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Left ventricular hypertrophy in young hypertensives: the possible crosstalk of mTOR and angiotensin-II -a case-control study

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Abstract

Background Hypertension is a major cause of cardiac dysfunction. The earliest manifestation is left ventricular remodeling/hypertrophy. The occurrence of adverse cardiac remodeling and outcomes occurs irrespective of age in blacks. This necessitated an estimate of the prevalence of left ventricular hypertrophy (LVH) and an assessment of the roles of the mammalian target organ of rapamycin (mTOR) and angiotensin-II (Ang II) as possible pathogenic markers of LVH among young hypertensives.

Methods This prospective case-control study involved 110 hypertensive and 60 normotensive (control) participants aged 18–45 across tertiary hospitals in Ekiti state. Ethical approval was obtained from all the various institutions. Participants were recruited consecutively after giving informed consent. Sociodemographic/clinical information, resting electrocardiogram and echocardiography were obtained. Venous blood was obtained to estimate mTOR, Ang II, Chemerin, lipids – triglyceride (TG), high-density lipoprotein (HDL), total cholesterol (TC), troponin-T, NF-Kβ, and Galectin-3 using enzyme-linked immunosorbent assay.

Results The prevalence of LVH among the hypertensive group was 20.9%, 39%, 11.01%, and 15.74% using 2D-transthoracic echocardiography, Sokolow-Lyon, Cornell's and Cornell product ECG criteria. Also, hypertensives with LVH had a significantly increased blood pressure, body mass index, serum level of TG, TG/HDL, TC/HDL, chemerin, troponin T, Galectin-3 and total mTOR compared to normotensive and hypertensives without LVH. At the same time, serum NF-kβ and Ang II were only significant when compared with normotensive but not hypertensives without LVH. The total mTOR moderately correlated positively with ANG-II.

Conclusions The results suggest an interaction between mTOR and Ang II in the development of LVH. In addition, it shows that LVH is associated with dyslipidemia, inflammation, and fibrosis.

Keywords Angiotensin II, Echocardiography, Hypertension, Left ventricular hypertrophy, Mammalian target organ of rapamycin

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Background

Hypertension (HTN) contributes largely to cardiovascular risks and adverse outcomes [1]. Although the prevalence of HTN rises with age it still occurs in young adults and it contributes greatly to the prevalence of cardiovascular events by middle age [2]. Left ventricular hypertrophy (LVH) is an early consequence of direct and persistent exposure of the heart to elevated blood pressure [3]. Several interplays occur between hemodynamic and non-hemodynamic factors to incite and consolidate the development of LVH [4]. The renin-angiotensin-aldosterone pathway is one of the pathways activated to maintain hemodynamic equilibrium in the setting of increased wall stress in pressure overload like hypertension [5]. Angiotensin-II has been shown to correspond to the degree of increase in left ventricular mass [6]. Angiotensin-II increases myocardial cell proliferation while aldosterone enlarges the collagen deposition hence promoting myocardial fibrosis [6]. Similarly, in pressure-overloaded myocardium, the mammalian target organ of rapamycin (mTOR) a serine-threonine kinase is activated in a phosphoinositide 3-kinase (PI3K)-dependent and/or independent manner with the involvement of specific protein kinase C (PKC) isoforms by adrenergic receptors, growth factor receptors, and integrin [7]. The role of the mTOR signalling in tissue proliferation pathway has been corroborated by the anti-proliferative property of mTOR inhibitors in drug-eluting stents and animal studies [8, 9]. Also, increasing age contributes significantly to the prevalence of LVH among hypertensives [10]. However, there is limited data regarding the prevalence of LVH among hypertensive young individuals, and the contribution of mTOR or Ang II to the development of LVH. Hence, the current study is focused on estimating the prevalence of LVH among young hypertensives and the possible interaction between mTOR and Ang II in the pathogenesis of LVH in young adults with hypertension.

Methods

Study participants

It is a multicentre study carried out at tertiary hospitals in Ekiti state, Nigeria. One hundred and ten (110) participants aged 18–45 with and 60 without hypertension who gave informed consent were recruited consecutively. Hypertension was defined as office BP ≥ 140/90 mmHg on two occasions or medication for hypertension. Left ventricular hypertrophy was defined as Left ventricular Mass Index (LVMI) ≥ 115 g/m^2 for males or 95 g/m^2 for females on 2D transthoracic echocardiography [11]. The participants were categorised as hypertensives with left ventricular hypertrophy (HWLVH) if hypertensive with LVMI ≥ 115 g/m^2 for males or 95 g/m^2 for females or hypertensives without left ventricular hypertrophy (HWOLVH) if hypertensive with LVMI ≤ 115 g/m^2 for males or 95 g/m^2 for females or normotensives (NORM) for participants with normal blood pressure (BP < 140/90 mmHg).

Ethical approval was obtained from the ethics and research committee of ABUAD Multisystem Hospital (AMSH/REC/BOO/184), Ado-Ekiti; Ekiti State University Teaching Hospital Ado-Ekiti (EKSUTH/A67/2023/11/005) and Federal Teaching Hospital, Ido-Ekiti (ERC/2024/01/15/1066B) respectively.

Inclusion and exclusion criteria

The inclusion criteria included all individuals with hypertension (secondary causes were not excluded) between 18 and 45 years old, who gave informed consent and had good echo windows. On the other hand, individuals < 18 years of age or > 45 years, individuals with diagnosed cancers or LVH attributable to other causes other than HTN were excluded.

Data collection

The socio-demographics, weight, height, BP of all participants were obtained. The BP measurement was taken using an upper arm BP monitor (Omron HBP-1320, Omron Corporation, Kyoto, Japan) after the participant had been allowed to rest for 10–15 min. Three readings were taken but only the average of the last two readings were reported. Also, 5 mL of venous blood was taken using an aseptic technique by a phlebotomist into a plain bottle.

They all had resting ECG using an electrocardiogram machine (GE MAC 800, England; Edan ECG machine: 6 channels, China) and transthoracic echocardiography done using GE Medical System Vivid T8, China or Toshiba Xario 200, America echo machine.

Protocol for echocardiography

Transthoracic 2D, 2D-derived M-mode echocardiography was performed according to standard protocols on all subjects, with ECG gating while in the left lateral decubitus position using an adult probe (frequency 5SU). The LVM was estimated with the Devereux–modified ASE cube formula $[0.8 \times 1.04 \times (IVSD + LVIDD + LVPWD)^3 - LVIDD^3) + 0.6]$ where IVSD is IVS diastole, LVIDD is LVID diastole, and LVPWD is LVPW diastole [12]. Intraobserver and interobserver variability were reduced to the minimum by ensuring that all images were analyzed twice by the same person at participant recruitment and at least a month later. At the same time, a second observer also analyzed the images without knowledge of the previous results.

Collection of blood samples

Venous blood (5 mL) was obtained from all participants in a plain bottle. The blood sample was centrifuged at 3500 rpm for 10 min. The obtained serum was stored in a plain cryovial at -80^{0}C until they were required for analysis.

Biochemical assays

The plasma levels of mTOR, chemerin, troponin T, Galectin-3, NF-kb, and Angiotensin II were determined using the ELISA technique. The following ELISA kits were used human mTOR ELISA Kit (Cat: ELK9237), human CHEM (Chemerin) ELISA Kit (Cat: ELK1953) and human GAL3 (Galectin 3) ELISA Kit from ELK Biotechnology Co. Ltd. (1312 17th Street #692 Denver, CO 80202 USA), human Ang-II (Angiotensin II) ELISA Kit from Elabscience Biotechnology Inc. (Wuhan, Hubei, P.R.C., China), human Troponin T ELISA kit produced by BT laboratories (Cat No: E2285Hu) and NF-kβ (human p50) Transcription Factor Assay Kit (Cat # KA1339 V.01) produced by ABNOVA.

The total cholesterol (TC), triglyceride (TG) and high-density lipoprotein (HDL) were assayed using assay kits purchased from Fortress Diagnostics Ltd. (Antrim, UK) while low-density lipoprotein (LDL) was calculated using the Friedewald Equation [13].

Statistical analysis

STATA 17 (Stata Corp LP, College Station, TX, USA) and Graphpad Prism version 10.2.3 were used. The prevalence of LVH was presented as percentages and pie charts. Shapiro-Wilk test of normality was performed on all continuous variables. Parametric data were reported as mean ± SEM while non-parametric data were reported as median and interquartile ranges (IQR). The continuous data were presented as tables and bar charts with error bars and scatter plots. Comparison of parameters were performed using Analysis of variance for parametric data and Kruskal-Wallis were used for non-parametric data respectively. Correlation between the continuous variables was assessed with Spearman's rank correlation or Pearson's correlation and presented using scatter plots with a line of best fit. Statistical significance was defined as $p<0.05$.

Results

Socio-demographic factors and clinical characteristics

The mean age of the participants with LVH was 34.5 years while that of the HWOLVH was 32.42 years. The SBP, DBP, BMI and LVM were significantly increased among HWLVH compared to NORM and HWOLVH. Also, the HWLVH group had significantly decreased eGFR compared to other groups (Table 1).

Prevalence of LVH in young hypertensives

The prevalence of LVH in this study was 20.9% (2D-transthoracic echocardiography), 39% (Sokolow-Lyon), 11% (Cornell's criteria) and 15.74% (Cornell's product criteria) (Fig. 1).

Left ventricular mass in young hypertensives

There was a significant increase in LVM and LVMI among HWLVH compared with NORM. Similarly, both LVM and LVMI were significantly higher among HWLVH compared with HWOLVH (Fig. 2).

Lipid profile

The TG/HDL, TC/HDL and LDL were significantly higher among HWLVH when compared to HWOLVH and NORM (Fig. 3).

Serum levels of biochemical parameters

HWLVH had significantly higher Troponin T, Galectin-3 and Chemerin when compared to HWOLVH and

Table 1 The clinical characteristics of the study population according to subgroups

Variables	NORM	HWOLVH	HWLVH
Age (years)	31.0 ± 7.57	32.42 ± 9.48	34.56 ± 8.42
PR (BPM)	79.5 (72–87)	83 (72–94)	84 (71–97)
SBP (mmHg)	112 (114–130)	143 (134–153) *	154 (135–172) *
DBP (mmHg)	72 (64–79)	90 (80–98) *	94 (87–108) *
Weight (Kg)	71.6 (62.5–81.5)	82.9 (68.2–94.4) *	88 (62.8–97.4) *
Height (cm)	173(168–179.5)	168 (163–178)	169 (162–175)
BMI (Kg/m^2)	24.05(20.9–27.6)	28.28 (24.8–24.8) *	30.27 (22.34–35.2) *
LVM (g)	142.69(121- 150.05)	153.42 (132.8-183.7) *	271.56(233.7-309.6) *#
LVMI (g/m^2)	75.65 (66.23–78.94)	76.91(66.35–92.9) *	132.21 (116.03–157.8) *#
eGFR (ml/min/1.73m^2)	113.7 ± 18.44	101.6 ± 20.58	80.87 ± 25.64*#
FBG (mmol/L)	5.05 (4.35–4.95)	5.25(4.93–5.78)	5.25 (4.68–5.5)

[K]mean (± standard deviation), ANOVA; [#]Median (interquartile range), Kruskal Wallis; BMI – body mass index; DBP – Diastolic blood pressure; eGFR – estimated glomerular filtration rate: FBG – fasting blood glucose; LVM – Left ventricular mass; LVMI– Left ventricular mass index; PR – pulse rate; SBP – Systolic blood pressure (*$p<0.05$ vs. NORM; [#]$p<0.05$vs. HWOLVH)

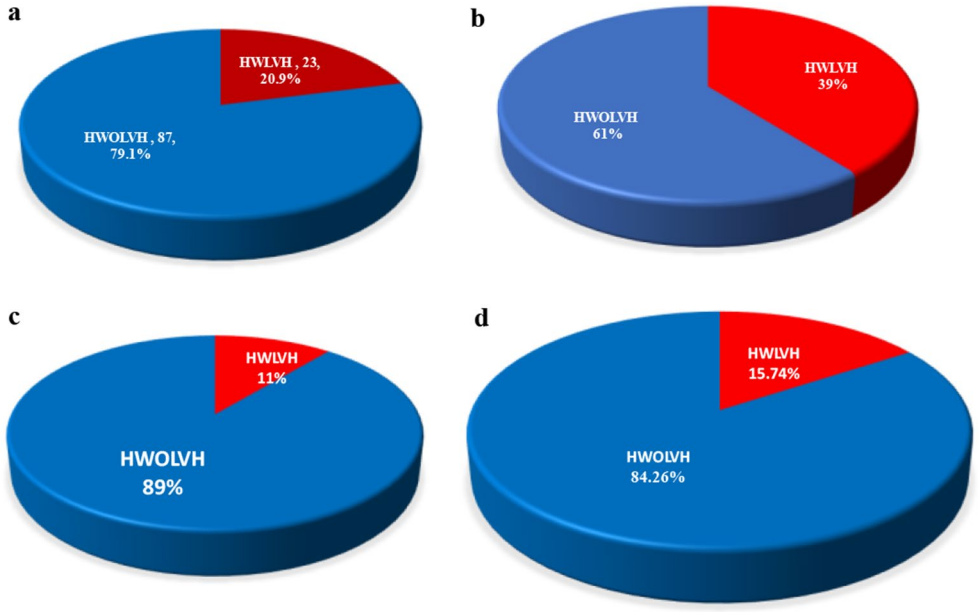

Fig. 1 shows the prevalence of left ventricular hypertrophy using Echocardiography (**a**), Sokolow-Lyon (**b**), Cornell's voltage criteria (**c**), and Cornell's product criteria (**d**)

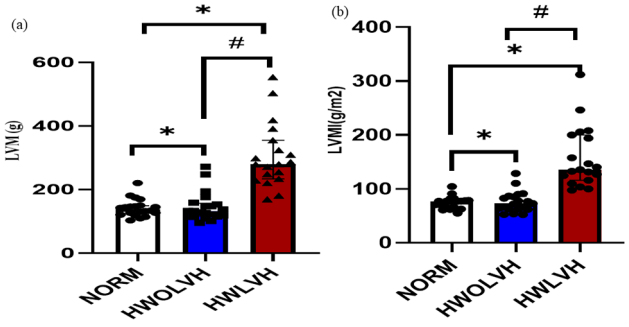

Fig. 2 shows LVM (**a**) and LVMI (**b**) in normotensive, HTN with or without LVH. Values are represented as median and analysed by Kruskal-Wallis. (*$P < 0.05$ vs. NORM; #$p < 0.05$ vs. HWOLVH). NORM (Normotensive); HWOLVH (Hypertension without left ventricular hypertrophy); HWLVH (Hypertension with left ventricular hypertrophy); LVM (Left Ventricular Mass); LVMI (Left Ventricular Mass Index)

NORM respectively (Figs. 4 and 5). Similarly, HWLVH had significantly exacerbated mTOR when compared to HWLVH and NORM while NF-Kβ and Ang II were not significantly higher when HWLVH was compared to HWOLVH but were significantly higher when compared to NORM (Figs. 5 and 6).

Relationship between mTOR and other biochemical parameters and LVM/LVMI in HWLVH

There was a moderate positive correlation between mTOR and Ang II. However, there was no relationship between Galectin-3, chemerin, NF-kβ, Troponin-T, LDL, TG/HDL, TC/HDL and mTOR (Figs. 7 and 8). In addition, Ang II, LVM, LVMI and mTOR had moderate positive correlation ($r=0.4699$, $p=0.04$) and ($r=0.469$, $p=0.043$) (Fig. 9).

Discussion

The heart is one of the organs affected by hypertension [14]. Left ventricular remodeling is a common initial adaptive mechanism of the heart to HTN [4, 15]. Left ventricular remodeling can manifest as concentric or eccentric hypertrophy. The development of LVH further worsens cardiovascular outcomes irrespective of age [1, 14–16]. This probably accounts for tagging HTN in ages 18–44 as a public health concern as it is associated with increased CV risk and mortality [9, 17]. This necessitated the need to assess the prevalence of LVH in Ekiti State, hence assessing those with increased cardiovascular events risk.

This study found that the HWLVH group had significantly higher BP, BMI and LVM but significantly lower eGFR when compared to HWOLVH and normotensives. In addition, the present study also found that the prevalence of LVH was 20.9%, 39%, 11% and 15.74% using echocardiography, Sokolow-Lyon voltage criteria, Cornell's criteria and Cornell's product respectively. Also, HWLVH had a significantly higher serum level of TG, TG/HDL, TC/HDL, chemerin, troponin T, Galectin-3 and mTOR when compared to normotensive and HWOLVH, while serum NF-kβ and Ang II were only significant when compared with normotensive but not HWOLVH. In addition, the total mTOR correlated positively with Ang II. Angiotensin-II and galectin-3 are well-documented pro-fibrotic markers [18, 19]. The present

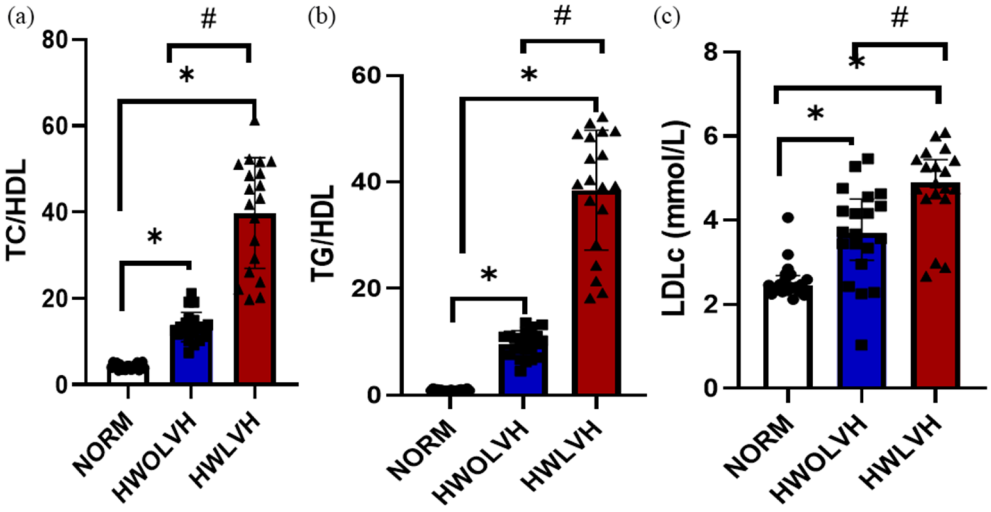

Fig. 3 shows atherogenic lipids TC/HDL (**a**) TG/HDL (**b**) and LDL_C (**c**) in normotensive, HTN with or without LVH. Values are represented as median and analyzed by Kruskal-Wallis. *$P < 0.05$ vs. NORM, #<0.05 vs. HWOLVH. LDL_C (Low-density lipoprotein); HDLc (High-density lipoprotein); TC (Total cholesterol); TG (Triglyceride)

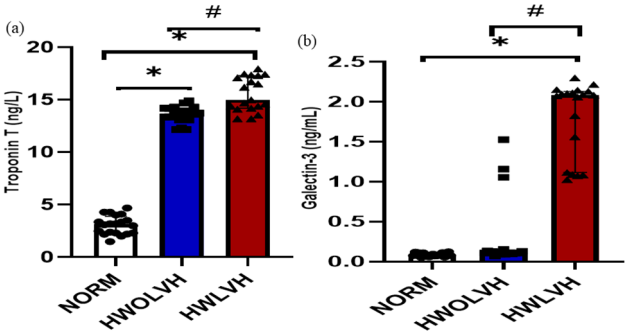

Fig. 4 shows Troponin -T (**a**) and Galectin −3 (**b**) in normotensive, HTN with or without LVH. Values are represented as median and analysed by Kruskal-Wallis. *$P < 0.05$ vs. NORM, #<0.05 vs. HWOLVH

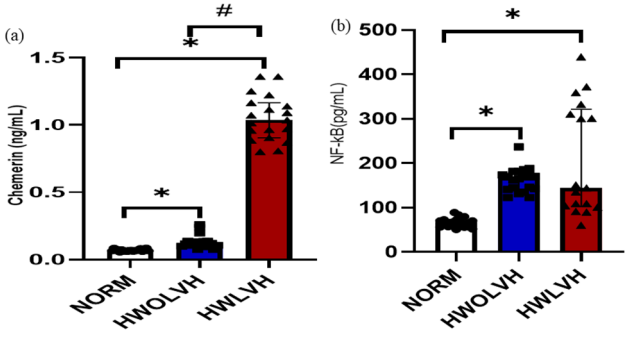

Fig. 5 shows Chemerin (**a**) and NF-kb (**b**) in normotensive, HTN with or without LVH. Values are represented as median and analysed by Kruskal-Wallis. *$P < 0.05$ vs. NORM, *<0.05 vs. HWOLVH. NF-Kβ (nuclear factor kappa B)

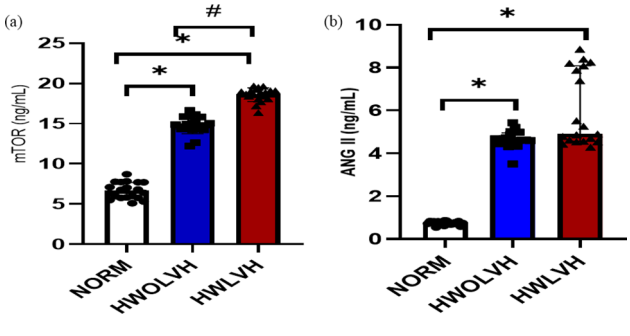

Fig. 6 shows mTOR (**a**) and Ang II (**b**) in normotensive, HTN with or without LVH. Values are represented as median and analysed by Kruskal-Wallis. *$P < 0.05$ vs. NORM, #<0.05 vs. HWOLVH. Ang II (Angiotensin II); mTOR (mammalian target organ of rapamycin)

observations therefore suggest that mTOR and Ang II possibly play a role in hypertension-related LVH. Also, hypertension-related LVH in this study is associated with increased atherogenic risk, elevated markers of fibrosis and inflammation.

This study found that the prevalence of LVH was 20.9% using echocardiography, which is the investigation modality of choice considering its sensitivity and availability [20]. This prevalence is less than 36% and 41% reported in a pooled study which could be because this study was conducted in a younger population as increasing age has been associated with increasing LVH prevalence [10, 21]. But comparable to 19.5% reported among Ugandans and 20% reported by Apitz et al., among Swiss although the median age in their study was 56% [22, 23]. It is also lower than 32.4% by Ngabea et al., 34% by Dada et al., and 32.2% by Ogunlade and Akintomide et al., which could be accounted for by the age difference between their study population and this study population

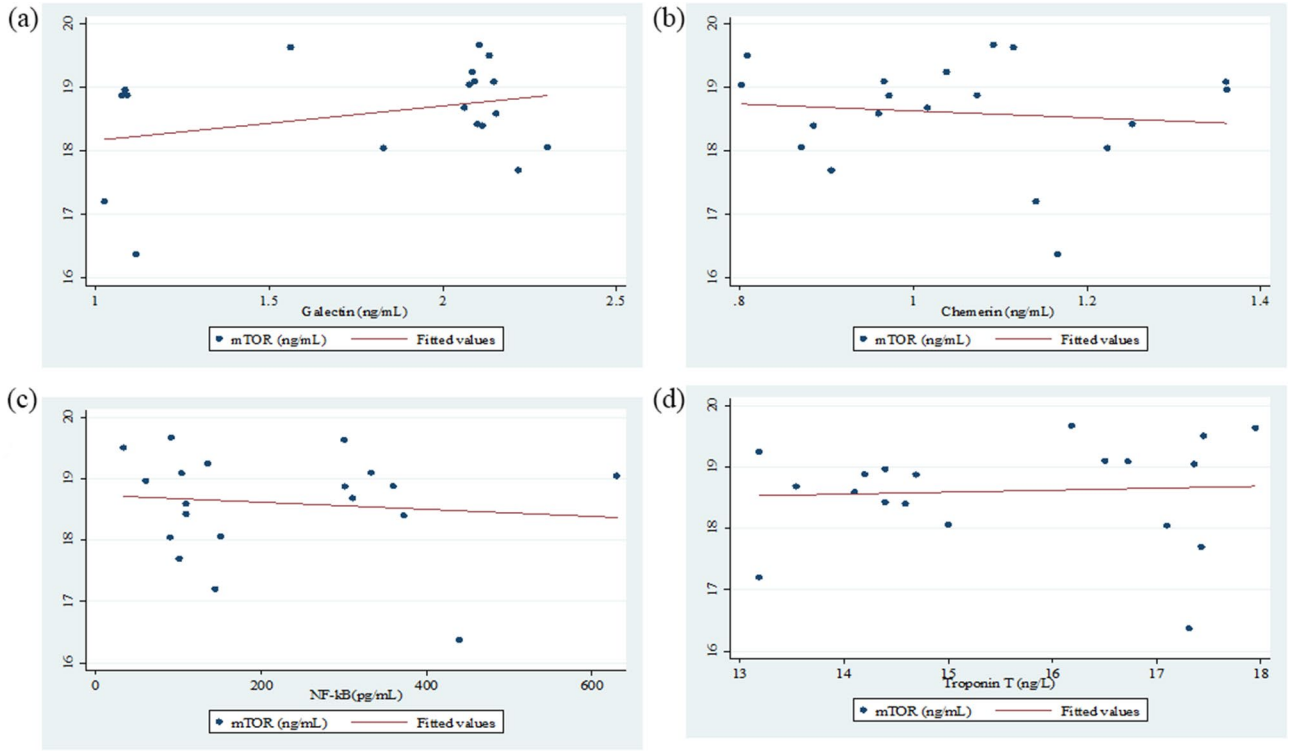

Fig. 7 shows the correlation between Galectin (**a**), Chemerin (**b**), NF-Kβ (**c**), Troponin T (**d**) and mTOR in HWLVH. Galectin (r = 0.063, p = 0.048), Chemerin (r = -0.107, p = 0.663) [β], NF-Kβ (r = -0.176, p = 0.470) [#], troponin-T (r = 0.178, p = 0.465) [#], NF-Kβ (nuclear factor kappa B); HWLVH (Hypertension with left ventricular hypertrophy). [β]Pearson correlation; [#]Spearman correlation.

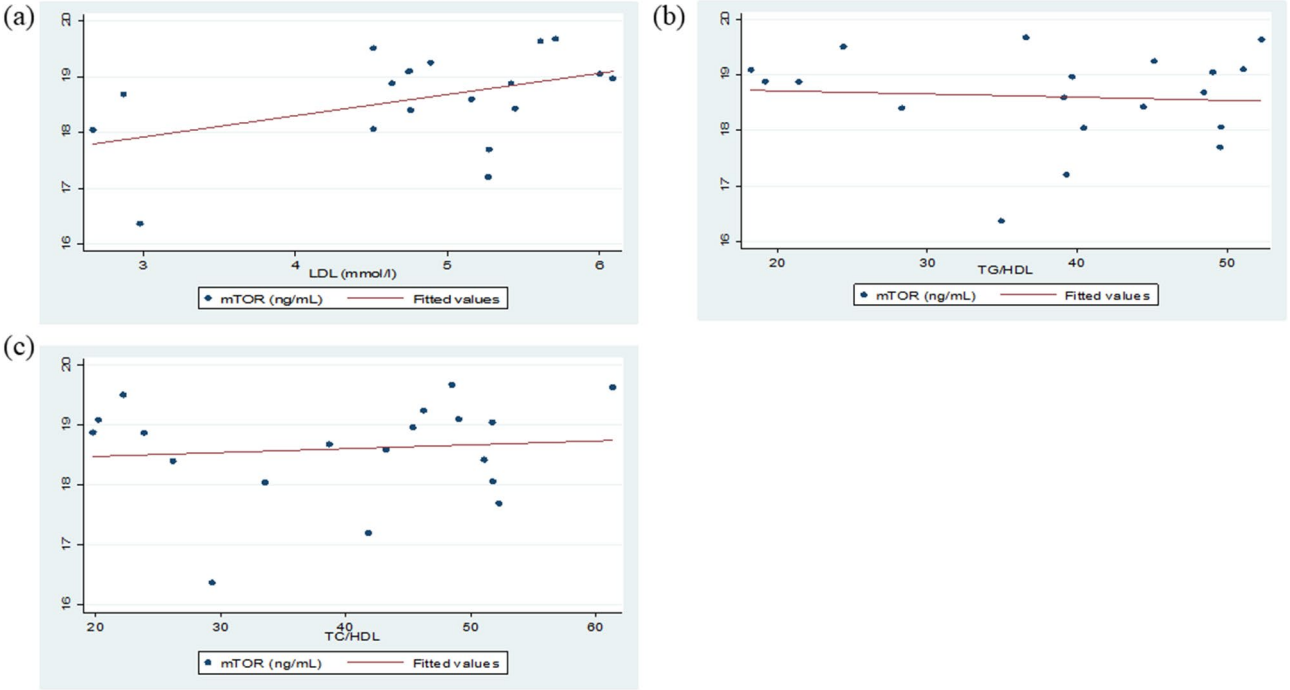

Fig. 8 shows the correlation between LDL (**a**), TG/HDL (**b**), TC/HDL (**c**) and mTOR in HWLVH. LDL (r = 0.345, p= 0.147) [#], TG/HDL (r = -0.0777, p = 0.752*) [β], TC/HDL (r = 0.0985, p = 0.688) [#], HWLVH (Hypertension with left ventricular hypertrophy) LDL (Low-density lipoprotein); HDL (High-density lipoprotein); TC (Total cholesterol); TG (Triglyceride). [β]Pearson correlation; [#]Spearman correlation

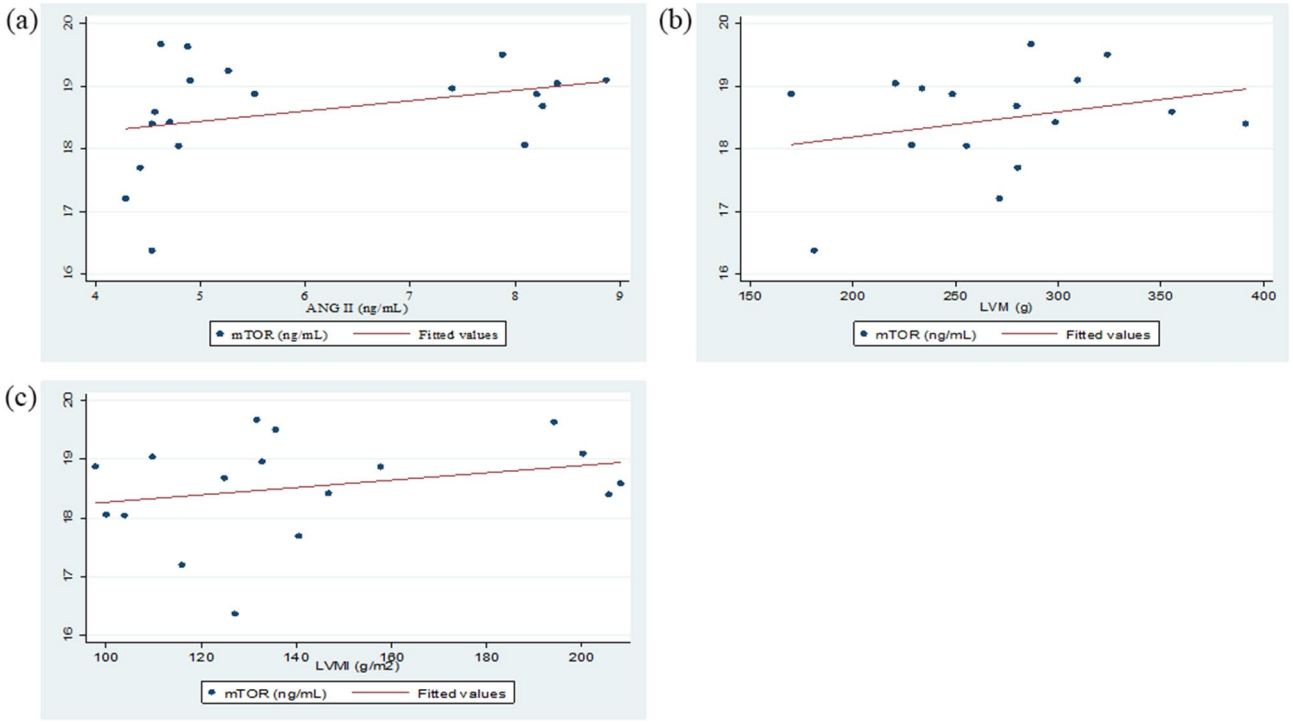

Fig. 9 shows the correlation between Ang II (**a**), LVM (**b**), LVMI (**c**) and mTOR in HWLVH. Ang-II ($r=0.489$, $p=0.034$) * [#]; LVM ($r=0.419$, $p=0.06$) [β]; LVMI ($r=0.210$, $p=0.417$) [#]; Ang II (Angiotensin II). [β]Pearson correlation; [#]Spearman correlation; *statistically significant ($p<0.05$)

[24–26]. The ECG prevalence of LVH was 39%, 11% and 15.74% Sokolow-Lyon voltage criteria, Cornell's criteria and Cornell's product respectively. The variation between the Sokolow-Lyon voltage and echocardiography prevalence could be due to the presence of higher ECG voltages among male blacks without cardiovascular disease when compared to Caucasians [27]. Also, some of the participants were obese which could have accounted for variations in LVH prevalence noted in this study [28].

This study also found that LVH was associated with higher cardiovascular risk factors like SBP, DBP, BMI, LDL, TC/HDL, TG/HDL and lower eGFR. This corroborates reports that HTN, obesity, lipid profile importantly elevated TG are associated with LVH [29, 30]. Also, a directional relationship has been described between renal function and prevalence of LVH [31, 32]. Hence, supporting the relationship between metabolic syndrome/hyperinsulinemia and LVM [29]. Also, suggests that young hypertensives with LVH may also be at increased risk of cardiovascular morbidity and mortality like the older population [33].

The exaggerated troponin T among HWLVH compared to HWOLVH and marked elevation compared to NORM can be attributed to the incident HTN and or possibly microcirculation dysfunction, or myocardial perfusion mismatch that has been described in the setting of LVH. Although coronary artery disease was not assessed or ruled out in this study [34]. Chemerin and Galectin-3 were markedly elevated between HWLVH and HWOLVH compared to between HWOLVH and NORM, this marked difference in galectin-3 suggests higher myocardial fibrosis, inflammation and probable early cardiac dysfunction why the significantly higher features of metabolic syndrome (BMI, dyslipidemia) could account for the aggravated chemerin among HWLVH [14, 35–37].

Angiotensin II was significantly higher when HWLVH was compared to NORM but not HWLVH. Circulating and tissue Ang II has been shown to play a significant role in pressure overload and LVH [38]. It is also a major therapeutic target in the management of LVH [38, 39]. Myocardial fibrosis has been associated with increased renin-angiotensin-aldosterone (RAAS) pathway activity and genomic alterations [14]. Angiotensin-II increases myocardial cell proliferation while aldosterone enlarges the collagen deposition, promoting myocardial fibrosis [6].

The total mTOR was aggravated when HWLVH was compared to HWOLVH and NORM. This corroborates reports that compensatory LVH secondary to pressure overload is dependent on mTORC1 and mTORC2. Also, mTOR has been implicated in inflammation in the CV system which underlies atherosclerosis (chronic inflammation)[43]. This study further suggests that elevated total mTOR is associated with left ventricular mass, BP, obesity, dyslipidemia, activation of the RAAS pathway,

inflammation and myocardial injury/dysfunction. The moderate positive correlation between Ang II and total mTOR corroborated the relationship between RAAS pathway and total mTOR in the development of LVH.

Conclusion

This study demonstrated that 20.9% of studied hypertensive young adults have LVH using 2D-transthoracic echocardiography. The results also suggest a possible interaction between mTOR and Ang II in the development of LVH. Also, it shows that LVH is associated with dyslipidemia, inflammation, and fibrosis.

Limitations

Although the present result provides a clinical relevance in the prevalence and management of hypertension in young adults as well as a platform for future molecular research. Nevertheless, the etiology of secondary HTN were not considered, also the cause-effect relationships of mTOR and other biochemical parameters in hypertensives with LVH.

Abbreviations

Ang II	Angiotensin II
BP	Blood Pressure
CV	Cardiovascular
DBP	Diastolic Blood Pressure
HDL	High-Density Lipoprotein
HF	Heart failure
HMOD	Hypertension-mediated organ damage
HTN	Hypertension
HWLVH	Hypertensives with Left Ventricular Hypertrophy
HWOLVH	Hypertensives without Left Ventricular Hypertrophy
LV	Left Ventricle
LVH	Left Ventricular Hypertrophy
LVM	Left Ventricular Mass
mTOR	Mammalian target of rapamycin
RAAS	Renin-Angiotensin-Aldosterone
SBP	Systolic blood pressure
TC	Total Cholesterol

Author contributions

B.O: Conceptualization, methodology, investigation, resources, writing-original draft, investigation, visualization, project administration, funding; S.O: formal analysis, resources, writing-review and editing, funding; O.E: resources, validation, project administration; P.A: validation, investigation, formal analysis; O.A: supervision; K.S.: supervision, conceptualization, methodology, writing-review and editing, investigation visualization, validation.

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Data availability

Data will be made available on request.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the ethics and research committee of ABUAD Multisystem Hospital (AMSH/REC/BOO/184), Ado-Ekiti; Ekiti State University Teaching Hospital Ado-Ekiti (EKSUTH/A67/2023/11/005) and Federal Teaching Hospital, Ido-Ekiti (ERC/2024/01/15/1066B) respectively.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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