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Intima–Media Thickness in Primary Aldosteronism Compared with Essential Hypertension: A Meta-analysis

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Abstract

AIM: This study was comparison of the intima–media thickness in the primary aldosteronism (PA) patients versus essential hypertension (EH) patients.

METHODS: We searched on PubMed for studies about intima–media thickness in PA and found 317 articles. After the title and abstract reading, we excluded 291 studies because they did not fit in our criteria. After the final assessment of the 26 articles, seven of them were chosen as final studies to be included in the meta-analysis.

RESULTS: In this study, we included seven studies with a total of participants of 534 patients. The main outcome was a comparison of intima–media thickness between patients with PA, EHs and healthy controls. The result shows a thicker intima media in PA patients in comparison with EH patients and more over with healthy controls, but this was not statistically significant.

CONCLUSION: PA predisposes to a thicker intima media in comparison to EH, but we need for larger studies to have significant results.

Introduction

Primary aldosteronism (PA) is recognized as the most frequent cause of endocrine hypertension and accounts for about 5–15% of hypertensives [1], [2]. It can result from either aldosterone-producing adenoma (APA) or idiopathic adrenal hyperplasia and has a high prevalence of approximately 11% among *de novo* hypertensive patients who are referred to a specialized center. Basic research studies suggest that aldosterone may directly impact on vascular function, inflammation, and fibrosis and therefore favoring arterial stiffening [3]. Arterial stiffness and intima–media thickness are increased in patients with PA as different studies show [4], [5], [6], [7]. As observation studies have demonstrated, aldosterone stimulates cell growth and vascular remodeling, which can evoke an increased left ventricular mass and an increased tunica media to lumen ratio in small resistance arteries [8], [9], [10]. Several studies also indicate that patients with PA are more likely to experience cardiovascular events and renal complications compared to patients with essential hypertension (EH) [11], [12], [13]. A meta-analysis demonstrated that PA was associated with significantly increased risk of stroke, coronary artery disease, and LVH when compared with EH group [14], [15]. Moreover, PA resulted in significantly higher levels of SBP, DBP, and urinary potassium. Hyperaldosteronism is held to cause structural changes in the heart, that is, inflammation, fibrosis, remodeling, hypertrophy, and functional and electrophysiologic alterations [16]. The excess of plasma aldosterone correlated with LVH, early diastolic dysfunction, and left ventricular enlargement with evidence of subclinical systolic dysfunction [17], [18], [19]. Complex mechanisms including endothelial damage, increased oxidative stress, activation of inflammation, and fibroproliferation may lead to functional and/or structural blood vessel wall abnormalities in PA. The occurrence of these vascular changes seems to be higher in patients with PA than in EH, independent of blood pressure levels. Aldosterone may thus act as an independent risk factor for vascular damage [20]. Both peripheral and central PWV were significantly higher in PA patients compared to EH patients, while clinical blood pressures were similar.

Plasma aldosterone level was the main predictor of peripheral PWV in PA. Fibroproliferative effect of higher aldosterone levels leads to alteration of central-elastic as well as peripheral-muscular arteries with subsequent increase in its stiffness [21]. The effect of aldosterone in the vascular wall of the carotid arteries is seen in several studies. The aim of these meta-analyses is to obtain more solid results about the intima–media thickness in patients with PA versus those with EH.

Methods

Inclusion and exclusion criteria and data extraction

The inclusion criteria are as follows

- Age above 18-year-old
- Patients with PA
- Comparison with EH patients
- Studies having also a healthy control group.

Exclusion criteria

The following criteria were excluded from the study:

- Studies on animals
- Non-comparative studies (which no not include two groups of patients or a control group)
- Studies not in English
- Reviews, letters, and meta-analyses.

Data extraction

We searched on PubMed for studies about intima–media thickness in PA and found 317 articles. After the title and abstract reading, we excluded 291 studies because they did not fit in our criteria. Twenty-six studies were evaluated as full text and the final assessment of the articles, seven of them were chosen as final studies to be included in the meta-analyses. Two researchers E. M and I. L searched on PubMed independently using the following mesh terms:

Search: (((hyperaldosteronism) OR (primary aldosteronism)) OR (essential hypertension)) AND (carotid intima–media thickness) (“hyperaldosteronism” [MeSH Terms] OR “hyperaldosteronism” [All Fields] OR “hyperaldosteronisms” [All Fields] OR (“hyperaldosteronism” [MeSH Terms] OR “hyperaldosteronism” [All Fields] OR (“primary” [All Fields] AND “aldosteronism” [All Fields]) OR “primary aldosteronism” [All Fields]) OR (“essential hypertension” [MeSH Terms] OR (“essential” [All Fields] AND “hypertension” [All Fields]) OR “essential hypertension” [All Fields])) AND (“carotid intima–media thickness” [MeSH Terms] OR (“carotid” [All Fields] AND “intima media” [All Fields] AND “thickness” [All Fields]) OR “carotid intima–media thickness” [All Fields] OR (“carotid” [All Fields] AND “intima” [All Fields] AND “media” [All Fields] AND “thickness” [All Fields]) OR “carotid intima–media thickness” [All Fields]).

PICO strategy

Population: patients with arterial hypertension. There are two main groups included in this analysis, patients with PA, and patients with EH. Some of the studies also have a healthy control cohort.

Intervention

Diagnostic carotid assessment for intima–media thickness.

Comparison

The comparison of intima–media thickness between the two patients groups and the healthy control group.

Outcome

The expected outcome is the greater value of intima–media thickness in the PA group guided by the hypothesis of the aldosterone effect on the vascular system (Figure 1).

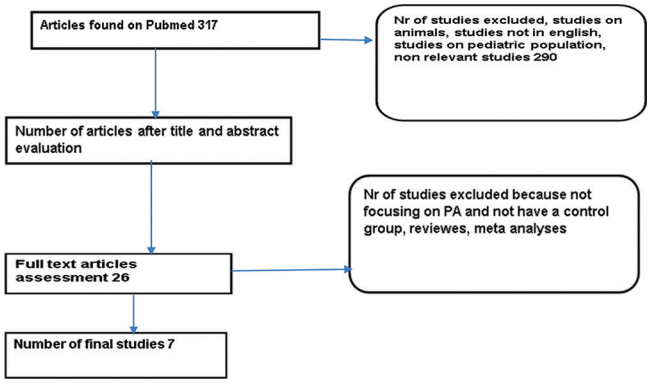

Figure 1: Study Prisma Flowchart

Endpoints

Primary endpoint is the presence of thicker intima media in the PA patients compared to the EH group.

Statistical analysis

Statistical analysis was realized through JASP software, a software developed in R metaphor-project. Method was set based on Omnibus test of Model Coefficients and Test of Residual Heterogeneity. Effect

size and standard error were calculated according to the software`s producer recommendations. The estimated result of each study for the intervention was represented through intercept and 95% Confidence Interval. Funnel and forest plots were produced. Egger's test was performed to evaluate asymmetry.

Results

The details of the seven studies included in the meta-analyses are reported in Table 1.

Table 1: Characteristics of the studied included in the meta-analyses

First author	Year of publication	Country	Study design	Sample size	PA	EH	Control	IMT PA	IMT EH	IMT Control	IMT N	ES (95%-CI)*	SE
Bernini Giampaolo	2008	Italy	3	62	23	24	15	0.84	0.69	0.59	0,74	0.2 [-4.33, 4.73]	2,31
Demirkiran Ahmet	2019	Turkey	1	70	29	41		0.9	0.8		0,74	0.12 [-4.29, 4.53]	2,25
Gonzalez Perez Paloma	2008	Spain	1	44	17	10	17	1.1	0.82	0.7	0,74	0.29 [-4.01, 4.60]	2,20
Holaj Robert	2007	Czech Republic	1	118	33	52	33	0.987	0.892	0.812	0,74	0.10 [-4.21, 4.41]	2,20
Lee Min Yi	2014	Taiwan	1	111	32	49	30	0.87	1.19		0,74	-0.31 [-4.56, 3.93]	2,17
Lin Yen Hung	2011	Taiwan	1	41	20	21		0.64	0.53		0,74	0.19 [-4.67, 5.05]	2,48
Lottspeich Christian	2021	Germany	1	88	44	44		0.77	0.75		0,74	0.03 [-4.50, 4.55]	2,31

Outcomes

Risk of carotid intima–media thickness in the PA patients compared to the EH patients. Primary hyperaldosteronism was associated with an increased thickness of intima media compared to EH in the random effects model (RR: 0.08, 95% CI: −1.6–1.76) (Figure 1). The Funnel plot shows symmetry. FE model represents that "the weighted average of the effect sizes," is the estimate value of intercept which is not significant (p = 0.924). There is a positive increase of intima–media thickness in PA compared to EH, but non-significant. In the three studies with controls, the presence of carotid intima thickness was more accentuated in the PA group but still statistically non-significant (RR: 0.33, 95% CI: −2.2–2.9).

Forest plot

In Figure 2, in the forest plot, numbers next to each study graphical presentation show each study "effect size." In square brackets are 95% CI (95% confidence interval values) for each study. The larger

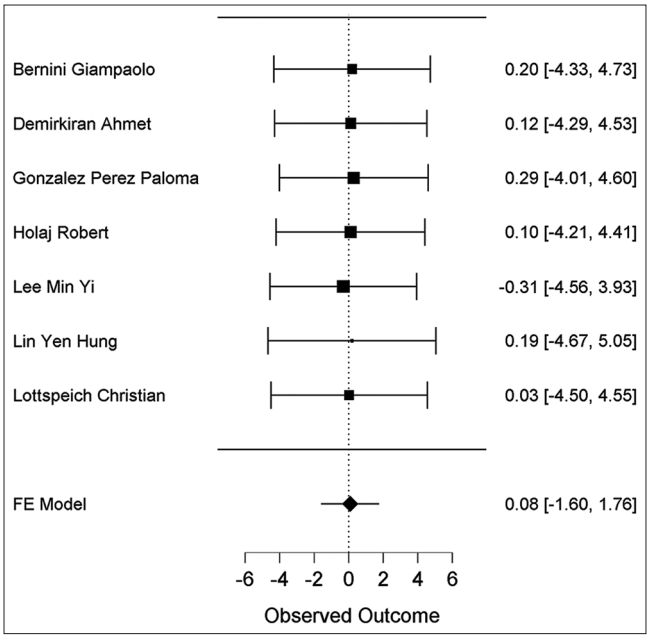

Figure 2: Forest plot

the central figure the larger the effect in calculation of the generalized effect value.

FE model represents that "the weighted average of the effect sizes," is the estimate value of intercept. It is non-significant (p = 0.924).

Funnel plot

Funnel plot: Each point in the graphical is a study placed on the "standard error" scale. The funnel represents 95% CI intervals. Symmetry must be statistically proved (Table 2).

Table 2: Regression test for Funnel plot asymmetry ("Egger's test")

Value	Z	p
Sei	0.084	0.933

("Egger's test") evaluates asymmetry which in our case results insignificant (p = 0.933). This favors the absence of publication bias.

There are only three studies with controls. "Omnibus test of the Model Coefficients" and (Test of Residual Heterogeneity), and both are non-significant, with p-values above 0.100, refuting the null hypothesis of no effect, and the hypothesis of homogeneity.

FE model represents that "the weighted average of the effect sizes," increases from 0.081 to 0.332 but still non-significant (p = 0.801).

Funnel Plot

The model is repeated 4 times(Figures 3-5):

- First, IMT PA – intima–media thickness in PA is correlated to IMT EH – intima–media

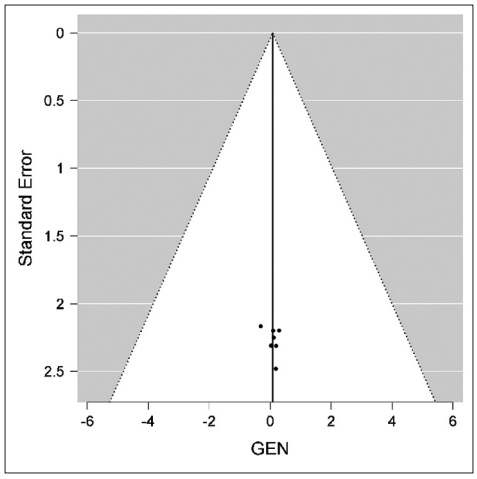

Figure 3: Funnel plot

thickness EH as a control group. There is no heterogeneity, the weighted average of the effect sizes equals 0.08, not significant.

- Second, to the above model are added, sample size as a covariate and study design a factor. There is no heterogeneity, the weighted average of the effect sizes equals 0.434, thus statistically not significant.
- Third, IMT PA – intima–media thickness in PA is correlated to IMT control – intima–media thickness in healthy controls as a control group. There is no heterogeneity, the weighted average of the effect sizes equals 0.332, thus not significant.

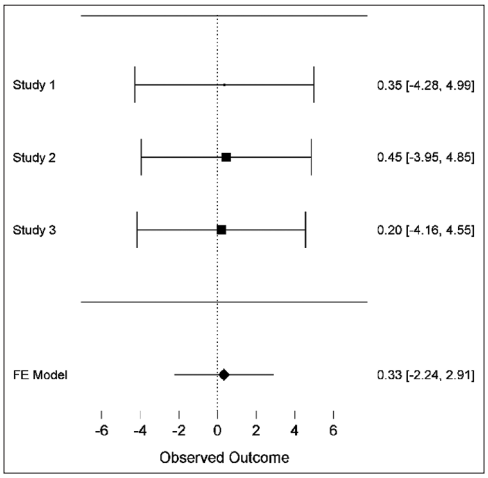

Figure 4: Forest plot of the studies with the controls

- Fourth, IMT PA – intima–media thickness in PA is correlated to IMT control – intima–media thickness healthy controls as a control group. To the above model are added, sample size as a covariate and study design a factor, no heterogeneity, the weighted average of the effect sizes equals 0.605, not significant.

The fact that there is no heterogeneity between studies show the fact that there is no important publication bias. There are greater values of intima–media thickness in the PA group than the EH group, and the values increase more when compared to a control group.

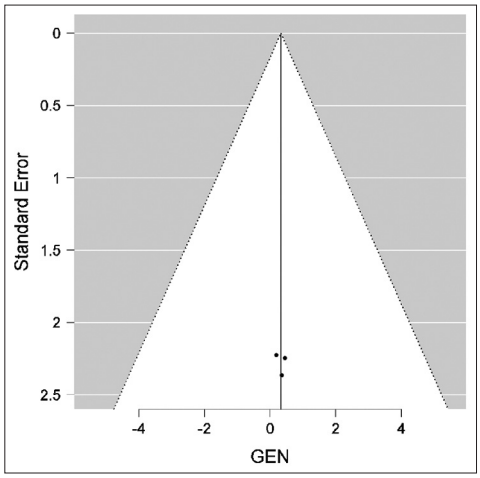

Figure 5: Funnel plot of the studies with the controls

Discussion

The outcome of this meta-analysis was that in comparison with EH and healthy controls, the PA patients have the tendency to show thicker intima media of the carotid artery. Even thaw our results are week, they could have been influenced by several limitations, as the low number of studies and patients. Patients with PA have been shown to have more cardiovascular events, including coronary artery disease, stroke, and atrial fibrillation than EH patients, which are independent of blood pressure effects [12].

Some studies reported that arterial wall damage in PA patients is more profound than in EH patients, possibly due to excessive aldosterone production, thereby resulting in thickening the intima–media layer of carotid artery [6]. PA patients were found to have not only increased CIMT and arterial stiffness, but elevated corrected integrated backscatter signal of the carotid arteries compared to EH patients [7]. These studies implied that aldosterone seems to increase fibrosis in both heart and vascular system. In the presented study, the increases in both arterial stiffness and CIMT found in PA patients may provide another support for the aldosterone related vascular damage.

Another s-tudy reveals that APA patients have higher degree of the early atherosclerosis and vascular stiffness and demonstrates that adrenalectomy not only corrects the high blood pressure and biochemical data but also reverses adverse vascular change in APA patients. The findings emphasized that the arterial stiffness and increased CIMT in APA patients seemed to be reversed by adrenalectomy [5], [22]. The present study demonstrates that aldosterone is responsible for vascular morphological and functional damage, which

may explain the elevated cardiovascular risk of patients with PA. Our results show that arterial hypertension associated with aldosterone excess induces vascular alterations to a greater extent than comparable EH. This damage involves wall thickening and increased collagen deposition with vascular fibrosis of the carotid arteries.

Conclusion

This meta-analysis show the intima–media thickness tendency is greater in PA patients compared to EH and more to healthy controls. The lack of statistical significance is due to the small number of patients present in the studies. Larger studies are needed to obtain more solid conclusions over the bond between PA and developing of carotid artery thickness and disease.

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