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Multidisciplinary Academic Journal Publisher

Association of polymorphism of the osteoprotegerin gene with left ventricular hypertrophy occurrence in hypertensive patients

Tarek A. Abd-El-Aziz[1]; Randa H. Mohammad[2]; Wael A. Khalil[1] and Mohamed R.M.A. Ahmed[1]*

[1] Cardiology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt
[2]Medical Biochemistry Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt
E-mail: mreda010090@gmail.com

Abstract: Background: The major cause of mortality and morbidity worldwide is hypertension (HTN). Left ventricular hypertrophy (LVH) is an abnormal increase in left ventricular mass which is a marker for and contributes to coronary events, stroke, heart failure, peripheral arterial disease, and cardiovascular mortality in patients with hypertension. Osteoprotegerin (OPG) is a member of the (TNFRS) of cytokines and a soluble receptor for the (RANKL). We examined the relationship of polymorphism in the osteoprotegerin gene with the incidence of left ventricular hypertrophy in patients that are hypertensive. **Patients and methods:** Fifty hypertensive patients were included in the research; 25 with left ventricular hypertrophy (category A) and 25 without left ventricular hypertrophy (category B). All patients underwent a comprehensive history and medical examination. There was ECG and echocardiography performed. To show the existence or absence of LV hypertrophy, LV mass was computed. In order to identify osteoprotogrin gene polymorphism in PCRs, DNA was then derived from blood specimens and each DNA specimen was amplified. **Results:** The average age was 62.2±9.24 years for category A instances and 57.36 ± 6.42 years for category B instances, with statistically substantial differences among the two categories. In category A, there had been 60% men and 40% women, and 48% men and 52% women in category B, with no statistically substantial differences among the two categories. There have also been statistically relevant variations among the two categories with regard to duration of the disease, SBP, prominent a wave, forcible apex, fourth heart sound, Sokolowlyon index, but there were statistically high significant differences regarding LV mass index, E/A ratio, PWEDd, IVSDd and LV mass. The CC genotype has been found in 24% of the instances in category A and in 28 % of the instances in category B, the CG genotype has been found in 40% of the instances in category A and 48 % of the instances in category B, whereas the GG genotype has been present in 36% of the instances in category A and 24 % of the instances in category B with no statistically substantial variation among the two categories. Disease duration, age, smoking, prominent a wave, E/A ratio and grade of diastolic dysfunction were significant predictors of LVH. **Conclusion:** Polymorphism of the osteoprotegerin gene has been shown to be independent risk factors for the occurrence of LVH in patients with hypertension.

[Tarek A. Abd-El-Aziz, Randa H. Mohammad, Wael A. Khalil and Mohamed R.M.A. Ahmed. **Association of polymorphism of the osteoprotegerin gene with left ventricular hypertrophy occurrence in hypertensive patients.** *Nat Sci* 2020;18(11):3-10]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 2. doi:10.7537/marsnsj181120.02.

Keywords: Hypertension complications, left ventricular hypertrophy, osteoprotegerin

1. Introduction

In the cardiovascular system, harmful morphological and functional alterations include left ventricular hypertrophy (LVH), are correlated with high blood pressure. **(1)**. **Zhan et al. (2)** found that in Chinese patients with essential hypertension (EH), the prevalence of LVH was around 25% to 35%.

An independent risk factor for cardiovascular morbidity and mortality is known to be LVH. The frequency and degree of LVH may be affected by several variables, i.e., blood pressure level, hypertension duration, age, diet, obesity and pharmacological treatment. Moreover, the genetic factors are related to LVH as well **(3)**. Osteoprotegerin (OPG) is a member of the tumor necrosis factor receptor superfamily of cytokines and a soluble receptor for the receptor activator for nuclear factor-kB ligand. In the case of type 1 and type 2 diabetes mellitus (DM), serum OPG is included in vascular remodeling and dysfunction. In African-American adults with hypertension and in the general population, the correlation of serum OPG with left ventricular mass was recorded **(4)**.

A single-copy gene with 5 exons spanning 29 kb of the human genome represents the human OPG gene found on chromosome 8. There are different binding

sites in the promoter region of the human OPG gene that are capable of mediating OPG gene expression stimulation. Several OPG promoter polymorphisms have been documented to be related to vascular morphology and function in various populations **(5)**.

The function of OPG gene polymorphisms and serum OPG levels has not, however, been addressed in the development of cardiac remodeling, such as the development of LVH under hypertensive conditions. In the current research, we examined the relationship of polymorphism in the osteoprotegerin gene with Incidence of LVH in patients with hypertension.

2. Patients and methods

This is a case- control study in patients with hypertension to evaluate the correlation among osteoprotegerin and gene polymorphism with the incidence of LVH. In the Departments of Cardiology and Medical Biochemistry, Zagazig University Hospital, Egypt, this research was carried out. The research involved 50 instances of patients with hypertension with LVH (category I) and patients with hypertension without LVH (category II), which were split into two categories of 25 instances each.

Inclusion criteria:

Patients of basic hypertension with no other comorbidity.

Exclusion criteria:

1- Athletes.

2- Patients who are experiencing hypertension.

3- Patients that have DM.

4- Patients with congenital or valvular heart disease.

5- Cardiomyopathy patients.

Methods:

1 Taking Full History:

- Data from demographics.
- Current illness history.
- Surgical and clinical history.
- Drug intake history.
- Family history.

2. Clinical examination:

- Blood pressure.
- Pulse.
- Measurement of height, weight, waist circumference, body mass index (BMI).
- Local inspection for the assessment of sound, apical impulse and jugular venous pulse.

3. ECG: for evaluation of LVH signs.

4. Echocardiography.

5. Determination of LV mass: The LV mass measurement was performed to determine the existence or absence of LV hypertrophy in compliance with the following law: LV mass = 0.8 x (1.04 x ((LVIDd + PWTd + SWTd)3 - (LVIDd)3))

6. PCR- detection of osteoprotegerin gene polymorphism.

Statistical analysis

Using SPSS (Statistical Package for Social Sciences) version 22 for Windows ® (SPSS Inc, Chicago, IL, USA), the data collected was coded, processed and analyzed. The number (frequency) and percent were represented as qualitative data. The Chi-Square test ($\chi 2$) was used to compare groups. The Kolmogorov-Smirnov test examined quantitative data for normality. Mean ± SD was represented as normally distributed data. The student t-test was utilized to compare (expressed as t) among two groups. Median (min-max) was represented as non-parametric data. For comparison among categories, the Mann-Whitney test (expressed as z) was used. For univariate and multivariate analysis for LVH prediction, logistic regression analysis was utilized. To evaluate the quantitative variable's predictive potential (LV mass index) to distinguish instances with and without LVH, the receiver operator curve was used. It was deemed that $P < 0.05$ was statistically substantial.

3. Results

The average age was 62.2 ± 9.24 years for category A instances and 57.36 ± 6.42 years for category B instances, with a statistically substantial variation among the two categories (p=0.025). In category A, there were 60% men and 40% women, and 48% men and 52% women in category B, with no statistically substantial variation among the two categories (table 1).

The different items of examination in the cases within the two groups are shown in table (2). The average SBP was 127.8 ± 6.47 mmHg in category A and 124.4 ± 5.24 mmHg in category B, with statistically substantial differences (p=0.047) among the two categories (p=0.047). There were 12 instances in category A with a prominent a wave, and just 1 case in category B with a statistically substantial variation (p=0.001) among the two categories. There were 8 instances with forcible apex in category A and only 2 instances in category B with statistically substantial differences among the two categories (p=0.037). There were 8 instances with fourth cardiac sound in category A and 2 instances with statistically substantial differences among the two categories in category B (p=0.037).

In both study groups, the average RBS and serum creatinine levels did not indicate a substantial variation among the two categories. However, in category A there were 9 instances with a positive Sokolowlyon index, and in category B there were only 2 instances with a statistically substantial variation among the two categories (p=0.019) (table 3).

The average LV mass index in category A was 129.97 ± 17.21gm / m2 and in category B it was 82.95 ± 14.26gm / m2 with a high statistically substantial difference ($p < 0.001$) among the two categories. The data are shown in table (4).

The analysis of the different items of the echocardiography in the two study categories is illustrated in table (5). The mean EF, FS (%) and LVEDD didn't reveal statistically substantial variation among the two categories. The average E/A ratio in category A was 0.81 ± 0.24 and in category B it was 1.46 ± 0.28 with high statistically substantial variation among the two categories ($p< 0.001$). There were 2 cases with diastolic dysfunction grade 0, 23 cases with grade 1 and no cases with grade 2 in group A while in group B. There were 20 cases with diastolic dysfunction grade 0, no cases with grade 1 and 5 cases with grade 2 with high statistically substantial variation among the two categories ($p< 0.001$). The average PWEDd, IVSDd and LV mass (gram) also showed a high statistically substantial variation in category A among the two categories ($p < 0.001$).

The OPG analysis in the two sample categories as seen in table (6), the CC genotype was found in 24% of Category A instances and in 28% of category B instances, the CG genotype was found in 40% of Category A instances and in 48% of category B cases, whereas the GG genotype was present in 36% of Category A instances and in 24% of category b instances with no statistically substantial variation among the two categories.

With a univariate risk analysis, age, disease duration, smoking, wave prominence, EA ratio and grade of diastolic dysfunction were significant predictors of LVH. Increasing disease duration and The/Met genotype increased risk of developing LVH among hypertensive patients by about 2 and 4 folds respectively (table 7).

Table (1): Demographic data analysis of the two study groups

		Groups		Test of significance
		Group A HTN with LVH (N=25)	Group B HTN without LVH (N=25)	
Age (years)		**62.2 ± 9.24**	**57.36 ± 6.42**	**p= 0.037***
Gender	**Male**	**15 (60%)**	**12 (48%)**	**p= 0.776**
	Female	**10 (40%)**	**13 (52%)**	
Height		**168.42± 7.18**	**173.2 ± 10.14**	**p= 0.052**
Weight		**75.4 ± 13.62**	**78.8 ± 15.78**	**p= 0.419**
Waist-circumference		**87.76 ± 6.7**	**88.28 ± 6.86**	**p= 0.787**
BMI		**26.54 ± 3.71**	**26.04 ± 3.31**	**p= 0.619**
BSA		**1.87 ± 0.19**	**1.94 ± 0.24**	**p= 0.266**

P: probability. *: When ($p < 0.05$) statistically significant

Table (2): Clinical data analysis in the two study groups

		Groups		Test of significance
		Group A HTN with LVH (N=25)	Group B HTN without LVH (N=25)	
SBP (MMHg)		**127.8 ± 6.47**	**124.4 ± 5.24**	**p= 0.047***
DBP (MMHg)		**83.6 ± 3.96**	**81.6 ± 4.73**	**p= 0.111**
HR (beat/min)		**80.92 ± 12.4**	**75.96 ± 11.65**	**p= 0.151**
Prominent a wave		**12 (48%)**	**1 (4%)**	**p= 0.001****
Dyspnea grade	**Grade 0**	**11 (44%)**	**17 (68%)**	**p= 0.06**
	Grade 1	**10 (40%)**	**7 (28%)**	
	Grade 2	**4 (16%)**	**1 (4%)**	
Lower limb edema		**4 (16%)**	**0 (0%)**	**p= 0.11**
Forcible apex		**8 (32%)**	**2 (8%)**	**p= 0.037***
Fourth heart sound		**8 (32%)**	**2 (8%)**	**p= 0.037***

P: probability. SBP: systolic blood pressure DBP: diastolic blood pressure
HR: heart rate *: When ($p < 0.05$) statistically significant

Table (3): **Analysis of laboratory investigations in the two study groups**

	Groups		Test of significance
	Group A HTN with LVH (N=25)	Group B HTN without LVH (N=25)	
RBS	**102.92 ± 12.72**	**108.32 ± 13.2**	**p= 0.152**
Serum creatinine	**0.883 ± 0.146**	**0.853 ± 0.143**	**p= 0.466**
Sokolowlyon index	**9 (36%)**	**2 (8%)**	**p= 0.019***

P: probability. Continuous data as mean±SD is represented. Categorical data represented as Number (%)
*: When ($p < 0.05$) statistically significant RBS: random blood sugar

Table (4): LV mass index in the two study groups

	Groups		Test of significance
	Group A HTN with LVH (N=25)	Group B HTN without LVH (N=25)	
LV mass index (gm/m^2)	**129.97 ± 17.21**	**82.95 ± 14.26**	**p< 0.001***

Table (5): Analysis of echocardiographic index of the two study groups

		Groups		Test of significance
		Group A HTN with LVH (N=25)	Group B HTN without LVH (N=25)	
EF (%)		**66.96 ± 7.18**	**68.4 ± 6.63**	**p= 0.465**
FS (%)		**37.56 ± 4.98**	**38.96 ± 5.15**	**p= 0.334**
E/A ratio		**1.46 ± 0.28**	**0.81 ± 0.24**	**p < 0.001***
Diastolic dysfunction grade	**Grade 0**	**2 (8%)**	**20 (80%)**	**p < 0.001***
	Grade 1	**23 (92%)**	**0 (0%)**	
	Grade 2	**0 (0%)**	**5 (20%)**	
LVEDD		**5.15 ± 0.64**	**4.82 ± 0.54**	**p= 0.057**
PWEDd		**1.32 ± 0.16**	**1.04 ± 0.1**	**p < 0.001***
IVSDd		**1.304 ± 0.117**	**0.998 ± 0.095**	**p < 0.001***
LV mass (gram)		**263.73 ± 46.5**	**167.26 ± 37.01**	**p < 0.001***

P: probability. *: When ($p < 0.05$) statistically significant EF: ejection fraction
FS: fraction shortening. LVEDD: left ventricular end diastolic diameter
PWEDD: posterior wall end diastolic diameter. IVSDD: interventricular septum diameter in diastole
LV mass: left ventricular mass

Table (6): **Analysis of osteoprotegerin genotype in the two study groups**

		Groups		OR (95 % CI)	Test of significance
		Group A HTN with LVH (N=25)	Group B HTN without LVH (N=25)		
OPG	**CC**	**6 (24%)**	**7 (28%)**	**1 (reference)**	
	CG	**10 (40%)**	**12 (48%)**	**0.97 (0.25- 3.85)**	**0.968**
	GG	**9 (36%)**	**6 (24%)**	**1.75(0.39-7.86)**	**0.464**
Alleles	**G**	**22 (58%)**	**26 (44%)**	**1 (reference)**	
	C	**28 (42%)**	**24 (56%)**	**1.38 (0.63-3.03)**	**0.423**

P: probability. OPG: Osteoprotegerin gene

4. Discussion

The major causes of heart failure include high blood pressure, valvular heart diseases, congenital heart diseases, coronary heart disease and cardiomyopathy. High blood pressure is a world main cause of mortality and morbidity. The prevalence of the disease and its incidence are rising internationally **(6)**.

Left ventricle compensates for these cardiovascular attacks by either dilation or hypertrophy to enhance and improve heart pump capacity. Left ventricular hypertrophy relative to arterial high blood pressure is a dynamic cardiac phenomenon arising from the reaction to mechanical and neuro-humoral stimulation of myocyte and non-myocyte component. Left ventricular hypertrophy and increased Left ventricular mass (LVM) are trigger factors for coronary artery disease, heart attack and cerebral stroke **(7)**.

Bella and Göring (3) have shown that LVH is caused by overload of mechanical stress, neurohormonal variables, and different genetic variables which independently exert trophic influence on myocytes and non-myocytes of the heart.

Several single nucleotide polymorphisms (SNPs) correlated with LVH echocardiography have been identified by genome-wide association studies (GWAS). OPG is a traditional inflammatory cytokine associated with the regulation of bone remodeling **(8)**. OPG has been related to cardiovascular diseases by **Liu et al. (9)**. In angiography, for example, Plasma OPG was shown to represent the magnitude of coronary artery disease and to anticipate the occurrence of cardiovascular disease and deaths in the population. In human patients, improved myocardial protein levels of OPG were found in experimental as well as clinical heart failure.

The goal of this research is to assess the relation of polymorphism of the osteoprotegerin gene with the incidence of LVH in patients with hypertension. The research involved 50 instances, split into two categories of 25 instances as follows; category A: patients with hypertension with LVH and category B: patients with hypertension without LVH.

Another research in patients with essential hypertension (EH) was performed by Shen et al. (10) to examine the function of osteoprotegerin (OPG) in the development of (LVH). 1092 patients in total with EH-diagnosis were enrolled. The LVHs were described and the genotyping of OPG gene polymorphisms was carried out.

In this research, the average was 63.12 ± 7.23 years for category A instances and 58.24 ± 7.16 years for category B instances, with a statistically substantial differences among the 2 categories (p=0.025). This was partly accepted with **Bahramali et al. (11)** who found that the average age in left ventricular hypertrophy instances was higher than in instances without left ventricular hypertrophy (63.3±12.01 years versus 61.70±13.26 years respectively), but there was no statistical relevance for this variation.

Also, **Kabil et al. (12)** assessed the effect of osteoprotegerin polymorphism with the incidence of LVH in patients with hypertension. The research involved fifty patients with hypertension: 25 with LVH (category A) and 25 without LVH (category B). The average was 63.12 ± 7.23 years for category A instances and 58.24 ± 7.16 years for category B instances, with a statistically substantial disparity among the two categories (p = 0.025). There had been 52 % men and 48 % women in category A and 64 % men and 36 % women in category B with no statistically substantial differences among the two categories.

In our research, men were more impacted than women; in group A, there were 60% men and 40% women, and in group B, 48% men and 52% women, with no statistically substantial differences among the two categories. This was in line with **Ariyandy et al. (13)**, who stated in their research that in the two study categories (18/8 in the LVH category and 34/17 in instances without LVH); men had been more than women, with no statistically substantial differences among the two categories. However, in a study conducted by **Bahramali et al. (11)**, the overall study showed a high incidence of women over men (124 women vs. 52 men) with high statistically substantial differences among the two categories.

The mean period of the disease in category A was 5 years, ranging from 3 to 15 years, while in category B it was 4 years, ranging from 2 to 8 years, and the differences among the two categories was statistically substantial (p=0.004). This was the case, unlike **Shen et al. (10)** that found no substantial differences in the mean HTN length in groups with or without HTN.

In our study, the average SBP was 127.8 ± 6.47 mmHg in group A and 124.4 ± 5.24 mmHg in group B, with a statistically substantial differences (p=0.047) among the two categories. There were 12 cases with prominent a wave in group A and only 1 case in category B with statistically substantial differences among the two categories (p=0.001). There had been 8 cases with forcible apex in category A and only 2 instances in category B with statistically substantial differences among the two categories (p=0.037) There had been 8 cases with fourth heart sound in category A and 2 instances in category B with high statistically

substantial differences among the two categories (p=0.037).

In another research, the average SBP was 149.7± 10.2 mmHg in LVH instances and 145.2± 8.8 in instances without LVH, with a statistically substantial differences (p= 0.049) among the two categories. **(10)**. **Kabil et al. (12)** also observed statistically substantial variations among the two categories with respect to SBP, prominent a wave and second split sound, and high statistically substantial variations with respect to forcible apex and fourth heart sound.

However, **Ariyandy et al. (13)** did not record any statistically substantial differences in the average SBP among instances with and without LVH, even though it was stated to be higher in instances with LVH. This can be interpreted by the fact that impaired glycemic control is typically correlated with HTN or attributable to the condition of heart affection.

In both sample categories, the average RBS and serum creatinine levels did not indicate substantial variation among the two categories. This was consistent with the outcomes of Shen et al. (10), who did not demonstrate any statistically substantial variations among the two categories with and without left ventricular hypertrophy.

The average LV mass index in category A was 129.97 ± 17.21gm / m2 and in category B it was 82.95 ± 14.26gm / m2 with a high statistically substantial variation (p < 0.001) among the two categories. This was in line with **Bahramali et al. (11),** who demonstrated that the average LV mass index was 129.49±29.69 gm / m2 in the LVH category and 80.34±19.05 gm / m2 in the category without LVH, with a high statistically substantial variation among the two categories (p< 0.001). **Kabil et al. (12)** also discovered that in category A the average LV mass index was 131.52 ± 11.82 gm / m2 and in category B it was 84.63 ± 14.87 gm / m2 with a high statistically substantial variation among the two categories (p < 0.001).

In this study, the mean EF didn't reveal statistically substantial variation among the two categories. This was in line with Ariyandy et al. (13), who found that the mean EF was 64.0 ± 12 % in instances without LVH and 65.7 ± 9.2 % in instances with LVH, with no substantial variation among the two categories.

The average E/A ratio was 0.81 ± 0.24 in category A and 1.46 ± 0.28 in category B, with a high statistically substantial variation (p < 0.001) among the two categories. **Kabil et al. (12)** also observed statistically substantial variation with respect to the average E/A ratio among the 2 categories. However, this disagreed with **Bahramali et al. (11)** who, in instances with and without LVH (p= 0.17), found no statistically substantial variation in the E/A.

In this study, there were 2 cases with diastolic dysfunction grade 0, 23 cases with grade 1 and no cases with grade 2 in group A while in group B There were 20 cases with diastolic dysfunction grade 0, no cases with grade 1 and 5 cases with grade 2 with high statistically substantial variation among the 2 categories (p< 0.001). Also, **Kabil et al. (12)** found statistically significant differences between the two groups regarding grade of diastolic dysfunction.

The average PWEDd, IVSDd and LV mass (gram) also showed a high statistically substantial variation in category A among the two categories (p < 0.001). This was consistent with Bahramali et al. (11), which indicated that both the following IVS, LVPW and LVEDD were significantly higher in LVH instances (p<0.001) with a statistically substantial variation. Also, **Kabil et al. (12)** revealed high statistically significant difference between the two groups regarding PWEDd, IVSDd and LV mass being higher in group A. However, **Ariyandy et al. (13)** did not found any substantial variation among instances with and without left ventricular hypertrophy (p= 0.52 and 0.97 respectively) in the average value of the LV end-diastolic dimension and the LV end-systolic dimension.

In this research, with the OPG gene sequence analysis, the CC genotype was found in 24 % of Category A instances and in 28 % of category B instances, the CG genotype was found in 40 % of category A instances and in 48 % of category B instances, whereas the GG genotype was present in 36 % of category A instances and in 24 % of category B cases, with no statistically substantial variation.

In another analysis, the genotype frequencies of the LVH+ve and LVH-ve OPG polymorphisms revealed that the genotype and allele frequencies of 163 A > G and 245 T > G did not vary substantially among the categories of LVH+ve and LVH-ve (all P>0.05). However, the genotypes and allele frequency of 1181 G>C were substantially different among the two categories. Patients with LVH+ve had a slightly lower CC genotype than patients with LVH-ve (18.06% vs 31.12%, global P<0.001). As a reference multivariate logistic regression analysis, 1181GG genotypes showed that 1181CC genotype carriers had a substantially lower risk of developing LVH **(10)**.

The polymorphism appears to be more correlated with cardiovascular disease at the 1181 G > C locus than the other genetic variants. **Celczyńska et al. (14)** found that, as compared to heterozygotes for CG or homozygotes for GG, homozygous CC carriers of the 1181 OPG gene have been shown to have normal coronary arteries more often, but not 209 C/T and 245 C/TC polymorphisms. **Choe et al. (15)** failed, however, to demonstrate a substantial correlation

among OPG and RANK polymorphisms and the occurrence of acute coronary syndrome.

Similar findings have been reported by **Ariyandy et al. (13),** the frequency of the Thr / Met genotype was found in 13.7 % of instances in the category without LVH and in 42.3 % of instances in the LVH category, whereas the frequency of the Thr / Thr genotype was found in 86.3 % of instances in the category without LVH and in 57.7 % of instances in the LVH category, with a statistically substantial variation among the two categories.

Similar results were reported also by **Kabil et al. (12)**, the CC sequence was found in 20 % of the instances in Category A and in 32 % of the instances in category B, the CG sequence was found in 44 % of the instances in Category A and 48 % of the instances in category B, whereas the GG sequence was present in 36 % of the instances in Category A and 20% of the instances in category B with no statistically substantial variation among the two categories ($p = 0.387$).

In this research, with univariate regression analysis, age, disease duration, smoking, prominent a wave, EA ratio and grade of diastolic dysfunction, were significant predictors of LVH. Increasing disease duration and The/Met genotype increased risk of developing LVH among hypertensive patients by about 2 and 4 folds respectively. A report from the Framingham Heart Study found that, irrespective of traditional risk factors, elevated LV mass highly predicted all-cause and cardiac deaths and coronary heart disease incidents in adults above 40 years **(16)**.

Kabil et al. (12) shows that significant LVH predictors were age, disease duration, prominent wave, EA ratio, grade of diastolic dysfunction, PWEDd, IVSDd, LV mass and LV mass index with univariate risk analysis. Independent risk factors for Left ventricular hypertrophy using multivariate regression analysis were E/A ration, PWEDd, LV mass and smoking.

Conclusion

Polymorphism of the osteoprotegerin gene has been shown to be independent risk factors for the occurrence of LVH in patients with hypertension.

Conflict of Interest:

No financial or personal relations with other entities or organizations that could impact the present study improperly.

Financial Disclosures:

No particular financial interests, relationships or affiliations related to the subject of the manuscript have been identified.

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10/31/2020