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RESEARCH ARTICLE

COMPARISON OF SERUM ADIPONECTIN LEVEL BETWEEN EARLY ONSET AND LATE ONSET MIGRAINEURS AND ITS COMPARISON WITH CONTROLS

Dr. Monika Porwal (BAGUL), *Dr. Koustubh R. Bagul and Dr. J.S. Kathpal

Choithram Hospital and Research Centre, Indore (M.P.) India

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ABSTRACT

Background: Migraine is one of the most common neurological disorders in general population worldwide. There is no imaging or other tests for diagnosing migraine, so clinicians mainly rely on patients' own self-reported symptoms therefore we have undertaken this study. This research offers important insights into potential mechanisms behind migraine and hypothesizes adiponectin as a potential biomarker for migraine, which can become first laboratory investigation that can aid in diagnosis of migraine. To our knowledge; this is the first survey that aimed at evaluating the symptomatology of migraine and adiponectin levels in patients over 45 years of age.

Aims and Objectives: 1) To compare serum Adiponectin levels in migraine patients and healthy controls. 2) To correlate serum Adiponectin levels in migraine patients with other clinical parameters including Migraine Impact and Allodynia. 3) To compare clinical characteristics of migraine attacks occurring in elderly (45 years and above) and in younger migraineurs (20 to 44 years).

Material and Methods: A cross sectional observational study, Patients with Migraine diagnosed according to the International Classification of Headache Disorders, 3rd edition and controls without headache constitute study population. Patient's between ages 20 to 44 years were considered in Early - onset migraine group and those 45 years and above were considered in Late – onset migraine group. All these patients were subjected to detailed history, Clinical examination (BP, BMI etc.) & Sociodemographic profile was noted. Lipid profile was done. Migraine Disability Score (MIDAS) & Allodynia Symptom Checklist (ASC) 12 scales applied. ELISA was done for serum adiponectin level determination.

Results and Conclusions: Serum adiponectin levels are raised in migraine, higher in late onset migraineurs compared to early onset patients; in chronic migraineurs compared to episodic migraineurs and in migraine without aura compared to migraine with aura patients. But precise pathophysiological role of ADP in migraine remains to be elucidated. There was increased prevalence of migraine in those with high BMI and those who fall in the category of overweight and obese. Also total serum cholesterol levels were raised in migraine patients. There was significant positive correlation between migraine related disability and allodynia symptoms with serum adiponectin levels.

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INTRODUCTION

Migraine is a common disabling primary headache disorder. Epidemiological studies have documented its high prevalence and high socio-economic and personal impacts. In the Global Burden of Disease Survey 2010, it was ranked as the third most prevalent disorder and seventh-highest specific cause of disability affecting about 11% of adult populations' worldwide. Approximately1/3rdindividuals with migraine experience aura symptoms, usually consisting of transient visual, and also sensory, aphasic, or motor disturbances.

Corresponding author:* **Dr. Koustubh R. Bagul,
Choithram Hospital and Research Centre, Indore (M.P.) India.

Migraine may occur at all ages, but is most common in 3rd–5th decades of life. The prevalence of migraine is higher between ages 20 to 55 years, peaking at about age 40 and declining thereafter. It has been suggested that both prevalence and characteristics of migraine change with age. Migraine may attenuate over time (reduced frequency, severity, and/or duration). In middle-aged and elderly adults, vegetative symptoms (nausea, vomiting) are less prominent, and less intense pain, mostly localized in the neck, is frequently reported. Typical aura may also be experienced more frequently without headache. In literature, very few papers focus on migraine, and especially migraine with aura, in patients over 50 years of age. Also pathogenesis of migraine is very complex and has not been thoughtfully elucidated,

general consensus exists to date that this condition should be considered a primary neurovascular disorder with an important tinflammatory component. Previous evidence has implicated inflammation in migraine predisposition. Recently, obesity has also been associated with higher risk of migraine, worse migraine prognosis, more frequent and severe crises. The adipose tissue secretes several inflammatory cytokines such as tumoral necrosis factor (TNF), interleukin (IL)-6, and adipokines including Adiponectin (ADP) and Leptin, which are related with obesity and have been studied in the migraine pathophysiology.ADP has anti-inflammatory properties and its plasmatic levels are reduced in proinflammatory conditions such as obesity, insulin resistance, and metabolic syndrome; while, its levels were shown to be raised in inflammatory autoimmune diseases such as rheumatoid arthritis and inflammatory bowel disease. Altered levels of ADP have also been reported in neuropsychiatric disorders including depression and bipolar disorder.

Need for this research

Serum Adiponectin levels seem to be increased in migraine patients compared with controls. Also, it has been suggested that migraine attacks may enhance ADP levels. The pathophysiological meaning of ADP in migraine is not understood. Moreover, association of ADP levels with other migraine factors such as migraine impact and allodynia is still unknown. The goal of this study was to describe specifically the clinical characteristics of migraine with aura in patients over the age of 45 and to compare serum adiponectin level and other clinical parameters between early onset and late onset migraineurs and also its comparison with controls.

Aims and objectives

- To compare serum Adiponectin levels in migraine patients and healthy controls.
- To correlate serum Adiponectin levels in migraine patients with other clinical parameters including Migraine Impact and Allodynia.
- To compare the clinical characteristics of migraine attacks occurring in the elderly (45 years and above) and in younger migraineurs (20 to 44 years).

MATERIALS AND METHODS

Study population

Patients with Migraine diagnosed according to the International Classification of Headache Disorders, 3rd edition (ICHD-III Criteria, beta version) and controls without headache constitute study population. Patient's between ages 20 to 44 years were considered in Early - onset migraine group and those 45 years and above were considered in Late – onset migraine group.

Study duration: January 2016 to January 2017 [1 year]
Study design: Cross Sectional Observational Study.
Sampling method: Simple Random Sampling

Inclusion criteria

- All out patients diagnosed with Migraine according to ICHD-III Criteria, beta version.
- Patients in the age group of 20 to 60 years.
- Patients who give written informed consent for the study were included in the present study.

Exclusion criteria

- Patients with neurological impairment due to stroke, trauma, multiple sclerosis, or other neurological disorders.
- Patients with history of Hypothyroidism, Intracranial Space Occupying Lesions, Inflammatory, Infectious, Allergic, Autoimmune, Hepatic, Cardiovascular, Renal, Neurodegenerative, Tumor diseases and immunosuppressant drugs.
- Patients who are pregnant or early menopause.
- Patients who have not given consent for the study.

METHODOLOGY

All these patients were subjected to Detailed history and thorough Clinical examination including

- Sociodemographic Profile and Case Record Sheet
- International Classification of Headache Disorders, 3rd edition
- Migraine Disability Score (MIDAS)
- Allodynia Symptom Checklist (ASC)
- ELISA: For adiponectin level determination.

Description of the tools

Sociodemographic Profile and Case Record Sheet

It is used to record Sociodemographic data (Name, Age, MaritalStatus, Occupation, Address etc.) of patients. Case record sheet include general examination, systemic examination, mental status examination and neurological examination including headache characteristics (time of disease, frequency of attacks in the last month) as well as body mass index (BMI) were recorded. B.P. &Lipid profile was also assessed.

International Classification of Headache Disorders

3rd edition (ICHD-III Criteria, beta version) for diagnosis of Migraine.

Migraine disability score (MIDAS)

A test used to determine how severely migraines affect a patient's life. Patients are asked questions about frequency and duration of their headaches, as well as how often these headaches limited their ability to participate in activities at work, at school, or at home. Test was evaluated by professional journal Neurology in 2001; it was found to be both reliable and valid. It measures impact of migraine on daily functioning over past 3 months. MIDAS score is derived as sum of 5 questions: missed days due to headache at work, in household work, and in non-work activities, and days at work and in household work where productivity was reduced by half or more. MIDAS grade is derived from MIDAS score - Grade I = 0-5 points; Grade II = 6-10 points; Grade III = 11-20 points; Grade IV = 21, and more points. 2 additional questions inquire about no. of headache days (MIDAS-A) and average headache intensity (MIDAS-B) over past 3 months. No. of headache days per month was calculated as MIDAS-A divided by 3.

12-item Allodynia symptom checklist (ASC)–12

proposed by Richard B. Lipton, is a modified Jakubowski and colleagues allodynia questionnaire, collects information on frequency of various allodynia symptoms in association with headache attacks. Response options were never (0), rarely (0), < 50% of the time (1), ≥50% of the time (2), and none (0). Based on the psychometrics, this scale distinguishes Cutaneous Allodynia (CA): No CA (scores 0–2), Mild CA (scores 3–5), Moderate CA (scores 6–8), and Severe CA (scores ≥9). It consists of 12 questions and permits identification of Cutaneous Allodynia (CA) and its classification in terms of degree of severity (0.72-0.80), a fact that demonstrates the similarity of construct of the questions and no construct redundancy. Reproducibility was also acceptable for clinical practice since it was considered to be moderate to excellent. The maintenance of the self-reported administration and changes made in questionnaire format without influence on its reproducibility ensured the operational equivalence.

ELISA

For adiponectin level determination. 8 ML of whole blood collected from all participants. Serum obtained after centrifugation will be kept at -80 °C until analysis. ELISA performed as per procedures provided by the manufacturer. The assay conditions were controlled, standardized and pre-optimized to ensure repeatability and reproducibility. All samples were assayed in duplicate, and analyses were blinded. Normal levels of adiponectin are as follows: Males = 1.9 – 10.2 mcg/ml, Females = 4.5 - 13.7 mcg/ml.

Data collection and statistical analysis

All patients of present study were subjected to detailed history, thorough clinical examination, routine and special investigations. The cases were explained about the nature of the study and informed consent was taken. Each case was evaluated and discussed in details with senior neurologists.

The data was entered in pre-tested proforma meeting the objective of study & observations were tabulated. SPSS 17.0 used for analysis of Continuous data variables &Microsoft word - Excel used to generate graphs, tables etc. Data obtained were expressed as Mean ± SD for continuous variables. Student t-test for unpaired data used for comparison of mean values. Group comparisons performed by use of Analysis of variance (ANOVA) to find statistical significance of study parameters between Study & Control Groups. $p< 0.05$was considered statistically significant. Verification of normal distribution of data performed using Kolmogorov–Smirnov test. Mann–Whitney and Kruskal–Wallis tests were used for median comparisons of continuous data. Demographic characteristics compared using chi-square analyses. The correlation analyses between ADP levels and other continuous variables performed with Spearman test. Binary logistic regression analysis will be performed in the presence of migraine as the dependent variable.

RESULTS

The present study was carried out on 61 patients with Migraine diagnosed according to ICHD-III Criteria, beta version, out of which 49 patients (80.3%) were in early onset group (20 to 44 years) and 12 patients (19.6%) were in late onset group (> 45 years) and its comparison with 50 controls without headache. age range = 20 - 60 years, with mean age of patients in study (migraine) group = 40.23 ± 7.83 years and Male-Female (M: F) ratio = 1: 1.259. Mean serum Adiponectin level = 10.97 ± 6.63 mcg/dl, Mean BMI = 28.45 ± 4.30 kg/m^2 and Serum total cholesterol = 181.9 ± 45.3 (mg/dl) was statistically higher compared to control group. Among migraine patients, in early onset migraineurs, mean adiponectin level, mean MIDAS score, mean ASC12 scores were10.75 ± 6.48 mcg/dl, 13.10 ± 6.22 and 6.27 ± 2.68 respectively while in late onset migraineurs it was 11.89 ± 7.45 mcg/dl, 12.17 ± 3.71 and 6.00 ± 2.1 respectively and differences of these parameters was statistically higher in late onset group.

Table No. 1. Comparison Of Mean Serum Adp Level B/W Control & Case GROUP (N=111)

Group	Number	Mean ± SD	't' Value	P Value
Control	50	7.41 ± 4.38	-3.26, df=109	0.001*
Case	61	10.97 ± 6.63		

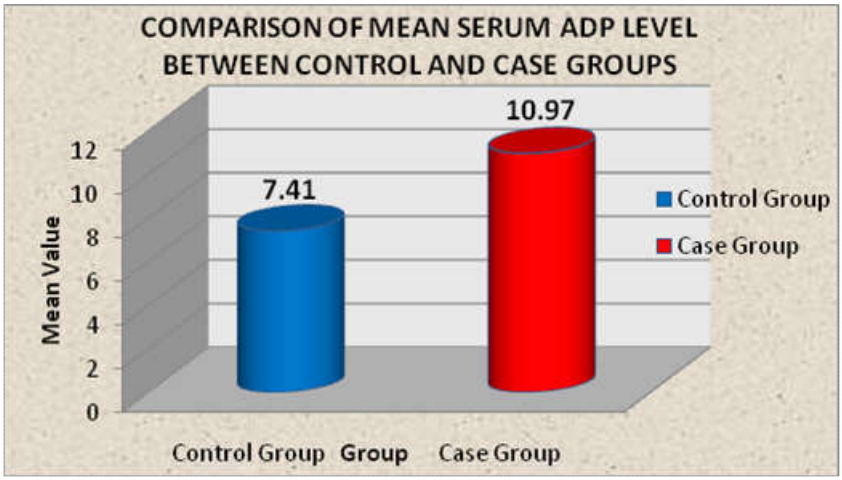

Fig 1. Bar diagram showing comparison of mean serum ADP level between control and case groups.

Table 2. Comparison of mean sadl value between early and late onset migraine patients (n=61)

Group	Number	Mean ± SD	't' Value	P Value
Early onset	49	10.75 ± 6.48	-0.53, df=59	0.598, NS
Late onset	12	11.89 ± 7.45		

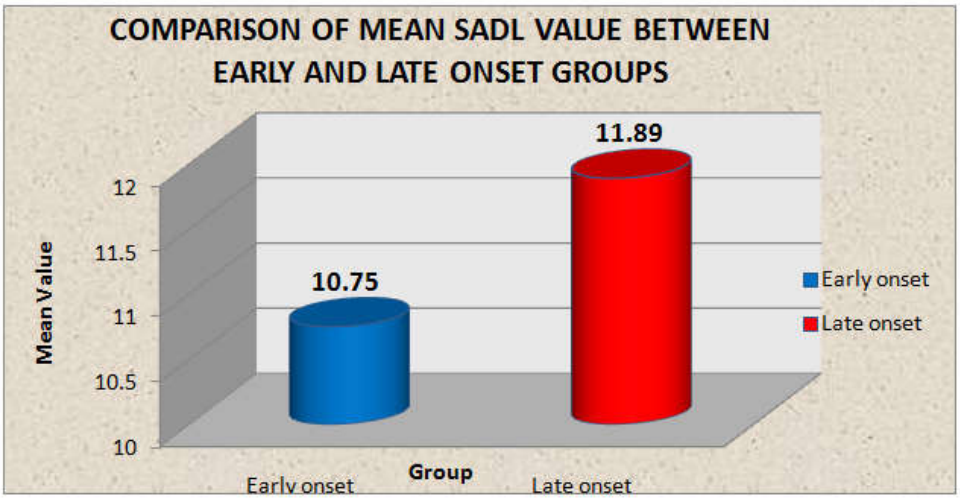

Fig 2. Bar diagram showing comparison of mean SADL value between early onset and late onset groups

Table No. 3. Association of Midas Severity With Early And Late Onset Migraine Patients (N=61)

Group	MIDAS Severity			Total
	Mild	Moderate	Severe	
Early onset	24	15	10	49
Late onset	4	8	0	12
Total	28	23	10	61

$\chi 2$=6.286, df=2, P value = 0.043, Significant.

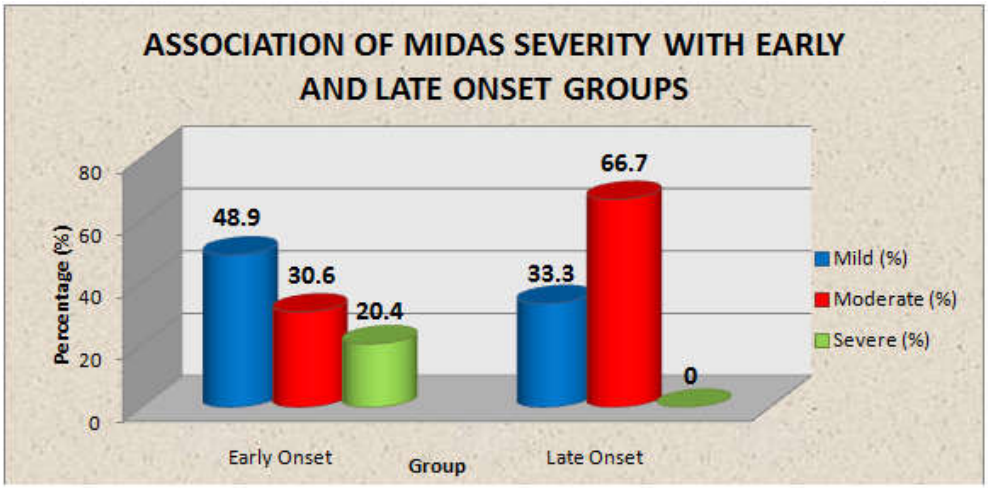

Fig 3: Bar diagram showing the association of MIDAS severity with early and late onset

Table no. 4: association of asc12 severity with early and late onset migraine patients (n=61)

Group	ASC12 Severity			Total
	Mild	Moderate	Severe	
Early onset	24	15	10	49
Late onset	4	8	0	12
Total	28	23	10	61

$\chi 2$=6.286, df=2, P value = 0.043, Significant

Table 5. Comparison of Various Study Parameters In Study (Migraine) And Control Groups

Study Parameters	STUDY (MIGRAINE GROUP) n =61		CONTROLGROUP n = 50		t test	p value
	Mean	± SD	Mean	± SD		
Age (years)	40.23	7.83	39.48	7.77	-0.50, df=109	0.616, NS
BMI (kg/m^2)	28.45	2.76	26.39	4.3	-2.92, df=109	0.004*
Serum Adiponectin Level	10.97	6.63	7.41	4.38	-3.26, df=109	0.001*
CHL (mg/dl)	181.9	45.3	161.6	37.6	-2.54, df=109	0.013*
LDL (mg/dl)	107.5	32.0	103.7	32.7	-0.62, df=109	0.535, NS
HDL (mg/dl)	33.1	12.8	34.4	11.8	0.55, df=109	0.587, NS
VLDL (mg/dl)	31.5	16.1	29.8	16.0	-0.56, df=109	0.579, NS
TGL (mg/dl)	119.7	± 41.2	107.6	± 38.6	-1.58, df=109	0.118, NS

Table 6. Comparison of early and late onset migraine patients in case group patients

Study Parameters	EARLY ONSET MIGRAINEURS n = 49		LATE ONSET MIGRAINEURS n = 12		t test	p value
	Mean	± SD	Mean	± SD		
Age (years)	40.23	7.83	39.48	7.77	-0.50, df=109	0.616, NS
BMI (kg/m^2)	28.78	4.84	26.36	4.21	-0.30, df=59	0.766, NS
Serum Adiponectin Level	10.75	6.48	11.89	7.45	-0.53, df=59	0.598, NS
CHL (mg/dl)	181.5	44.9	183.8	48.9	-0.16, df=59	0.873, NS
LDL (mg/dl)	108.3	28.7	104.6	44.5	0.36, df=59	0.724, NS
HDL (mg/dl)	33.9	12.3	30.0	14.8	0.94, df=59	0.350, NS
VLDL (mg/dl)	30.9	14.9	34.0	20.7	-0.59, df=59	0.556, NS
TGL (mg/dl)	119.6	42.8	120.1	35.4	-0.04, df=59	0.970, NS
Mean MIDAS Score	13.10	6.22	12.17	3.71	0.50, df=59	0.620, NS
Mean ASC12 Score	6.27	2.68	6.00	2.17	0.32, df=59	0.752, NS
Mean Frequency of Attacks	7.71	5.07	7.17	3.35	0.35, df=59	0.724, NS

Table 7. Correlation between the various parameters (N=61)

Pair	'r' value	P value	Interpretation
MIDAS Score -SADL value	0.597	0.000*	Strong, positive, statistically significant correlation
ASC12 score – SADL value	0.627	0.000*	Strong, positive, statistically significant correlation
ASC12 score – MIDAS score	0.863	0.000*	Strong, positive, statistically significant correlation

Pearson coefficient of correlation test applied. P value < 0.05 was taken as statistically significant

Chronic migraineurs had statistically higher adiponectin levels compared to episodic migraineurs. (CM = 15.27 ± 6.72 mcg/dl vs. EM = 7.08 ± 3.36 mcg/dl). Patients of migraine without aura had high adiponectin levels compared to patients of migraine with aura (12.72 ± 6.92 mcg/dl vs. 7.11 ± 3.79 mcg/dl).

DISCUSSION

The present study was carried out on 61 patients with Migraine, out of which 49 patients (80.3%) were in early onset group (between 20 to 44 years), 12 patients (19.6%) were in late onset group (45 years and above) and serum adiponectin level and other headache characteristics, BMI, Lipid profile were compared with 50 controls without headache. 5 manuscripts included evaluations of interictal blood levels of ADP in those with migraine as compared to controls.Crude total ADP levels were significantly increased in migraineurs as compared to controls in 3 of these 5 manuscriptsand were not significantly different in rest 2.Peterlin *et al*. in 2008 conducted a small cross sectional study of that evaluated T-ADP and ADP multimers in non-diabetic, normotensive reproductive-aged (<50) women with episodic migraine (EM n=13), 12 women with chronic daily headache with either chronic or transformed migraine (CM/TM) and 12 female controls.

Excluding those with lipid and thyroid disorders and migraineurs were matched to non-headache controls by age and BMI. Crude levels of T-ADP in those with CM/TM, EM and controls, respectively, were 10.1 (64), 8.6 (63.5), 7.5 (62.4) and adjusting for WHR, these levels varied significantly among 3 headache groups (P=0.024). Peterlin *et al*. in 2013 did Interventional study on 20 women with episodic migraine (11 responders and 9 non-responders to sumatriptan / naproxen) and found significant reduction in adiponectin in patients who responded to the therapy. This study was followed by 2 manuscripts by Bernecker *et al* in 2011 evaluating non-adipokine blood markers in non-obese individuals but which included crude ADP evaluations. First study included overweight or normal weighted women and men (controls: 28 men, 46 women; migraine: 8 men, 42 women); second included an expanded cohort of women (48 controls; 48 migraine patients). Crude ADP levels were not different in women and men with EM vs. controlsand remained insignificant insubsequent manuscript. Duarte *et al* to evaluated interictal ADP in migraineurs (n=133) predominantly reproductive aged women and men. T-ADP was increased in those with migraine (EM and CM combined; n=68) as compared to non-headache controls (n=65). More recently, Dearborn *et al* reported a general population case-cohort study from the Atherosclerosis Risk in Communities study evaluating T-ADP and HMW-ADP in older (>45 years)

non diabetic migraineurs (EM and CM combined; probable/ definitive migraine: n=131, definite migraine: n=72 as compared to non-migraine controls (i.e., including those who had non-migraine headaches, n=850). In this study, crude T-ADP was increased in migraineurs (EM and CM) as compared to controls. However, after adjustments, notably including for BMI and plasma glucose levels, the relative odds of migraine increased with increasing T-ADP and HMW-ADP in men but not in women. Tietjen *et al*. in 2010 conducted a cross sectional study among 125 women with migraine and 50 females controls. They found that concentration of total adiponectin not significantly different between migraineurs and controls. Again in 2012 Tietjen *et al*. performed cross sectional study of 100 women with migraine and 41 female controls and found that concentration of total adiponectin not significantly higher in subjects with adverse childhood experiences of migraine.

Age and gender

Age range - 20 to 60 years, Mean age – overall = 40.23 ± 7.83, in early onset group = 37.92 ± 6.48 and in late onset group = 49.67 ± 5.68 years. Male-Female (M: F) ratio in study group was 1: 1.259 while in control group it was 1.08. Also in early onset and late onset migraine patients, (M: F) ratio was 1: 1.22 and 1:1.4 respectively with P >0.05, showing comparable distribution of gender in both groups.

Body mass index [BMI]

Mean BMI in study group was 28.45 ± 4.30 kg/m2 and in control group was 28.45 ±4.30 kg/m2. This difference was statistically significant and higher compared to controlgroup (P<0.05) suggesting a high prevalence of migraine in those with high BMI and those who fall in the category of overweight and obese.

Dyslipidemia: Mean value of serum total cholesterol was 181.9 ± 45.3 (mg/dl) in study group and in control group it was 161.6 ± 37.6 (mg/dl) which showed statistically significant association of study group (migraine patients) with increased serum Cholesterol levels (P<0.05), while there was no statistically significant association of study group with serum HDL, LDL, VLDL and Triglyceride levels (P>0.05). Also, there was no significant difference found when lipid profile was compared between early and late onset migraineurs.

ICHD-3 Classification of migraine

In study group, 29 out of 61 patients hadchronic migraine (47.54%) and 32 (52.45%) had episodic migraine. Also,migraine with aura was seen in 19 (31.14%) out of 61 migraine patients andrest 42 (68.85%) migraine patients had no aura symptoms.

Frequency of headache attacks

In study group, mean frequency of migraine attacks in early onset migraineurs was 7.71 ± 5.07 days per month and in late onset migraineurs was 7.17 ± 3.35 days per month and this difference was statistically non-significant (P>0.05).

Migraine disability assessment scores (MIDAS): In the study group, mean MIDAS score in early onset migraineurs was 13.10 ± 6.22 and in late onset migraineurs it was12.17 ± 3.71 and this difference was statistically significant (P<0.05) suggesting higher migraine related disability in early onset migraineurs.

Allodynia symptom checklist (ASC12) Score

In the study group, mean ASC12 score in early onset migraineurs was 6.27 ± 2.68 and in late onset migraineurs it was 6.00 ± 2.17 and this difference was statistically non-significant (P>0.05).

Serum adiponectin level

- Mean serum ADP level in migraine group was 10.97 ± 6.63 mcg/dl and in controls was 7.41 ± 4.38 mcg/dl and this finding was statistically significant (P<0.05) suggesting high adiponectin levels in migraine patients compared to controls.
- In study group, mean serum ADP level in late onset migraine patients was 11.89 ± 7.45 mcg/dl and in early onset migraineurs was 10.75 ± 6.48 mcg/dl and this was statistically significant (P<0.05) suggesting high adiponectin levels in late onset migraineurs compared to early onset migraineurs.
- In addition, mean serum ADP level in chronic migraine patients was 15.27 ± 6.72 mcg/dl and in episodic migraine patients was 7.08 ± 3.36 mcg/dl. This difference was found to be statistically significant (P<0.05), showing that chronic migraineurs had high adiponectin levels compared to episodic migraineurs.
- Also mean serum ADP level in patients of migraine without aura was 12.72 ± 6.92 mcg/dl while in patients of migraine with aura it was 7.11 ± 3.79 mcg/dl. This difference was also found to be statistically significant (P<0.05), showing that patients ofmigraine without aura had high adiponectin levels compared to patients of migraine with aura.

Correlation between various study parameters

There was Strong positive statistically significant correlation between following parameters

- MIDAS score & Serum Adiponectin level (R=0.597; P=0.000)
- ASC12 score & Serum Adiponectin level (R=0.627; P=0.000)
- MIDAS score & ASC12 score (R=0.863; P=0.000)
- This suggests that among migraine patients, higher the migraine related disability and allodynia symptoms, higher are the adiponectin levels, irrespective of the age of onset of migraine.

Conclusions

The present study concludes and supports that serum adiponectin levels are raised in migraine, higher in late onset migraineurs compared to early onset patients; in chronic migraineurs compared to episodic migraineurs and in migraine without aura compared to migraine with aura patients. But the precise pathophysiological role of ADP in migraine remains to be elucidated. There was increased prevalence of migraine in those with high BMI and those who fall in the category of overweight and obese. Also total serum cholesterol levels were raised in migraine patients.

Also, there was significant positive correlation between migraine related disability and allodynia symptoms with serum adiponectin levels. The results of our study indicate that late-life onset migraine symptoms may occur for the first time after 45 and is not rare in clinical practice. This has clinical implications, since accurate diagnosis is crucial for disease management. In the elderly headache patient, diagnosis of migraine with aura should be based on the clinical features of the attacks and on the exclusion of TIA and seizure disorders.

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