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Auto-Immune Cardiac Degeneration as a Complication of Essential Hypertension

Odewusi, O.O.[1], Olaifa B.A.[2], Bamishaye D.A.[3], Omon E.A.*[4], Ogunfolakan O.O.[5], Oguntase, M.O.[6], Alake, O.A.[7], Akindele, O.A.[8]

[1,2,3,4,5,6,7,8] Department of Medical Laboratory Science, College of Medicine and Health Sciences, Afe Babalola University, Ado-Ekiti, Ekiti State, Nigeria.

[4]ORCiD: 0000-0001-9949-3682

ABSTRACT

Essential hypertension is persistent high blood pressure in the systemic arteries with no identifiable secondary cause. The study was designed to assess auto-immune cardiac degeneration in essential hypertensive patients in Ekiti State. The study included 40 subjects with no history of hypertension (control), 40 hypertensive subjects undergoing treatment and 40 hypertensive subjects without treatment. Body Mass Index (BMI) was calculated, systolic and diastolic blood pressure (SBP and DBP) readings were taken using digital sphygmomanometer, Aspartate Aminotransferase (AST) was measured using spectrophotometer, Cardiac Troponin (CTnI) and Anti-mitochondrial antibody M7 (AMA-M7) were estimated using ELISA. Results obtained were expressed as mean ± SD and statistical analysis was done using SPSS. Values were statistically significant at $p<0.05$. The results obtained showed that BMI and DBP of treated hypertensive patient was insignificant when compared with control subjects ($p>0.05$), whereas SBP, AST, AMA-M7 and CTnI were significantly higher ($p<0.05$) in treated hypertensive patients compared with the control subjects. Similarly, BMI, SBP, DBP, AMA-M7, AST and CTnI of untreated hypertensive patient were significantly higher ($p<0.05$) compared with non-hypertensive subjects (control). Furthermore, BMI, SBP, DBP, AMA-M7, AST and CTnI were significantly lower ($p<0.05$) in treated hypertensive patient compared with untreated hypertensive subjects. In conclusion, AMA-M7 is more sensitive marker in detecting auto-immune cardiac degeneration faster than the routine serum AST and Cardiac Troponin I in indicating the functional state of the heart. Therefore, early detection of auto-immune cardiac degeneration in hypertension subjects is important as there is a link between autoimmunity and hypertension.

KEYWORDS: Cardiac degeneration, Essential hypertension, Autoimmune antibodies, Cardiac troponin-I, AST

ARTICLE DETAILS

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INTRODUCTION

Essential hypertension also known as primary hypertension or idiopathic hypertension can be defined as persistent high blood pressure in the systemic arteries with no identifiable secondary cause (1). Essential hypertension which constitutes about 95% of all hypertension cases is likely to be the consequence of an interaction between environmental and genetic factors (2). Prevalence of essential hypertension increases with age and individuals with relatively high blood pressure at younger ages are at increased risk for the subsequent development of hypertension later in life. Hypertension increases the risk of cerebral, cardiac and renal events (3). In Nigeria, essential hypertension is the most frequently diagnosed risk of heart diseases with complications accounting for approximately a quarter of emergency admissions in urban hospitals. The pathogenesis of essential hypertension is multifactorial (etiology and genetic factor) with different mechanisms contributing to its origin in different individuals. One of such factors is presence

such as auto-immune antibody generation from autoimmunity (4).

Autoimmunity can be defined as the presence of antibodies produced either by B-lymphocytes and/or T-lymphocytes directed against normal components of a person (autoantigens). The antibodies and T-lymphocytes that recognize autoantigens are called autoantibodies and autoreactive T-cells respectively (5). Autoimmunity is a common medical condition affecting approximately 5-8% of the world population and known to be a major factor causing well-known health problems including type I diabetes, multiple sclerosis, rheumatoid arthritis and celiac disease (6). Autoimmune antibodies arise because of an imbalance between effector and regulatory immune responses, typically developed through stages of initiation and propagation, and often show phases of resolution (indicated by clinical remissions) and exacerbation (indicated by symptomatic flares). The fundamental underlying mechanism of autoimmunity is defective elimination and/or control of self-reactive lymphocytes. Several types of autoantibodies against heart muscle and other autoantigens have been described in some forms of cardiac diseases indicating that autoimmune processes may play a role in those diseases (7).

Anti-mitochondria antibody M7 (AMA-M7) have been critically linked to heart degeneration among the numerous circulating autoantibodies. AMA-M7 class of antibodies targets mitochondrial epitopes, identified as sarcosine dehydrogenase and enzymes associated with flavin adenine dinucleotide, in patients with hypertension, cardiomyopathy and myocarditis (8). Generally, AMA-M7 originates from Mitochondria organelle part of the cell that contributes to the production of respiratory adenosine triphosphate (ATP) (Brand *et al.,* 2013). Different sets of anti-mitochondrial antibodies (AMA), namely AMA-M1 to AMA-M9, have been characterized (9). The most relevant mitochondrial antigens M1, M2 and M7 are located in the inner mitochondrial membrane, whereas M3, M4, M5, M6, M8 and M9 are located in the outer mitochondrial membrane (10). AMA-M7 antibodies are detectable in patients with dilated cardiomyopathy (DCM) and there are reports on their functional relevance. Thus, anti-M7 antibodies were observed in blood of 31% of DCM patients, 33% of hypertrophic cardiomyopathy patients and 13% of acute myocarditis patients. Recent advances have considerably expanded our understanding of the underlying mechanisms of essential hypertension towards autoimmunity (11). However, despite several research works on the pathogenesis of essential hypertension and cardiac degeneration, paucity of information still exists on mechanism of autoimmunity induced cardiac degeneration in essential hypertensive patient. Hence, this study was carried out to assess the level of auto-immune cardiac degeneration in hypertensive subjects.

METHODS

Study design

A case-control research design using stratified random sampling techniques was employed in this study.

Study area

The study was carried out in Ado-Ekiti and its immediate environs. Ado-Ekiti is the capital city of Ekiti State in Southwest Nigeria. It is situated in the northern part of the state where the routes from Oyo, Osun and Kwara State respectively converge. The state is mainly an upland zone, rising over 250 meters above sea level. Its coordinates are 7^0 40'N 5^0 15'E.

Sample size

The minimum sample size (N) was calculated using the formula: $N= Z^2p(1-p)/w^2$

Where Z = confidence level at 95, N=Minimum sample size, w= allowance for error=0.05, P= estimated prevalence of diabetes patients at 8.9% (Adeloye *et al*., 2021).

q = 1, p =1 – 0.081 = 0.919

$$N = \frac{1.96^2 \times 0.081 \times 0.919}{0.05^2} = 114$$

A total of 120 samples comprising of 40 apparently healthy subjects (control), 40 newly diagnosed essential hypertensive subjects and 40 essential hypertensive subjects on treatment were recruited for this study

Inclusion criteria

Men and women within the age range 20-60 years who have been diagnosed with essential hypertension whether on therapy or not partook who gave their consent were included in the study. Inclusion was based on the cut-off of at least 140mmHg systolic or 90mmHg diastolic blood pressure.

Exclusion criteria

Subjects below the age of 18 years, pregnant women, nursing mothers, diabetes mellitus subject, chronic kidney disease and sufferers of other disease conditions were excluded.

Ethical clearance

Ethical approval was sought for from Ethics and Health Research Committee of Afe Babalola University, Ado-Ekiti, Ekiti State. Informed consent was obtained from each subject who participated in the study before sample collection.

Sample collection

After overnight fasting of 12 hours, venous blood sample of about 5mls was collected under from the cubital fossa using 22G needle and syringe from each participant. The sample was dispensed into plain non-anticoagulated sample bottle and was allowed to clot first before centrifuging at 5000rpm for 5minutes to separate the serum from cells and dispensed into another plain non-anticoagulated sample

bottle. The serum samples were stored at temperature of -20degree Celsius for a maximum of 21 days before assayed for cardiac markers (Troponin and AST) and presence/level of auto-immune antibodies.

Anthropometric analysis

Blood Pressure: Blood pressure was determined with digital sphygmanometer.

Height and weight were obtained using a meter gauge and a bathroom scale respectively.

Body Mass Index (BMI): BMI was derived from the height and weight using the formula:

$$BMI = \frac{\text{Weight (kg)}}{\text{Height}^2 (m^2)}$$

It was expressed in kg/m^2

Sample analysis

Anti-mitochondria antibody (M7): Anti-mitochondria antibody (M7) was determined using Enzyme linked Immuno-absorbent (ELISA) assay kit and the procedure was according to manufacturer's instruction.

Human Troponin I: Human Troponin I was determined using ELISA technique (Wilson and Foster, 1992).

Aspartate Aminotransferase (AST): AST was estimated using NADH (with P-5'-P) spectrophotometric method (Tietz *et al.,* 1989)

Statistical analysis

Results obtained presented in tables and charts were statistically analyzed using IBM SPSS version 24.0. Values of all parameters were expressed as mean ± SD. Comparison of parameters between group was done using Student t-test and

RESULTS

Table 1 showed the mean ± SD of all parameters (SBP, DBP, BMI, AST, AMA-M7 and CTnI) in treated and untreated hypertensive subjects and control. The result obtained showed that BMI ($p=0.4930$), DBP ($p=0.5467$) of treated hypertensive patient was insignificant when compared with control subjects, whereas SBP ($p=0.0044$), AST ($p<0.0001$), AMA-M7 ($p<0.0001$) and CTnI ($p<0.0001$) were significantly higher in treated hypertensive patients compared with the control subjects. Similarly, BMI ($p=0.0002$), SBP ($p<0.0001$), DBP ($p<0.0001$), AMA-M7 ($p<0.0001$), AST ($p<0.0001$) and CTnI ($p<0.0001$) of untreated hypertensive patient was significantly higher when compared with non-hypertensive subjects (control). Furthermore, BMI ($p=0.0455$), SBP ($p<0.0001$), DBP ($p<0.0001$), AMA-M7 ($p<0.0001$), AST ($p<0.0001$) and CTnI ($p<0.0001$) were significantly lower in treated hypertensive patient compared untreated hypertensive subjects.

Figure 1 showed the mean values of AST between treated and untreated hypertensive subjects in different age group. Significantly higher values was observed in the mean AST in age group 41-50 years when untreated hypertensive patients were compared with treated hypertensive patients ($p<0.0001$) and control ($p<0.0001$) respectively. Whereas, no significant variation was observed in the mean AST in age group 41-50 years when treated hypertensive patients were compared with control ($p=0.2920$). Significant difference was also observed in the AST of age group 51-60 years, 61 years and above when untreated hypertensive patients were compared with treated hypertensive subjects ($p<0.0001$) and control ($p<0.0001$), and between treated hypertensive subjects compared to control subjects ($p<0.0001$) respectively. No significant variation was observed in the mean AST in age group 61-70 years when treated hypertensive patients were compared with control ($p=0.0595$).

Figure 2 showed the mean values of AMA-M7 between treated and untreated hypertensive subjects in different age group. The result obtained showed that significantly higher values ($p<0.0001$) was observed in the AMA-M7 in age group 41-50 years, 51-60 years, 61 years and above when untreated hypertensive patients were compared with treated hypertensive and control subjects respectively. Furthermore, higher variation was observed in the AMA-M7 level of age group 41-50, 61 and above when treated hypertensive patients were compared with control subjects ($p<0.0001$), ($p<0.0003$) respectively. No significant variation was observed in the AMA-M7 age group 51-60 years when treated hypertensive patients were compared with non-hypertensive patients ($p=0.1572$).

Figure 3 showed the mean values of CTnI between treated and untreated hypertensive subjects in different age group. From the result obtained, higher ($p<0.0001$) values was observed in the CTnI in age group 41-50 years, 51-60 years, 61 years and above when untreated hypertensive patients were compared with treated hypertensive patients and control respectively. Significant variation ($p<0.0001$) was also observed in the CTnI of age group 41-50 years, 51-60 years, 61 years and above when treated hypertensive patients were compared with non-hypertensive patients.

Table 1: Mean ± SD of all parameters (SBP, DBP, BMI, AST, AMA and CTnI) in treated and untreated hypertensive subjects compared with control

PARAMETERS	UNTREATED Mean ± SD (n = 40)	TREATED Mean ± SD (n = 40)	CONTROL Mean ± SD (n = 40)
BMI (Kg/m^2)	27.85±3.62^a	25.62± 6.77^b	25.76±0.46^b
SBP (mmHg)	126.9±8.41^a	104± 8.09^b	109.5± 4.99^c
DBP (mmHg)	79.7±4.94^a	71.8± 3.28^b	73.2± 7.44^b
AST (U/L)	27.87±4.18^a	10.89±1.75^b	13.26±2.07^c
AMA (µg/ml)	3.27±0.49^a	2.01±0.32^b	1.63±0.25^c
CTnI (ng/ml)	4.68±0.70^a	2.58±0.42^b	1.19±0.18^c

*Values in a row with different superscript is significant at p<0.05

Keys: n = number of subjects, **BMI**: Body Mass Index, **DBP**: Diastolic Blood Pressure, **SBP**: Systolic Blood Pressure, **AST**: Aspartate Aminotransferase, **AMA**: Anti-mitochondrial antibody M7, **CTnI**: Cardiac Troponin I

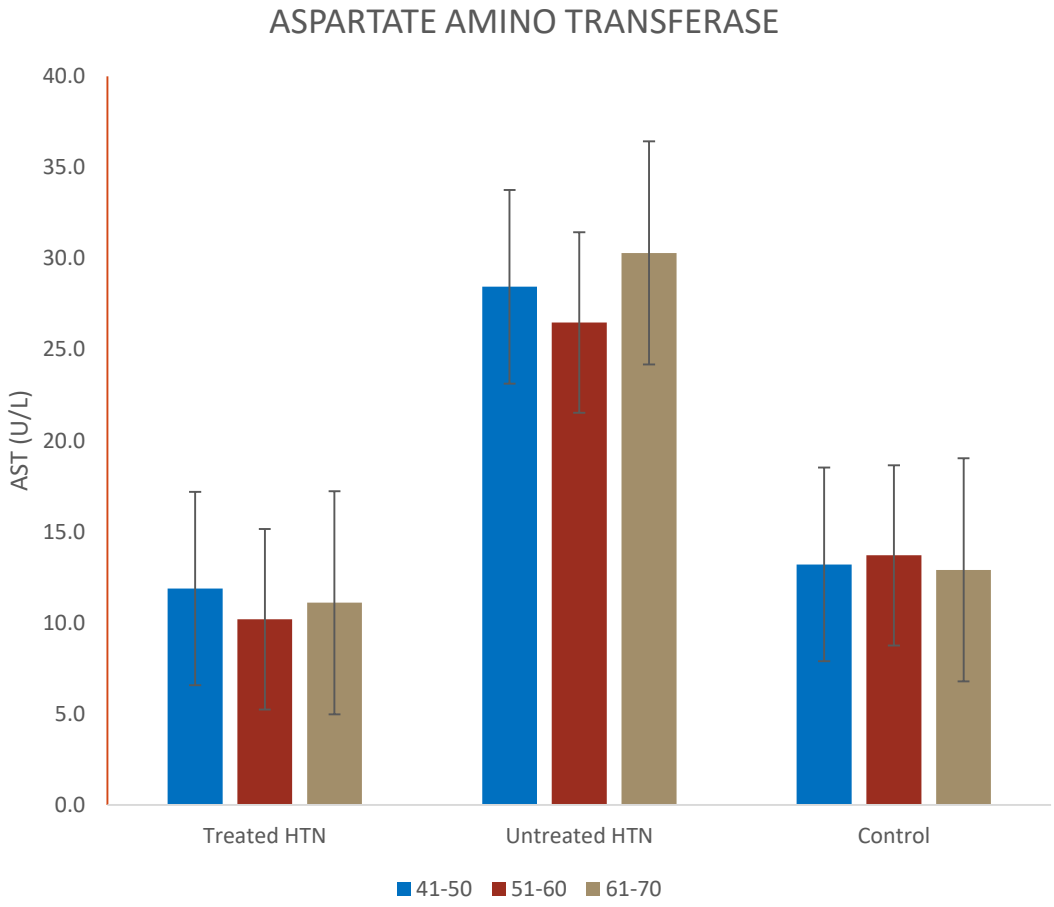

Figure 1: Aspartate aminotransferase (AST) between treated and untreated hypertensive subjects in different age group.
Keys: Treated HTN: Treated hypertension, Untreated HTN: Untreated hypertension

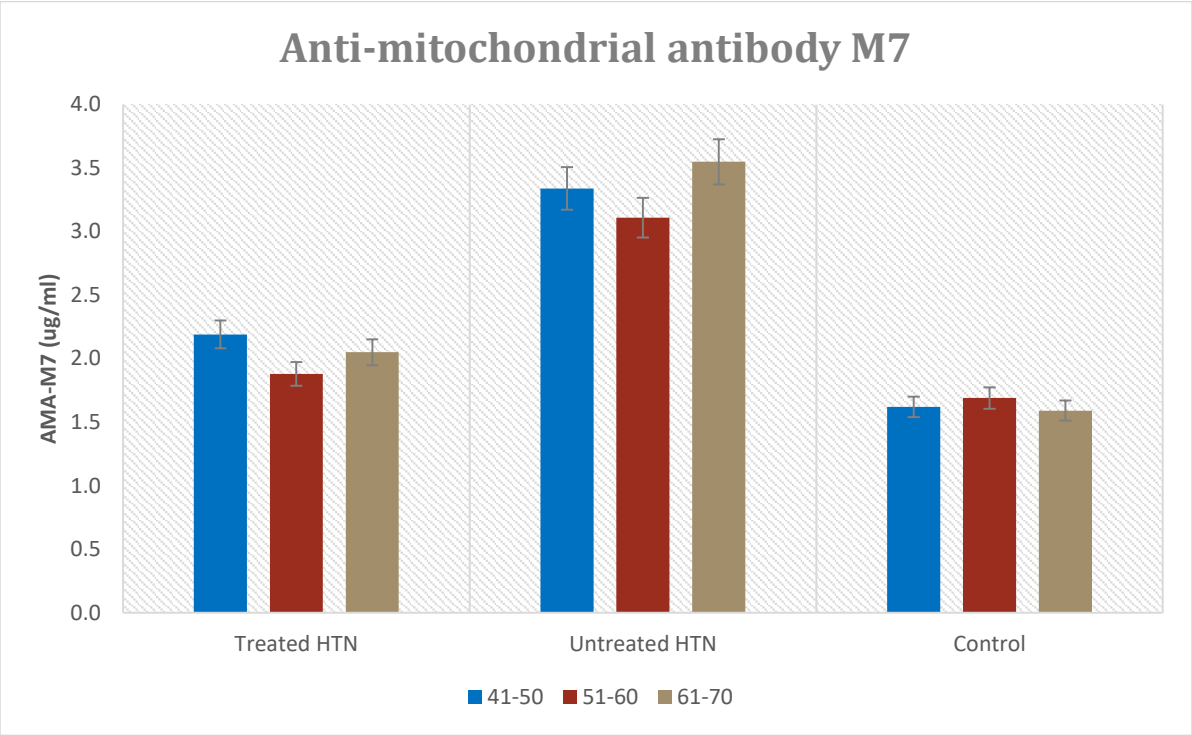

Figure 2: A chart showing Anti-mitochondrial antibody (AMA-M7) between treated and untreated hypertensive subjects in different age group.

Keys: Treated HTN: Treated hypertension, Untreated HTN: Untreated hypertension

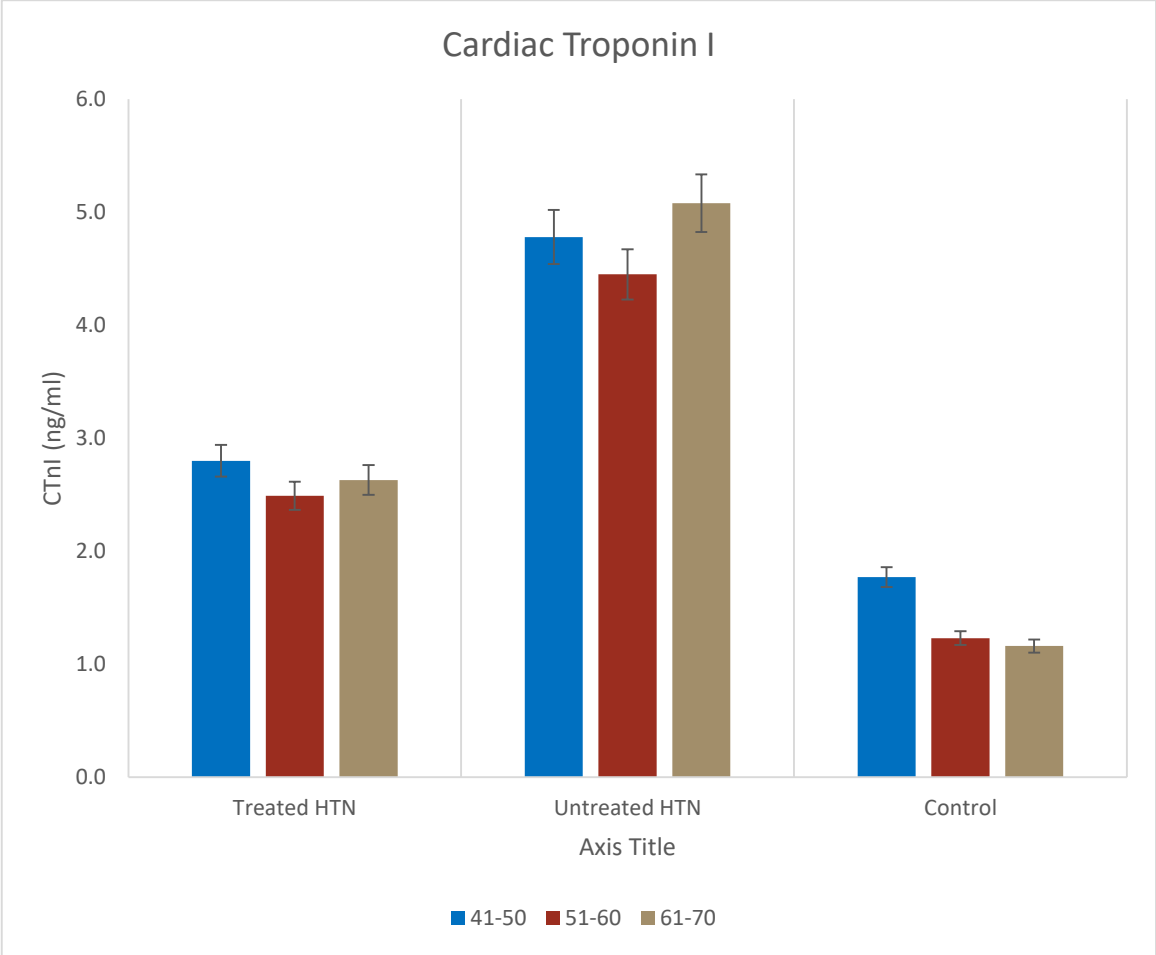

Figure 3: Cardiac Troponin I between treated and untreated hypertensive subjects in different age group.

Keys: Treated HTN: Treated hypertension, Untreated HTN: Untreated hypertension

Table 2: Correlation of AMA-M7 with other parameters of treated and untreated hypertensive subjects and control

Parameter	Treated hypertension		Untreated hypertension		Control	
	r	p-value	r	p-value	r	p-value
BMI (kg/m^2)	0.3227	0.0423*	-0.4836	0.0021**	-0.2591	0.139
DBP (mmHg)	-0.124	0.446	-0.6647	0.0001***	0.4147	0.0148*
SBP (mmHg)	0.04624	0.777	-0.5376	0.0005**	0.109	0.5394
AST (U/I)	0.9999	0.0001***	1.0	0.0001***	0.9999	0.0001***
CTnI (ng/ml)	1.0	0.0001***	1.0	0.0001***	0.9998	0.0001***

Key: ***- correlation is significant at p< 0.0001 level; **- correlation is significant at p< 0.001 level; *- correlation is significant at p<0.05 level; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BMI: Body Mass Index, AST: Aspartate aminotransferase; CTnI: Cardiac Troponin I; AMA M7: Antimitochondrial Antibody M7

DISCUSSION

It has been suggested by various researchers that there is a need to curb the likely confounding factors for high blood pressure if better clinical outcomes are to be achieved. As a result of overt evidences that hypertension leads to physiological disruptions and organ damage (12), this research was designed to assess autoimmune cardiac degeneration in hypertensive subjects. Odewusi and Osadolor (13) demonstrated a higher pro inflammatory cytokine levels in hypertensive patients, supporting the theory that essential hypertension is an inflammatory clinical condition. In this study, BMI was significantly lower (p<0.05) in treated essential hypertensive subjects compared with controls, but significantly higher (p<0.05) in untreated hypertensive subjects compared with both treated hypertensive subjects as well as control subjects. The link between obesity and hypertension is complex, considering that obesity-related hypertension is closely associated with other diseases in the course of the obesity. In general, obesity, which is usually determined by BMI, is one the principal risk factors for hypertension and the prevalence of hypertension increases with rising BMI (14). Increased BMI among hypertensive patients like other lifestyle characteristics is an amendable health risk factor for the prevention of hypertension. Moreover, for therapeutic purposes, weight loss reduces blood pressure in most hypertensive subjects (15). Nevertheless, the overall results of lifestyle modification to reduce obesity are poor and in most long-term trials of weight reduction, it was found that in most cases weight returns to baseline levels after several years (16). This result is consistent with the findings of Vrettos *et al.* (16) who reported that treated hypertensive patients had higher BMI compared with control. Additionally, this study supported El-Meouchy *et al*. (15) findings that hypertensive patients had significantly higher body mass indices than control subjects, whether they were receiving treatment or not.

The systolic and diastolic blood pressures was significantly lower in treated hypertensive subjects and significantly higher in untreated (p<0.05) essential hypertensive subjects when compared with control. Isolated systolic hypertension, in most cases, develops as a result of the reduced elasticity of the arterial system. This is commonly seen among the elderly as there is increased deposition of calcium and collagen to the arterial wall (17). Hence, this may result in reduced compliance of the arterial vessels, decreased lumen-to-wall ratio, and increased thickening and fibrotic remodeling of the vascular intima and media. As a result, these stiffened conduit arteries lead to an increase in pulse pressure and pulse wave velocity, causing an elevation in SBP (18). This finding is in agreement with previous studies (18-19) majorly because the values obtained from treated hypertensive patients were in stage 1 and stage 2 classification of hypertensive subjects. This study also found that SBP was significantly higher in untreated hypertensive subjects when compared with treated hypertensive subjects (p<0.0001). Our results support previous evidence that treatment will interrupt the progressive course of hypertension (9,18).

Aspartate aminotransferase (AST) was significantly higher in treated (p<0.0001) and untreated (p<0.0001) essential hypertensive subjects when compared with control. This study showed that AST was significantly higher in untreated hypertensive subjects when compared with treated hypertensive subjects (p<0.0001). Several possible mechanisms have been proposed to explain the association between hepatic aminotransferases and development of hypertension. One explanation is the presence of underlying fatty liver disease, characterized by lipid deposition within hepatocytes. The “two-hit” hypothesis argues that a combination of insulin resistance and lipid accumulation leads to fatty infiltration of the liver, which is reflected by increased levels of aminotransferases in the circulation and results in increased risk of hypertension complications (20). Another theory is increased oxidative stress and inflammation secondary to excessive fatty acid deposition, which favors the release of pro-inflammatory adipocytokines and promotes a systemic inflammatory state (21). Chronic low-grade inflammation has consistently been shown to precede the development of hypertension and atherothrombotic diseases. However, it is difficult to determine the temporality of this relationship, as elevated aminotransferases may be a result of the inflammation rather than the cause (22). This finding is in agreement with recent studies (20,23-24).

Cardiac troponinin (CTn1) this present research study was significantly higher in treated ($p<0.0001$) and untreated ($p<0.0001$) essential hypertensive subjects when compared with control. This study also found that CTnI was significantly higher in untreated hypertensive subjects when compared with treated hypertensive subjects ($p<0.0001$). Elevated troponin frequently observed in hypertensive crisis may be attributed to myocardial supply-demand mismatch or obstructive coronary artery disease (CAD) (25-26). In a hypertensive crisis setting, left ventricular wall stress due to an increase in after load and subendocardial ischaemia due to an accompanying catecholamine surge can elevate cardiac troponin levels, even in the absence of CAD in hypertensive patients (27). It has been suggested that the assessment of cardiac troponin may be suitable for predicting the first and subsequent adverse events not only in patients with CAD but also in hypertensive patients (28). This finding is in agreement with previous studies (25-28).

Anti-mitochondrial antibody M7 was higher in treated ($p<0.05$) and significantly higher in untreated ($p<0.0001$) essential hypertensive subjects when compared with control respectively. This study found that AMA-M7 was significantly higher in untreated hypertensive subjects when compared with treated hypertensive subjects ($p<0.0001$). In this study, a negative significant correlation existed between AMA-M7 and CTnI for both treated and untreated hypertensive subject and a negative correlation exist between systolic blood pressure and AST, AMA-M7 and CTnI of untreated hypertensive subjects while significant positive correlation exists between SBP and AST, AMA-M7 and CTnI respectively. Antimitochondrial antibodies (AMAs) are an example of an autoimmune response that occurs when the body turns against its own cells, tissues, and organs. Accruing experimental and clinical evidence supports the inflammatory and autoimmune aspects of essential hypertension (5). Hypertension is the major modifiable risk factor for death in individuals with cardiovascular disease, therefore, the presence of autoantibodies in patients with essential hypertension offers clues about the possible autoimmune underpinnings of the disease (29). This finding is in line with the works of Solak *et al.* (5) were hypertension was theorized as an autoimmune clinical condition. Secondly, ageing as a risk factor for both autoimmunity and hypertension (29-30) lends credence to the findings in this research which could have also contributed to the increase in both AST and cardiac troponin-1 level seen in hypertensive subjects. This was the first study to be done in Nigeria on anti-mitochondrial antibody M7 among treated and untreated hypertensive patients and to correlate parameters together. This finding will therefore assist in filling the information gap about the link that exists between autoimmunity, hypertension and cardiac degeneration.

CONCLUSION

The management of high blood pressure in patients with autoimmune disease has been considered a major aspect of their treatment plan. This study has shown that hypertension is intrinsically associated with autoimmunity. The possibility of auto-immune cardiac degeneration in hypertension subjects is important because of the relationship between autoimmunity and hypertension which should encourage the use of more sensitive marker such as AMA-M7 in the diagnosis, treatment and prevention of hypertension and heart diseases.

Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

I. Iqbal, A.M. and Jamal, S.F. (2023): Essential Hypertension. In: StatPearls Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539859/

II. Avinas, R., Megumi, N., Ping, L., Limei, P., Yanglong, L., Guang, Y. and Xian, W. (2020): Adaptive immune disorders in hypertension and heart failure: focusing onT-cell subset activation and clinical implications. Journal of Hypertension, 38: 1878-1889.

III. World Health Organization (2019): Cardiovascular diseases (2019). New initiative launched to tackle cardiovascular disease, the world's number one killer.http://www.who.int/cardiovascular_diseases/en/ (23 July 2023).

IV. Forouzanfar, M.H., Liu, P. and Roth, G.A. (2017): Global burden of hypertension and systolic blood pressure of at least 110 to 115 mmHg, 1990–2015. JAMA, 317(2): 165-182.

V. Solak, Y., Baris, A., Nosratola, D.V., Gamze, A., Can, E.Y., Adrian, C. and Mehmet, K. (2016): Hypertension as an autoimmune and inflammatory Disease. Journal of Japanese Hypertension Research, 39: 567–573.

VI. Liu, C., Rodney, E.K. and Yang, X. (2017). Inflammation, Autoimmunity, and Hypertension: The Essential Role of Tissue Transglutaminase. American Journal of Hypertension. 30(8): 756-764.

VII. Caillon, A. and Schiffrin, E.L. (2016): Role of inflammation and immunity in hypertension: recent epidemiological, laboratory, and clinical evidence. Curr Hypertens Rep. 18: 21-24.

VIII. Becker, Y., Loignon, R.C. and Julien, A.S. (2019): Anti-mitochondrial autoantibodies in systemic lupus erythematosus and their association with disease manifestations. Sci Rep. 9: 4530-4533

IX. Chan, C.T., Sobey, C.G., Lieu, M., Ferens, D., Kett, M.M., Diep, H., Kim, H.A., Krishnan, S.M., Lewis, C.V., Salimova, E., Tipping, P., Vinh, A., Samuel,

C.S., Peter, K., Guzik, T.J., Kyaw, T.S., Toh, B.H., Bobik, A. and Drummond, G.R. (2015): Obligatory role for B cells in the development of angiotensin II-dependent hypertension. Hypertension, 66: 1023-1033.

X. Colapietro, F., Lleo, A. and Generali, E. (2022): Antimitochondrial Antibodies: from Bench to Bedside. Clinical Reviews in Allergy & Immunology, 63: 166–177.

XI. Santos-Moreno, P., Burgos-Angulo, G. and Martinez-Ceballos, M.A. (2021): Inflammaging as a link between autoimmunity and cardiovascular disease: the case of rheumatoid arthritis. RMD Open, 7: 1470-1473.

XII. Schmidt, B.M., Durao, S., Toews, I., Bavuma, C.M., Hohlfeld, A., Nury, E., Meerpohl, J.J. and Kredo, T. (2020: Screening strategies for hypertension. Cochrane Database Syst Rev. 5(5): 13212.

XIII. Odewusi, O.O. and Osadolor, H.B. (2019): Interleukin 10 And 18 Levels in Essential Hypertension. Journal of Applied Sciences and Environmental Management. 23 (5) 819-824.

XIV. Landi, F., Calvani, R., Picca, A., Tosato, M., Martone, A.M., Ortolani, E., Sisto, A., D'Angelo, E., Serafini, E., Desideri, G., Fuga, M.T. and Marzetti, E. (2018): Body Mass Index is Strongly Associated with Hypertension: Results from the Longevity Check-up 7+ Study. Nutrients. 10(12): 1976.

XV. El-Meouchy, P., Wahoud, M., Allam, S., Chedid, R., Karam, W. and Karam, S. (2022): Hypertension Related to Obesity: Pathogenesis, Characteristics and Factors for Control. Int J Mol Sci. 23(20): 12305-12308.

XVI. Vrettos, I., Voukelatou, P., Pappa, E., Beletsioti, C., Papadopoulos, A. and Niakas, D. (2020): Increased Body Mass Index and Hypertension: An Unbreakable Bond. Int J Prev Med. 11:155.

XVII. Tan, J.L. and Thakur, K. (2023): Systolic Hypertension. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-.Available from: https://www.ncbi.nlm.nih.gov/books/NBK482472/

XVIII. Zou, G., Witter, S., Caperon, L., Walley, J., Cheedella, K., Senesi, R. and Wurie, H. (2020): Adapting and implementing training, guidelines and treatment cards to improve primary care-based hypertension and diabetes management in a fragile context: results of a feasibility study in Sierra Leone. BMC Public Health. 20: 156-158.

XIX. Chang, H.K., Jeonggyu, K., Ara, C., Yoosoo, C., Seungho, R. and Ki-Chul, S. (2019): Optimal Target Blood Pressure and Risk of Cardiovascular Disease in Low-Risk Younger Hypertensive Patients. American Journal of Hypertension, 32(9): 833-841

XX. Cao, C., Hu, H. and Han, Y. (2023). The nonlinear correlation between alanine aminotransferase to high-density lipoprotein cholesterol ratio and the risk of diabetes: a historical Japanese cohort study. BMC Endocr Disord. 124(23): 452-458.

XXI. Xia, Y. and Kellems, R.E. (2019): Angiotensin receptor agonistic autoantibodies and hypertension: preeclampsia and beyond. Circ Research. 113: 78–87.

XXII. Lan, Q., Zhang, Y., Lin, F., Meng, Q., Buys, N.J., Fan, H. and Sun, J. (2022): Association Between Serum Aminotransferases and Risk of New-Onset Cardiometabolic Disease in a Healthy Chinese Population: A Cohort Study. Front Public Health. 10:902393.

XXIII. Rahman, S., Islam, S., Haque, T., Kathak, R.R. and Ali, N. (2020): Association between serum liver enzymes and hypertension: a cross-sectional study in Bangladeshi adults. BMC Cardiovasc Disorders. 20(1):128-130.

XXIV. Sakboonyarat, B., Poovieng, J. and Lertsakulbunlue, S. (2023): Association between raised blood pressure and elevated serum liver enzymes among active-duty Royal Thai Army personnel in Thailand. BMC Cardiovasc Disord. 143 (23): 2023-2028.

XXV. Pattanshetty, D.J., Bhat, P.K., Aneja, A. and Pillai, D.P. (2012): Elevated troponin predicts long-term adverse cardiovascular outcomes in hypertensive crisis: a retrospective study. Journal of Hypertension. 30(12): 2410-2415.

XXVI. Sternberg, M., Pasini, E., Chen-Scarabelli, C., Corsetti, G., Patel, H., Linardi, D., Onorati, F., Faggian, G., Scarabelli, T. and Saravolatz, L. (2019): Elevated Cardiac Troponin in Clinical Scenarios Beyond Obstructive Coronary Artery Disease. Med Sci Monit. 25:7115-7125.

XXVII. Kim, W., Kim, B.S., Kim, H.J., Lee, J.H., Shin, J. and Shin, J.H. (2022): Clinical implications of cardiac troponin-I in patients with hypertensive crisis visiting the emergency department. Ann Med. 54(1): 507-515.

XXVIII. Thygesen, K., Alpert, J.S. and Jaffe, A.S. (2018): Fourth universal definition of myocardial infarction Circulation. 138(20): 618–651.

XXIX. Wolf, V.L. and Ryan, M.J. (2019): Autoimmune Disease-Associated Hypertension. Curr Hypertension Report. 21(1):10-14.

XXX. Yokokawa, T., Yoshihisa, A., Misaka, T., Sato, T., Kaneshiro, T., Oikawa, M., Kobayashi, A., Yamaki, T., Kunii, H. and Takeishi, Y. (2021): Anti-mitochondrial Antibodies in Patients with Dilated Cardiomyopathy. Intern Med. 60(2):201-208.