significant decreases in vitamin C, selenium(Se), vitamin E, TAS concentrations were also detected among DFU patients recruited from University College Hospital and Adeoyo Hospital, Ring Road, Ibadan in a study carried out by Bolajoko et al [16]. The plasma levels of total peroxide potential (TPP), total antioxidant potential (TAP), malondialdehyde (MDA), oxidative stress index (OSI) and nitric oxide (NO) were significantly lower among rheumatoid arthritis (RA) patients compared with controls in a study carried out by Yeldu et al [17].

Many works done in Nigeria emphasised antioxidant deficiency in the various clinical state. This deficiency seemingly cuts across most diseases. Increase in free radicals generated in disease states cannot be overemphasised. The various disease state is often associated with anorexia due to central or peripheral mechanisms this can in turn lead to malnutrition which may be a major contributor to deficiency of antioxidant vitamins in a disease state. Hence, insinuations that exogenous antioxidant requirement is needful in various disease state. However, there are few works on large scale clinical trial experimenting the advantage of antioxidant therapy supplementation in management outcome. More so, Long-term prospective studies on long-term therapy of antioxidant therapy in chronic diseases such as hypertension, diabetes mellitus and cancers are also lacking. Increased generation of free radical in disease state may not always lead to oxidative stress as it seems because of the compensatory increase in endogenous antioxidant generation ability of the homeostatic system of the body in the face of excessive free radical challenge. Since, the physiological homeostatic mechanism maintains a delicate balance between level of

Table 1. Various clinical studies on antioxidants in Nigerian subjects

S/No	Research	Clinical state	Result	References
1	Antioxidant Status of Subjects with Essential Hypertension in a Nigerian Population	Hypertension	Vitamin A, Vitamin E, catalase and glutathione were reduced in hypertensives. Decreased blood pressures were observed after 2 weeks of vitamin A and E supplementation.	Ihemeje et al. [1]
2.	Antioxidant vitamins status of hypertensive subjects in Sokoto, Nigeria.	Hypertension	Decreased levels of antioxidant vitamins A, C and E observed in hypertensives.	Wali et al. [2]
3.	Antioxidant vitamin levels among preschool children with uncomplicated *Plasmodium falciparum* malaria in Sokoto, Nigeria	Malaria	(a) Antioxidant concentrations of vitamins A, C, and E were significantly lower among plasmodium-parasitized subjects. (b) The higher the level of parasitaemia, the lower the antioxidant concentration.	Aghedo et al. [3]
4.	Levels of Trace Elements and Antioxidant Vitamins in Type 2 Diabetic Patients in Ile-Ife, Nigeria	Diabetic Mellitus	Reduced Zn and vitamin E level in people with diabetes especially those with diabetic nephropathy and retinopathy.	Fagbohun et al. [4]
5.	Treatment of diabetes mellitus-associated neuropathy with vitamin E and Eve primrose(EP)	Diabetic neuropathy	Two weeks following usage of the combination of vitamin E and EP oil, eighty-eight percent of the patients admitted relief to neuropathic pain.	Ogbera et al. [5]
6.	Low Serum Vitamin C Status Among Pregnant Women Attending Antenatal Care at General Hospital Dawakin Kudu, Northwest Nigeria	Pregnancy	Low serum Vitamin C concentrations found among pregnant women.	Ugwa et al. [6]
7.	Oxidative Stress Indicators in Patients with Prostate Disorders in Enugu, South-East Nigeria	Prostate Disorders	BPH and Prostate Cancer patients had a significant decrease in GPx, SOD, vitamin C, and vitamin E level. This decrease was more in Prostate Cancer patients.	Duru et al. [9]
8.	Trace elements and Vitamin E status in Nigerian patients with prostate cancer	Prostate Cancer	SOD, Se and Zn were significantly lower in the Prostate Cancer patients.	Adaramoye et al. [10]

9.	Total Antioxidants Status and Some Haematological Values in Sickle Cell (SC) Patients in Steady State	Sickle Cell Anaemia	Total Antioxidant Status levels were lower in the SC patients compared to control subjects.	Fasola et al. [11]
10	Oxidative stress among subjects with metabolic syndrome in Sokoto, North-Western Nigeria	Metabolic syndrome	Metabolic syndrome subjects had higher MDA as compared to those without metabolic syndrome. SOD, GPx, Catalase and Vitamins (A, C, and E) were lower in subjects with metabolic syndrome than control.	Sabir et al. [12]
11	Lipid peroxidation and non-enzymatic antioxidants status in hypertension in diabetic and non-diabetic patients in Nigeria: a comparative study.	Diabetes mellitus	Concentrations of TBARS-MDA and vitamin C were found to increase in hypertensive patients while vitamin E was observed to be decreased. On the contrary, TBARS-MDA level was found to be decreased while vitamin C level increased significantly in hypertensive diabetic patients compared to normotensive patients	Ekeanyanwu et al. [13]
12	Evaluation of antioxidant status of Female diabetic patients in Nnamdi Azikiwe University Teaching Hospital, Anambra State, Nigeria	Diabetes mellitus	Glutathione Reductase and TAS were significantly lower in diabetics compared to the control group while vitamin C level increased significantly in hypertensive and hypertensive diabetic patients compared to normotensive subjects	Okuonghae et al. [14]
13	Antioxidant status of type 2 diabetic patients in Port Harcourt, Nigeria	Diabetes mellitus	TAS, vitamin C and E levels are reduced in diabetics patients compared with controls.	Odum et al.[15]
14	A relationship between selected micronutrient deficiencies and oxidative stress biomarkers in diabetes mellitus patients with foot ulcers in Ibadan, Nigeria	Diabetes foot ulcer	Significant increases in the levels of LPO and 8-OHdG and GPx activity and decreases in vitamin C, Se, vitamin E and TAS were found in DFU patients compared to controls.	Bolajoko et al.[16]
15	Oxidative stress factors in Nigerians with rheumatoid arthritis	rheumatoid arthritis	The plasma levels of TPP, TAP, MDA, OSI and NO were significantly lower among RA patients compared with controls	Yeldu et al .[17]

S/NO: Serial No, Se-Selenium, Zn-Zinc, GPx- Glutathione Peroxidase, SOD-Superoxide Dismutase, TBARS-MDA-Thiobarbituric acid reactions, TAS-Total Antioxidant status, 8-OHdG-8-hydroxyl-2'-deoxyguanosine, DFU-Diabetic Foot Ulcer, TPP- Total peroxide potential, MDA- Malondialdehyde, OSI- Oxidative stress index, NO- Nitric oxide, LPO - lipid peroxide

reactive oxygen species or free radical and antioxidant. Works comparing the usefulness of antioxidant drug/supplement and cheap readily available fruits and vegetable as source of antioxidant in various disease states are few. Antioxidant toxicity level in human study are also lacking in Africa. Nutraceuticals and food supplements most often contain large unestablished doses of antioxidants. Lipophilic antioxidants such as carotenoids and tocopherols despite their protective role persists longer in the system and thus characteristically subjects an individual to its toxicity especially when taken in prolonged duration. Therefore, caution should be emphasized on the use of antioxidant. Outcome of various clinical trials from other countries will be reviewed to emphasize why caution is being advocated in the use of exogenous antioxidant therapy in management and prevention of various diseases and to emphasize on the needs for more extensive study in these area in our environment.

3. CONTROVERSIAL ROLE OF ANTIOXIDANTS SUPPLEMENTS IN PREVENTION AND TREATMENT OF DISEASES

The use of antioxidants to prevent some diseases is controversial while some studies suggest that antioxidants are beneficial and protective, other interventional trials showed no health benefits [18]. There are some interventional studies which demonstrated the deleterious effects of antioxidants (high risk of cancer, increased mortality). Further, antioxidant supplements were found to diminish the beneficial effects of certain drugs. It is suggested that indiscriminate use of antioxidant supplements should be avoided. Perhaps, antioxidants may be prescribed (not exceeding the recommended daily allowance) to the elderly, strict vegetarians or people who are on calorie-restricted diets. It is advisable that the antioxidants are consumed from rich natural dietary sources rather than supplements. Further, healthy individuals should exercise utmost caution while overdosing themselves with antioxidant supplements [18].In a high-risk group like smokers, high doses of beta carotene increased the rate of lung cancer since high doses of beta-carotene in conjunction of high oxygen tension due to smoking results in a pro-oxidant effect and an antioxidant effect when oxygen tension isn't high [18,19].However, while consumption of food rich in vitamin E may reduce the risk of coronary heart disease in middle-aged to older men and women, using vitamin E supplement also appears to result in an increase in total mortality, heart failure, and haemorrhagic stroke [19,20] The American Heart Association therefore recommends the consumption of food rich in antioxidant vitamins and other nutrients, but does not recommend the use of vitamin E supplements to prevent cardiovascular disease [21]. In other diseases, such as Alzheimer's, the evidence on vitamin E supplementation is also mixed [22]. Based on the proven beneficial effects of antioxidants in nutrition, cytoprotection, regulation of cell growth and division, immune defence, protection against cancer, infections etc; Also, The synthetic polyphenolic antioxidant di-tert-butyl-bisphenol (BP)was found to ameliorate oxidative damage and preserves cerebral tissue during focal ischemic insult thereby contributing significantly to neuroprotection [23]. Antioxidants have potential role in the prevention and treatment of diseases. Generation of free radicals and oxidative stress have been implicated in the pathogenesis of many disease processes. Therefore, antioxidants have potential preventive and therapeutic roles against various diseases, such as cancer, Cardiovascular diseases, Diabetes Mellitus and Neurodegenerative diseases. Some randomized controlled trials of vitamin E and antioxidant cocktails have produced beneficial outcomes. Regular and adequate intake of antioxidants, especially antioxidant vitamins have been recommended for prevention of diseases such as: Cancer, Diabetes Mellitus, Cardiovascular Diseases, Sickle cell crises, Premature aging, Acute respiratory diseases Syndrome (acute lung injury) and Neurodegenerative diseases: Alzheimer’s disease, Parkinson’s disease. However, choice of antioxidant supplementation should be made cautiously.

Paschalis et al. [24] found that individuals who had low levels of vitamin C values showed decreased performance in aerobic exercise as well as increased oxidative stress. This does not support the need to supplement certain antioxidants. Rather, it supports the need for a well-balanced diet composed primarily of whole foods [24]. Fruits and vegetables are rich in natural antioxidants (very good dietary source of antioxidants). Also, antioxidant cocktail that contains a mixture of free radical scavengers (e.g. β-carotene, vitamin C, vitamin E, nicotinamide, selenium) have been used. Free radicals can be beneficial to the body. For example, during exercise extra free radicals are produced which is essential for the health

because it triggers cellular production of endogenous antioxidants. Intake of antioxidant supplements during exercise is unnecessary. Free radicals can also be helpful in an oxidative burst – this is when phagocytes release free radicals to get rid of bacteria and viruses. Therefore, total extinction of free radicals by the means of incessant antioxidant supplementation will cause more harm than good.

4. CONCLUSION

Antioxidant with no doubt is beneficial to health. However, Disruption in the homeostatic balance between endogenous, exogenous antioxidants and free radical predisposes to deficiency or toxicity. Hence, this homeostatic balance should be of paramount consideration in commencement of antioxidant therapies because free radicals also have some health benefits. Therefore, exogenous therapies may be harmful despite the seemingly important role it plays in diseased state especially in cases where there are no established doses. Antioxidant therapy may not always be necessary for prevention of diseases in our environment since same is found in natural fruits and vegetable. Therefore, emphasis should shift from antioxidant supplementation to encouraging consumption of cheap and readily available food sources of antioxidant. This should be encouraged in health and disease state since these antioxidants sources are easily handled by the absorptive mechanism of the gastrointestinal tract, boosts endogenous cellular antioxidant activity and are less prone to toxicity.

5. RECOMMENDATION

More studies should be carried out on the effect of antioxidant supplements on drug therapies used in various disease management. Studies on comparing the benefits of Fruits cocktails to exogenous supplements in various clinical states should be undertaken. More so, Longitudinal case controlled clinical trial, should be carried out to ascertain the outcome of long term antioxidant therapies in disease management of various chronic ailments. Dosages of these drugs should be ascertained considering varying demands of each ailment. More so, health policies are necessary to checkmate the influx of nutraceuticals in developing countries. Fair attention should also be given to reduction of exogenous sources of free radical such as environmental pollutions, unhealthy foods etc rather than antioxidant therapy.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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