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INCIDENCE OF METABOLIC SYNDROME IN ADULT PERSONS WITH EPILEPSY TREATED WITH LEVETIRACETAM

Narang D*	Junior Resident, Department of Pharmacology, PGIMS, Rohtak, Haryana. *Corresponding Author
Verma S	Professor, Department of Pharmacology, PGIMS, Rohtak, Haryana
Dabla S	Senior Professor and Head, Department of Neurology, PGIMS, Rohtak, Haryana
Singh R	Junior Resident, Department of Pharmacology, PGIMS, Rohtak, Haryana

ABSTRACT **CONTEXT:** Epilepsy, a prevalent neurological disorder affecting over 50 million people worldwide, presents challenges beyond seizures, impacting cognition, psychology, and overall well-being. Antiepileptic drugs (AEDs) are essential for seizure management but can lead to metabolic changes, potentially resulting in metabolic syndrome (MetS) **AIM:** To determine the incidence of MetS in newly diagnosed adult persons with epilepsy (PWE) started on levetiracetam (LEV) monotherapy **SUBJECTS AND METHODS:** This prospective, single-center, open labeled clinical study was conducted in a tertiary care center from January 2023 to December 2023. 70 newly diagnosed PWE, aged 18-40 years received LEV monotherapy (20-30 mg/kg/day). Patients were assessed at baseline, 3 months, and 6 months for metabolic parameters, including waist circumference, blood pressure, lipid profile, fasting blood glucose, and BMI. MetS was defined by the presence of at least three of these parameters above defined limits. **STATISTICAL ANALYSIS:** Data were analysed using SPSS Version 20.0. Descriptive statistics were used to express data, and statistical tests such as the Chi-square test and ANOVA were applied to analyze differences in MetS incidence and metabolic parameters over time. Multiple logistic regression was performed to identify predictors of MetS development, with a p-value ≤ 0.05 considered statistically significant. **RESULTS:** The incidence of MetS increased significantly from 7.14% at 3 months to 17.14% at 6 months ($p<0.001$). Males showed a higher incidence of MetS (19.23%) compared to females (15.9%) at 6 months. Central obesity, blood pressure, decreased HDL, increased triglycerides, and fasting blood glucose levels all showed significant increases over the study period. BMI was a significant predictor for MetS at 3 months ($p=0.009$), but no significant predictors were identified at 6 months. **CONCLUSION:** LEV monotherapy is associated with an increased risk of MetS and metabolic abnormalities in adult PWE over time.

KEYWORDS : Epilepsy, Levetiracetam, Metabolic Syndrome, Antiepileptic Drugs, Metabolic Abnormalities

Epilepsy, a prevalent neurological condition, presents challenges beyond seizures, affecting neurobiology, cognition, psychology, emotional and social well-being.[1] Globally, it impacts over 50 million people, with a significant burden in low- and middle-income countries like India.[2] Antiepileptic drugs (AEDs) are crucial for seizure management, aiming to maximize quality of life (QoL) while minimizing adverse effects. Long-term use of AEDs, essential for seizure management have their own difficulties including adverse events. These drugs can lead to metabolic changes, which over the time can lead to metabolic syndrome (MetS). MetS is a cluster of metabolic risk factors, such as glucose intolerance, dyslipidaemia, central obesity, and hypertension.[3]

Levetiracetam (LEV) is a commonly prescribed broad-spectrum second-generation AED.[4] MetS occurring due to first-generation AEDs therapy in persons with epilepsy (PWE) has been well established.[5-8] Although, studies in past have indirectly examined LEV's metabolic effects, focusing on lipid profiles, insulin resistance, and other parameters.[9-12] However, evidence on LEV's specific association with MetS is limited and conflicting. Therefore, this prospective interventional study was done to determine the incidence of metabolic syndrome in newly diagnosed adult persons with epilepsy started on LEV monotherapy.

SUBJECTS AND METHODS

The study was an interventional, prospective, single-center, and open-labeled clinical study conducted in a tertiary care center, between January 2023 to December 2023. The trial was registered prospectively with CTRI (CTRI/2023/01/048946) and was undertaken after the approval of protocol from the Biomedical Research Ethics Committee (BREC/22/Th/Pharma-03) and all the principles of Good Clinical Practice were followed.

INCLUSION CRITERIA

Patients of age between 18 to 40 years of either gender, with newly diagnosed epilepsy and willing to provide written informed consent were enrolled in the study.

EXCLUSION CRITERIA

Patients with a Body Mass Index (BMI) ≥ 30 kg/m^2, co-existing Type 2 Diabetes mellitus and/or Hypertension, dyslipidaemia on lipid-lowering agents, or taking medications known to interfere with body weight status like antidepressants, corticosteroids, and anti-thyroid drugs, as well as pregnant patients with epilepsy, individuals with a history of alcohol/substance abuse, those with personality or psychiatric disorders, and patients with severe physical disability, thyroid, liver, or renal dysfunction were excluded from the study.

INTERVENTION

Eligible patients received Tab Levetiracetam 20-30 mg/kg/day given twice a day. The drug therapy was initiated at a lower dose and was gradually increased to the lowest effective maintenance dose. Patients enrolled were assessed at baseline, 3 months, and 6 months for various metabolic parameters – waist circumference (central obesity), blood pressure (BP), lipid profile [High-density lipoprotein (HDL) and triglycerides (TGs)], and fasting blood glucose (FBG), and BMI (Body Mass Index). The diagnosis of MetS was defined as the presence of at least three of the above-mentioned parameters with their values above defined limits as per the Joint scientific statement of the International Diabetes Federation (IDF) Task Force on Epidemiology and Prevention.[13]

OUTCOME MEASURES

1. Incidence of metabolic syndrome over time
2. Changes in metabolic parameters over time
3. Change in body mass index over time

SAMPLE SIZE CALCULATION

A sample size of 70 participants in a single group was determined considering 10% proportion of MetS due to LEV monotherapy, with 95% level of confidence, 5% accepted deviation, adjustment for finite population due to limited number of cases in outpatient department fulfilling the inclusion criteria and 10% attrition rate.

STATISTICAL ANALYSIS

Data collected was entered into Microsoft Excel and analysed using SPSS Version 20.0. Descriptive statistics such as numbers, percentages, and Mean ± Standard Deviation (SD) were used to express the data. Categorical data including demographic profile, clinical characteristics and incidence of Metabolic Syndrome (MetS) were expressed as percentages. Statistical analyses included the use of the Chi-square (x^2) test to analyze differences in the incidence of MetS and its parameters over a single time interval, and Analysis of Variance (ANOVA) to analyze differences over multiple time intervals.

Multiple logistic regression analyses were performed to identify factors associated with MetS development in patients treated with LEV, with reported Odds Ratios (ORs) and 95% confidence intervals (CIs). A p-value ≤ 0.05 was considered statistically significant.

RESULTS

A total of 520 patients diagnosed with epilepsy by the neurologist were screened, out of which 175 newly diagnosed PWE were selected. 89 patients fulfilled the exclusion criteria and 16 were not willing to give written informed consent, so the rest of the 70 newly diagnosed patients of epilepsy on LEV monotherapy were enrolled in the study.

The mean age of the study population was 25.01 ± 5.09 years, with 82.85% of study participants being less than 30 years old at the time of enrolment in the study. There were 62.85% females and 37.14% males; however, this difference was not statistically significant (p=0.155). 61.42% of patients were married and 38.57% were unmarried, which was statistically significant (p=0.002). All the patients were literate. 55.71% of patients were from urban regions and 44.28% from rural

In the study population, 64 cases (91.42%) were of generalized onset epilepsy, 5 cases (7.14%) of focal onset epilepsy, and only 1 case (1.42%) of unknown onset epilepsy; however, this was not statistically significant (p=0.093).

At baseline, 69 (98.57%) patients were newly started on a 1000mg dose of LEV, and 1 (1.42%) patient was newly started on a 1500mg dose of LEV. At 6 months, 31 (44.28%) patients were maintained on a 1000mg dose of LEV, 38 (54.28%) patients were maintained on a 1500mg dose of LEV, and 1 (1.42%) patient was maintained on a 2000mg dose. The incidence of MetS in newly diagnosed PWE on LEV monotherapy in this study is shown in Table 1.

Table 1: Incidence of Metabolic Syndrome (MetS) in the Study Population

MetS (N = 70)	Baseline	3 months	6 months	p-value
Present (LEV dose Mean ± SD)	0 (0%) (1042 ± 138.2)	5 (7.14%) [#] (1375 ± 226.13) [$]	12 (17.14%) * (1500 ± 0) μ	<0.001
Absent (LEV dose Mean ± SD)	70 (100%) (1000 ± 0)	65 (92.85%) (1181 ± 259.86)	58 (82.85%) (1241.4 ± 268.87)	

[#,$] - p<0.001 at 3 months when compared with baseline
*- p=0.02 at 6 months when compared with baseline
μ - p<0.001 at 6 months when compared with baseline

MetS in the study population was 7.14% at the end of 3 months and 17.14% at the end of 6 months (p<0.001). Incidence of MetS was higher in males (19.23%) than in females (15.9%) at the end of 6 months (p=0.722). The mean dose of LEV monotherapy was higher in patients with MetS at 3 and 6 months when compared with the mean dose of LEV monotherapy in patients without MetS (p<0.001).

As shown in Table 2, the incidence of central obesity increased in the study population from baseline to 6 months. 23% of males and 40% of females had preexisting central obesity at the time of enrolment and it was increased to 34.6% in males and 61.4% in females at 6 months, however statistically these changes were not significant.

The overall incidence of high blood pressure increased in the study population over 6 months. At baseline, all the patients had normal blood pressure and it was increased to 15.4% in males and 11.4% in females, with both being statistically significant. There was an increase in the incidence of decreased HDL in both males (from 7.7% to 30.8%) and females (from 27.3% to 45.5%) at 6 months, however it was statistically significant only in males.

While there was a significant increase in the overall incidence of increased TGs over 6 months, gender-specific differences were observed, with a statistically significant increase in females only (from 13.6% to 31.8%).

The overall incidence of increased FBG increased in the study population over 6 months. At baseline, only 2.3% of females had increased FBG, which was increased to 13.6% in females and 15.4% in males at 6 months.

As shown in Table 3, the incidence of overweight participants remained stable throughout the study. However, obesity increased from 0% at baseline to 7.1% at 6 months in participants on LEV monotherapy. These changes were not statistically significant.

There was a gradual decrease in the percentage of males with normal BMI from 70% at baseline to 62.9% at 6 months. The percentage of overweight males remains relatively stable, but the percentage of

Table 2: Metabolic Parameters in Study Population

	Baseline	3 Months	6 Months	p-value
1. Central Obesity (High Waist Circumference = Males ≥ 90 cm, Females ≥ 80 cm)	24 (34.3%)	34 (48.6%)	36 (51.4%)	0.117
2. Blood Pressure (Increased BP = SBP ≥130 mmHg or DBP ≥ 85 mmHg)	0 (0%)	3 (4.3%)	9 (12.9%) [#]	0.004
3. High-Density Lipoprotein (Decreased HDL [mg/dL] = Males ≤ 40, females ≤ 50)	14 (20%)	23 (32.9%)	28 (40%) [#]	0.034
4. Triglycerides (Increased TGs [mg/dL] ≥ 150)	11 (15.7%)	14 (20%)	23 (32.9%) [#]	0.042
5.Fasting Blood Glucose (Increased FBG [mg/dL] ≥ 100)	1 (1.4%)	6 (8.6%)	10 (14.3%) [#]	0.020

[#] - p <0.05 at 6 months when compared with baseline

Table 3: Incidence of Increased BMI in the Study Population obese males increased from 0% at baseline to 7.1% at 6 months.

	Body Mass Index (BMI)		
	Normal (BMI ≤ 24.9)	Overweight (BMI = 25 - 29.9)	Obese (BMI ≥ 30)
Baseline	49 (70%)	21 (30%)	0 (0%)
3 Months	47 (67.2%)	22 (31.4%)	01 (1.4%)
6 Months	44 (62.9%)	21 (30%)	05 (7.1%)

The percentage of females with normal BMI decreases from 75% at baseline to 63.6% at 6 months. The percentage of overweight females remains relatively stable, but the percentage of obese females increases from 0% at baseline to 9.1% at 6 months.

A multivariate logistic regression model was employed to identify significant predictors for MetS at the 3 and 6 months. At 3 months, BMI emerged as a statistically significant predictor for MetS (p = 0.009). The Pseudo R square value for the model was 75%. However, was not found to be statistically significant at 3 months (p=1.000).

At 6 months, none of the variables included in the analysis were found to be statistically significant predictors for MetS. Despite this, the model still had a Pseudo R square value of 48.5%, suggesting that the variables considered explained 48.5% of the variability associated with MetS incidence at this time point (p=0.471)

DISCUSSION

Epilepsy is a prevalent chronic neurological disorder characterized by recurrent seizures, affecting millions of individuals worldwide.[1] The cornerstone of epilepsy management involves long-term AED therapy, which, while effective for seizure control, can lead to significant adverse effects and metabolic changes. These metabolic alterations, including weight gain, changes in lipid profiles, increased blood pressure, glucose tolerance, and ultimately MetS, develop insidiously and may present substantial health risks over time.[3] In our study, we focused on assessing the incidence of metabolic syndrome (MetS) and other metabolic parameters; to address the gap in the literature regarding the metabolic effects of LEV monotherapy, as existing studies have provided inconsistent results.

The study population comprised adults aged 18-40 years, with a mean age of 25.01 ± 5.09 years. The age distribution aligns with findings

from Fiest KM et al.[14], who reported a higher prevalence of epilepsy in the 20-29 age group globally. Similarly, Banerjee TK et al.[15] found the highest prevalence of epilepsy in the second and third decades of life in India, contrasting with Raina SK et al.[16], who observed a higher prevalence in the fourth decade.

Interestingly, our study had a higher percentage of female participants (62.85%) compared to males (37.14%). This contrasts with findings from Newale S et al.[17], who reported a higher prevalence of epilepsy in males (61.3%) in a large Indian cohort. However, Söylemez E et al.[7] found a higher prevalence of females (55.64%) in their study on MetS in epilepsy patients on AED monotherapy. The gender distribution in our study may reflect increased awareness and acceptance of treatment among females, who also demonstrated a greater willingness to participate.

Regarding marital status, a greater percentage of our participants were married (61.42%), which contrasts with the findings of Riasi H et al.[18], who reported lower marriage rates among epilepsy patients, with a higher divorce rate, especially among women. This discrepancy could be due to the literate status of our participants, leading to decreased stigma and better social support. Additionally, societal changes and improved healthcare services may contribute to earlier diagnosis and better acceptance of epilepsy treatment, as indicated by the lack of divorce cases in our study.

All participants in our study were literate, aligning with findings from Newale S et al.[17], who reported high literacy rates among epilepsy patients in India. High literacy rates in our young study population could be due to better acceptance of participation in the study among literate individuals. This contrasts with findings from Panagariya A et al.[19], who reported a significant proportion of illiterate epilepsy patients in a different Indian region.The majority of our participants were from urban areas (55.71%), differing from Gourie-Devi M et al.[20], who found a higher prevalence of epilepsy in rural Bangalore. However, Banerjee TK et al.[15] reported higher epilepsy prevalence in urban Kolkata, which aligns more closely with our findings.

Most participants had generalized onset epilepsy in this study, which is consistent with Newale S et al.[17], who reported similar percentages of generalized onset seizures. Goel D et al., however, found a higher prevalence of focal onset seizures in a north Indian district.

LEV was prescribed at an initial dose of 20-30 mg/kg/day, with most participants starting at 1000 mg/day. Doses were adjusted based on response. This dosing regimen aligns with recommendations from the SANAD II[22] study and findings from Jacob Jesurun R.S et al.[23], who reported similar titration practices based on seizure control. Findings in this study indicate a notable rise in MetS incidence from 7.14% at the third month to 17.14% at the sixth month of follow-up among newly diagnosed PWE on LEV monotherapy. Similarly, Ndayambaje FX et al.[8] found a 28.3% prevalence of MetS among LEV monotherapy patients. Söylemez et al.[7] also reported a 30.5% incidence of MetS in PWE on LEV. Contrasting results were observed in a study by S.S. Nair et al.[6], which reported a 29.5% incidence of MetS in a cohort of patients on various AEDs, but none in those on LEV monotherapy.

Our study revealed a higher incidence of MetS in males (19.23%) compared to females (15.9%), potentially due to biological differences and lifestyle factors. This aligns with study by Ndayambaje FX et al.[8], who also found a higher prevalence of MetS in males. In contrast, Vooturi S et al.[24] reported a higher MetS prevalence in females.

In this study, central obesity increased over six months, underscoring the need for monitoring central obesity in PWE on LEV. S.S. Nair et al.[6] and Ndayambaje FX et al.[8] reported similar findings in their studies. The incidence of increased blood pressure rose over six months, with a higher rise in males (15.4%) than females (11.4%). This highlights the importance of monitoring blood pressure in PWE on LEV. Bauer J et al.[25] reported a low incidence of hypertension (4.2%) in their long-term study of LEV, contrasting with S.S. Nair et al.[6], who found a 57.37% prevalence of increased blood pressure.

Decreased HDL incidence increased over six months, significantly higher than in Ndayambaje FX et al.'s[8] and Sharma J et al.'s[26] studies. Males showed a decrease in incidence at six months, while females showed an increased incidence. These findings emphasize the need for lipid profile monitoring in PWE on LEV.

Similar to trends were observed in Ndayambaje FX et al.'s[8] and S.S. Nair et al.'s[6] studies, incidence of increased triglycerides were observed in this study, necessitating regular lipid profile checks for PWE on LEV.

The incidence of increased fasting blood glucose at six months, with a higher prevalence in males than females, highlighting the need for regular glucose monitoring. Contrasting results were reported by Dehury S et al.[10], who found no significant changes in FBG levels associated with LEV therapy.

Obesity increased to 7.1% in study population at six months. These shifts were not statistically significant but indicate a trend toward weight gain in PWE on LEV. Similar results were observed by Pickrell WO et al.[27], while Gidal BE et al.[28] found no significant weight changes in LEV-treated patients.

Multivariate logistic regression analysis identified BMI as a significant predictor for MetS at three months, though no significant predictors were found at six months. This suggests a complex interplay of factors influencing MetS in PWE on LEV.

CONCLUSION

The study demonstrated a significant increase in the incidence of metabolic syndrome, suggesting that LEV monotherapy is associated with an increased risk of Metabolic syndrome and metabolic abnormalities in adult Persons With Epilepsy over time.

LIMITATIONS

Study's limitations include its single-center design, short follow-up period and lack of a control group. These constraints suggest that further research with larger, more diverse populations and longer follow-up is needed to fully understand the long-term metabolic effects of LEV monotherapy.

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Nil

CONFLICTS OF INTEREST

There are no conflicts of interest.

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