

## Relation of Hypertension with Migraine and Chronic Daily Headache in population of Rafsanjan Cohort Study

Movahedeh Mohammadi<sup>1</sup>, Fatemeh Ayoobi<sup>1</sup>, Parvin Khalili<sup>2</sup>, Narjes Soltani<sup>1</sup>, Carlo La Vecchia<sup>3</sup>, Alireza Vakilian<sup>1,4\*</sup>

<sup>1</sup>Non-Communicable Diseases Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

<sup>2</sup>Social Determinants of Health Research Centre, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

<sup>3</sup>Department of Clinical Sciences and Community Health, University degli Studi di Milano, Milan, Italy

<sup>4</sup>Department of Neurology, Ali-ebn-Abitaleb Hospital, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

\* **Correspondence to:** Alireza Vakilian, Non-Communicable Diseases Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran, Tel: 98343131500; E-mail: alirezavakilian7@gmail.com

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### Abstract

**Background:** Headache has a variety of types, such as Migraine and chronic daily headache (CDH) in its primary form. There is a positive correlation between these two types of headaches and hypertension (HTN), but in some works this correlation has been reported negatively. Therefore, we planned to study HTN-Migraine as well as HTN-CDH correlation in our population.

**Methods:** A sample of Rafsanjan population (10000 individuals) entered the cohort study, as a part of the prospective epidemiological research studies in IrAN (PERSIAN). In this population, we compared the frequency of HTN categories in cases with Migraine and CDH with a normal population (without Migraine).

**Results:** Out of 9990 participants (46.6% males and 53.4% females) about 29% had Migraine and 7.5 % had CDH. HTN was found in 24.27% of Migraine and 31.98% of CDH cases. HTN was also found to be associated with Migraine and CDH in the crude model. Two Categories of HTN (Long controlled and uncontrolled) were not associated with Migraine. On the other hand, CDH showed associations with all the HTN categories. Moreover, in a model, which included all variables and confounders, Migraine and CDH had association with HTN without any considerable changes.

**Conclusion:** Our study showed that there is strong HTN-Migraine as well as HTN-CDH correlations in the studied population.

**Keywords:** Headache; Migraine; Hypertension; Prospective Epidemiological Research Studies in IrAN (PERSIAN)

autonomic dysfunction and ischemic vascular disorders, which cause annoying problems for patients [1,2]. About 10%-20% of people around the world could be involved with Migraine in the most productive periods of their working lives. Women are four times more probable to suffer from Migraine than men [3]. Clinically, this type of headache is recognized by recurrent headache attacks, various gastrointestinal-related symptoms, and autonomic nervous system [4]. These patients are also at risk of ischemic and hemorrhagic stroke, ischemic heart disease, myocardial infarction, angina, coronary artery disease, and vascular mortality, especially with aura symptoms [5]. Migraine could obviously affect the vascular system, It has been also reported as an inherited brain disorder's. The possible relation between Migraine and vascular disorders has been studied for decades and some studies have reported a positive relation between Migraines and high blood pressure while others have not.

Additionally, Migraine, especially with aura symptoms has been shown to be associated with an increase in the risk of stroke and cardiovascular diseases, especially myocardial infarction [6].

About, 10 percent of referrals suffering headache, to clinics of general neurology have been diagnosed with chronic daily headache (CDH), which is usually associated with poor life quality. Many of these patients were underdiagnosed and undertreated. High prevalence of hypertension (HTN) has been also found in patients with CDH more than those with Migraine. In contrast with some papers, in a study, there was no difference in the prevalence of HTN between chronic Migraine (CM) and non-CM patients [6]. The relationship between Migraine and HTN has been also investigated in several case-control and cross-sectional studies. These works have represented conflicting outcomes [7]. According to a 5-year prospective population-based study, the risk of high blood pressure in patients with Migraine was about 1.4 times higher than those without Migraine.

### Introduction

As a primary headache disorder, Migraine has been recognized to be responsible for many disorders, such as

Moreover, some studies have revealed conflicting results on the relationship between Migraine and HTN (both diastolic and systolic blood pressure). For example, Pietrini et al. reported a positive relation between headache and high blood pressure in both sexes [9], while other studies did not prove this relation [10]. Accompaniment of Migraine and high blood pressure is important for occurrence of stroke. Explained the increasing risk of stroke in a group of people with both Migraine and high blood pressure compared with a group, who had only high blood pressure. Population-based studies have revealed the association between Migraine and ischemic stroke.

Therefore, given the high prevalence of both headache types (Migraine and CDH) and HTN more research on the relation between high blood pressure and headache types is necessary. Such research works could help us know if people with Migraines or CDH are at risk of high blood pressure. Adequate management of blood pressure and related disease could decrease the mortality rates in patients with each one. On this account, we intended to evaluate the HTN-Migraine as well as HTN-CDH correlations in the adult population of cohort study in Rafsanjan.

## Methods

### Study Design and Patient Selection

The Rafsanjan Cohort study (RCS) is a part of the prospective epidemiological research studies in Iran (PERSIAN). The population consisted of 10,000 residents (aged from 35 to 70) of Rafsanjan, a region in the southeast of Iran. 9990 residents were selected out of this population as the eligible to participate in the study. They were interviewed by validated questionnaires. The study protocol was also designed according to the Persian cohort study and approved by the Ethics Committee of Rafsanjan University of Medical Sciences.

### Data Collection

All participants completed validated questionnaires containing information on demography, medical history, smoking, opium use, and alcohol consumption, Body mass index (BMI) (kg/m<sup>2</sup>), family medical history (Diabetes, HTN, cardiovascular disease, stroke, neurological disease, Migraine, and chronic headache). Moreover, tests were used to measure cholesterol levels, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, and glucose.

Physical activity (PA) derived from standard PA questionnaire totally calculated as metabolic equivalent of task (MET) for 24 hours dependent of metabolic equivalent of activities and were also assessed.

High blood pressure is defined as 140/90 mm Hg or higher. As our research was a retrospective study, we had all the data about the participants before entering the study. They had been treated using regular or irregular antihypertensive drugs. The patients' blood pressure was first measured by Richter brand monitor and suitable size of blood pressure cuff and recorded

twice-once in each arm-with a 10-minute interval. The mean blood pressure of the right arm was used in the analysis.

Chronicity and control of blood pressure:

We also examined duration and control of HTN in participants. Duration of HTN had been already defined as the time interval between self-reported diagnosis of HTN and the date of enrollment. Further, the duration was categorized into  $\geq 6$  years and  $< 6$  years because 6 years is the median HTN duration in the participants. Controlled HTN also means blood pressure  $< 140/90$  mm Hg.

Accordingly, we classified the subjects into the four below groups:

- 1-Short duration ( $< 6$  years) controlled HTN.
- 2-Short duration ( $< 6$  years) uncontrolled HTN.
- 3-long duration ( $\geq 6$  years) controlled HTN.
- 4-Long duration ( $\geq 6$  years) uncontrolled HTN.

In cohort questionnaire, the status of Migraine and CDH was investigated through two questions:

1- Have you ever had recurrent headaches in your life for at least four consecutive hours?

2- Have you ever had chronic and recurrent headaches for at least half a month and for three consecutive months? Have you seen a doctor because of headache? Have you been treated?

### Statistical analysis

In this study, results were presented using mean, standard deviation (SD), and frequency for both quantitative and qualitative variables. The chi-square test as well as t-test was used to compare categorical and continuous variables between Migraine and non-Migraine groups. Logistic regression models were also used to investigate the relationships between HTN and the prevalence of Migraine and CDH. Based on scientific evidence on Migraine predisposition and the relevant epidemiological literature, confounders were sequentially entered the models according to their hypothesized strengths of association with HTN and Migraine and CDH. To reach this goal, the models were first run separately to obtain variables associated with Migraine and CDH. The variables, whose p-value  $< 0.2$  were considered in multivariate analysis. The first adjusted model included basic socio-demographic characteristics (age, sex, education years, and Occupational status), which were considered to be the most strongly related variables. The second model was adjusted for variables confounding lifestyle (cigarette smoking, alcohol drinking, and opium consumption), physical activity level, and the socio-demographic characteristics to additionally confound HTN-Migraine and CDH associations. The third adjusted model included all variables in the second model plus other variables, such as chronic headache family, hypercholesterolemia, body mass index, diabetes mellitus, triglycerides, LDL, and HDL cholesterol. As these variables were potential confounders on the casual pathways linking HTN-Migraine and CDH, these three models were created. In all the models, variables of age, education, hypercholesterolemia, body

mass index (BMI), triglycerides, LDL, and HDL cholesterol were continuously entered. In addition, the data were analyzed based on duration and control of hypertension in the hypertensive patients.

## Results

In this study, 9990 participants were included in the baseline phase of the RCS. From this population, 4655 (46.60%) were males and 5335 (53.40%) were females. Overall, the biological samples of 9941 participants were collected on which laboratory measurements were carried out. The rates of Migraine and CDH in the RCS participants were 29.07 (19.17 %of men and 37.70% of women) and 7.46 %( 4.18% of men and 10.32% of women), respectively.

(Table 1) shows the socio-demographic characteristics, lifestyle, personal habits, anthropometric measures, clinical risk factors, and blood laboratory assessment of the CDH and Migraine groups. There are differences between some socio-demographic characteristics, life style, habits, as well as measured clinical and laboratory indices of Migraine vs. non-Migraine and CDH vs. non-CDH groups (Table 1).

Moreover, HTN was found in 24.27% of Migraine and 31.98% of CDH patients. Also, about half of the hypertensive patients in Migraine and CDH groups had controlled and uncontrolled HTN.

(Table 2) shows the HTN-Migraine as well as HTN- CDH associations using crude and three adjusted models. Various HTN groups are shown in terms of their associations with duration and control of Migraine and CDH. It demonstrates that HTN is associated with Migraine and CDH in crude model as well as all the adjusted models. Short controlled HTN was also found to be associated with Migraine in crude model and in the second as well as the third adjusted. In contrast, Short uncontrolled HTN was not connected with Migraine in crude model; however, it was found to be linked with Migraine in all the three adjusted models. On the other hand, long controlled and uncontrolled models were not associated with Migraine. Considering CDH, it was associated with all HTN categories in crude and all the adjusted models.

In the crude regression model, the odds of Migraine (odds ratio (OR): 1.15, 95%CI 1.04 to 1.28) and CDH (OR: 1.69, 95%CI 1.44 to 1.99) were higher among patients with HTN compared to those without HTN. HTN-Migraine as well as HTN-CDH correlations continued until the confounders were adjusted in the second model. Furthermore, the corresponding adjusted ORs calculated for HTN vs. non HTN were 1.22 (95% CI 1.10 to 1.40) and 1.50 (95% CI 1.24 to 1.81), respectively for Migraine and CDH (Table2).

The third adjusted model included all the variables considered in the second adjusted model plus diabetes mellitus, triglycerides, cholesterol, LDL, and HDL, which could act as potential confounders in the HTN-Migraine as well as HTN-CDH associations. However, after considering new variables in the third adjusted model, the obtained results showed no more considerable changes the association of Migraine (OR: 1.26,

95%CI 1.12 to 1.43) and CDH (OR: 1.52, 95%CI 1.25 to 1.85) with HTN.

When the results were divided by categories of HTN based on duration and control in the hypertensive patients, higher ORs were observed in the following categories; short control HTN (SCH), and Short uncontrolled HTN (SUH) with Migraine; however, in CDH patients, higher ODs was found in all HTN duration and control categories.

## Discussion

In this cross-sectional study, we found a positive relation between Migraine and HTN in participants, especially in controlled and uncontrolled HTN of short duration groups. On the other hand, compared with Migraine, CDH had more positive relation with HTN and all of its categories. The prevalence of HTN, Migraine, and CDH was 22.5, 29.07, and 7.45%, respectively. In our cohort study, there were also general questions about Migraine and CDH without mentioning to their types. Therefore, observed Migraine prevalence higher than what we expected might have been due to the fact that our definition involved probable Migraine headaches as well. Other studies have reported the prevalence rates of Migraine and CDH to be 10-20% and almost 3%, respectively.

Another reason for higher frequency of the headaches, especially Migraine in our study may be due to more social and economic tensions and psychological stress in our society as global burden of disease (GBD)2016 emphasized that primary headache disorders are an important health priority.

Frequent Migraine attacks were revealed by women and the most Migraine's outbreak was observed among unemployed followed by participants with high BMI. Furthermore, 38.48% of Migraineurs reported a family history of Migraine. According to a population based-study in Spanish, the prevalence of Migraine in females was twice than that of males .

In Iran, the prevalence of Migraine was reviewed in 16 studies from 1998 to 2014 by Sadeghi et al., who reported the highest prevalence of Migraine (18.11%). The difference between our study and that study conducted in could be accounted for by our extended Migraine definition, which involved probable Migraine cases ( at least two attacks)in our cohort. Farhadi et al. also reviewed 30 studies and found far lower prevalence (about 14 %) than ours obtained from Rafsanjan as a part of kerman province. In Farhadi's et al. study, the overall distribution of Migraine in some provinces of Iran was presented as follows; 23% in Tehran province , 26% in Hrmozgan, 35% in Lorestan and East Azarbayegan. They did not examine completely the central part of Iran (as our study area) from which 11% prevalence has been reported. As none of the above-mentioned works was done in a cohort study, their results could not be compared with ours.

In addition to female predominance in Migraine, our results, like studies, showed a female-male ratio of about 3:1 in CDH and Migraine with a mild higher proportion of CDH.

Despite the uncertainty about the correlation between Migraine and HTN, there was a unifying view suggesting that

Migraine is positively correlated with diastolic blood pressure, while being negatively correlated with systolic blood pressure and pulse pressure. In another study, it was argued that poor control of blood pressure may exacerbate the frequency and severity of Migraine and other types of headaches.

In these studies, blood pressure and its correlation with Migraine was considered. We also found different results on the HTN-Migraine association. For instance, we found changing of HTN with headache in many cases and these results may point to these changes in HTN during headaches but the causal relationship was not approved in these situations. Some studies did not show any relationship between headache and HTN.

Furthermore, in our study, the prevalence of HTN in CDH patients was 31.95%, which is far higher than other studies such as Huang's et al. study in which HTN was 27.96% prevalent in CDH patients. Also, the prevalence of HTN among the cohort population (22.5%) was also less than its frequency in CDH group (31.98%), while it had a prevalence rate of 24.58% in Migraine group. These findings are consistent with other studies. Additionally, in consistence with 42 other studies reviewed systematically by Mirzaei et al. to obtain the pooled prevalence of HTN, we observed a HTN prevalence of 22% in RCS population.

An epidemiological studies carried out in Nord-Trøndelag Health Survey also revealed a strong negative relation between HTN and Migraine, while the Northern Manhattan study described a strong correlation between HTN and Migraine in controlled and uncontrolled HTN of long duration groups as well as in short duration uncontrolled, a weaker correlation. The prevalence of Migraine in a study performed in the Northern Manhattan was 20.40% which is less than what we found in the present work. Unlike the current research, the Northern Manhattan study found a strong HTN-Migraine correlation in controlled and uncontrolled HTN of short duration groups of cases.

Race could be an effective factor, which has led to these differences. For example, Hispanics have shown stronger long duration HTN correlation with Migraine than Caucasian. Environmental factors, life styles, and occupational factors have also proved to be able to influence hypertension and Migraine.

Moreover, in HTN categories, prolonged use of some antihypertensive drugs, such as angiotensin converting enzyme inhibitors and angiotensin receptor blockers may have been the reason for reducing Migraine in long duration HTN cases.

In line with our findings, an Italian cohort study presented that young females had a higher chance to catch Migraine. This Italian study also verified that Migraine is associated with HTN and tension-type headaches. However, they reported a strong association between tension-type headaches and myocardial ischemia. Furthermore, some studies have described an association between chronic kidney disease (CKD) and Migraine so that older patients with Migraine showed higher incidence of CKD. Furthermore, using non-steroid anti-inflammatory drugs (NSAIDs) and prophylaxis drugs in Migraineurs have shown a high

risk of HTN. In addition, our findings about HTN categories matched with CDH cases but not with Migraine cases in Gardner's et al. study.

The findings of the present research work might have been influenced by different kinds of bias, such as sample selection, imprecise response about previous headache or diagnosis of Migraine, and wrong recall of subject's Migraine information.

## Conclusions

Our study showed high prevalence of HTN in CDH and Migraine cases. Also, unemployed as well as high-BMI patients, who were not cigar, opium, or alcohol users, demonstrated higher risk of Migraine or CDH. All HTN categories showed higher prevalence of CDH in terms of duration and control than Migraine, which only displayed strong correlation with controlled HTN which has related more with controlled HTN categories.

Finally, further clarification of the Migraine-HTN relationship is necessary through performing prolonged cohort studies on younger patients divided in two groups of HTN and non-HTN to compare the prevalence of Migraine and CDH between them.

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