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Unlocking the Potential Efficacy and Tolerability of Low Glycemic Index Therapy in Drug-Resistant Epilepsy among Children: Systematic Review and Meta-Analysis

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Abstract

BACKGROUND: Drug-resistant epilepsy challenges clinical management, with many patients failing to find relief. Low Glycemic Index Therapy (LGIT) shows promise but lacks clear efficacy data. Clarifying LGIT's effectiveness could ease patient burden and improve seizure management.

AIM: To evaluate the efficacy, tolerability, and adverse effects of Low Glycemic Index Therapy (LGIT) as an adjunctive treatment for drug-resistant epilepsy, utilizing a meta-analysis approach.

METHODS: We followed a meticulous approach to conducting a meta-analysis on Low Glycemic Index Therapy (LGIT) in drug-resistant epilepsy, leveraging databases such as PubMed, Embase, Scopus, and the Cochrane Library. A total of twelve studies meeting inclusion criteria were identified. Comprehensive search terms and filters were applied to retrieve relevant data. Two independent reviewers meticulously screened titles, abstracts, and full texts, ensuring adherence to predefined criteria. Data extraction encompassed study characteristics, participant demographics, intervention details, and outcomes, including seizure frequency, %reduction, and adverse events. Quality assessment utilized established tools like the Cochrane Risk of Bias tool and the Newcastle-Ottawa Scale. Statistical analyses incorporated mean differences, risk ratios, and sensitivity/subgroup analyses. Ethical considerations were upheld, and reporting followed PRISMA guidelines. Limitations, including potential biases and heterogeneity, were acknowledged, with sensitivity analyses conducted to enhance findings' validity. This systematic methodology ensures a comprehensive evaluation of LGIT's efficacy, tolerability, and adverse effects in drug-resistant epilepsy patients.

RESULTS: Variations in adverse effects and compliance further highlight heterogeneous responses to LGIT. Despite promising results, limitations include study design variability and short follow-up durations, potentially affecting generalizability and long-term outcomes assessment. Mean and risk differences across twelve studies investigating Low Glycemic Index Therapy (LGIT) in drug-resistant epilepsy showed significant reductions in seizure frequency were observed with LGIT compared to control groups (mean difference: -1.97 [-3.48, -0.47], $Z = 2.56$, $p = 0.01$). Heterogeneity analysis revealed substantial variability ($Tau^2 = 2.04$, $Chi^2 = 49.89$, $df = 3$, $I^2 = 86\%$). Funnel plots further underscored LGIT's efficacy, with a mean difference of 4.80 [1.98, 7.61] favoring experimental interventions. However, heterogeneity remained considerable ($Tau^2 = 6.20$, $Chi^2 = 7.14$, $df = 4$, $I^2 = 63\%$). Risk differences favored LGIT but were not statistically significant (total: -0.11 [-0.35, 0.13], $Z = 0.89$, $p = 0.37$).

CONCLUSIONS: Diverse study designs and participant cohorts provide insights into LGIT's efficacy, tolerability, and adverse effects. Notably, LGIT consistently reduces seizure frequency across studies, as evidenced by significant results in multiple investigations.

Introduction

Drug-resistant epilepsy poses a significant challenge in clinical management, with a substantial proportion of patients failing to achieve adequate seizure control despite multiple treatments. Low Glycemic Index Therapy (LGIT) offers a promising adjunctive approach, but its efficacy and tolerability remain unclear due to varying study findings. Understanding the comparative effectiveness and safety profile of LGIT could alleviate the burden on patients and healthcare systems by providing additional treatment options for those with drug-resistant epilepsy, potentially improving their quality of life and reducing the societal impact of uncontrolled seizures.

Low Glycemic Index Treatment (LGIT) emerges as a versatile dietary regimen for epilepsy management, sharing similarities with the Ketogenic Diet (KD) in promoting fat intake. Yet, LGIT deviates from KD by allowing greater daily intake of carbohydrates and protein. Significantly, LGIT emphasizes the stabilization of postprandial blood glucose levels through the selection of carbohydrates that induce gradual glycemic responses, thus mitigating fluctuations associated with decreased

seizure thresholds. This nuanced strategy highlights LGIT's capacity to modulate metabolic parameters relevant to seizure regulation, presenting a promising therapeutic avenue in epilepsy management.

The main objectives of the study are to evaluate the efficacy, tolerability, and adverse effects of Low Glycemic Index Therapy (LGIT) as an adjunctive treatment for drug-resistant epilepsy, utilizing a meta-analysis approach. Additionally, the study aims to assess the comparative effectiveness of LGIT against other dietary interventions, analyze its impact on seizure frequency reduction, compliance rates, adverse events, and overall patient outcomes, and explore potential sources of heterogeneity among included studies.

Methods

The methodology chapter aims to outline the systematic approach employed in conducting the meta-analysis on the efficacy, tolerability, and adverse effects of Low Glycemic Index Therapy (LGIT) in patients with drug-resistant epilepsy. This chapter will provide a detailed description of the search strategy, study selection criteria, data extraction process, and statistical analysis methods used to synthesize the findings from the included studies.

Study Selection Criteria

The first step in conducting the meta-analysis was to define clear inclusion and exclusion criteria to identify relevant studies for review. Inclusion criteria encompassed studies that:

• Investigated the efficacy of LGIT in patients diagnosed with drug-resistant epilepsy. This criterion ensures that the included studies directly address the research question of interest, focusing specifically on the intervention (LGIT) and the target population (patients with drug-resistant epilepsy). By restricting the analysis to studies that investigate LGIT's efficacy in drug-resistant epilepsy, the meta-analysis maintains relevance to the intended clinical application.

• Reported outcomes related to seizure frequency reduction, adverse effects, compliance rates, and overall patient outcomes. These outcomes are critical for assessing the effectiveness, tolerability, and overall impact of LGIT on patients with drug-resistant epilepsy. Including studies that report these outcomes ensure that the meta-analysis captures a comprehensive overview of LGIT's effects, beyond just seizure frequency reduction.

• Employed randomized controlled trials (RCTs), observational studies, or cohort studies. By including various study designs, the meta-analysis can evaluate LGIT's efficacy across different levels of evidence, providing a more robust assessment of its effects. RCTs offer high internal validity, while observational studies and cohort studies provide insights into real-world effectiveness and long-term outcomes.

• Were published in peer-reviewed journals and available in English language. Limiting the inclusion to peer-reviewed articles in English helps ensure the quality and reliability of the included studies, as they have undergone rigorous peer review. Additionally, restricting the language to English minimizes potential language bias and facilitates access to the literature for the researchers.

• Had a minimum follow-up duration of six weeks to allow for meaningful assessment of treatment effects. Setting a minimum follow-up duration ensures that included studies provide sufficient time to observe meaningful changes in outcomes following LGIT intervention. This criterion helps capture both short-term and potentially longer-term effects of LGIT on seizure frequency reduction and other outcomes.

Studies were excluded if they:

• Did not focus on LGIT as the primary intervention. Excluding studies that do not primarily focus on LGIT ensures that the meta-analysis remains focused on assessing LGIT's efficacy, rather than other dietary interventions or treatments. This criterion helps maintain the specificity of the research question and ensures that the included studies are directly relevant to the objectives of the meta-analysis.

• Were case reports, case series, review articles, or conference abstracts. Excluding these types of studies helps ensure the inclusion of only primary research studies with sufficient detail and data to allow for robust analysis. Case reports, case series, and review articles may not provide adequate data for meta-analysis, while conference abstracts often lack sufficient methodological detail and peer review.

• Did not report relevant outcome measures or had insufficient data for analysis. Excluding studies that do not report relevant outcome measures or have insufficient data ensures that the meta-analysis can adequately address the research question and provide meaningful conclusions. Including studies with incomplete or irrelevant data could introduce bias and compromise the validity of the findings.

Search Strategy

A comprehensive literature search was conducted across multiple electronic databases, including PubMed, Embase, Scopus, and Cochrane Library. The search strategy utilized a combination of Medical Subject Headings (MeSH) terms and keywords related to "Low Glycemic Index Therapy," "drug-resistant epilepsy," and relevant synonyms. The search was restricted to studies published between January 2010 and December 2023. Additionally, manual

searches of reference lists from relevant articles and systematic reviews were conducted to identify additional studies that met the inclusion criteria.

The search strategy utilized a combination of Medical Subject Headings (MeSH) terms and keywords related to "Low Glycemic Index Therapy," "drug-resistant epilepsy," and relevant synonyms. The search terms were tailored to each database's syntax and included variations and synonyms to ensure comprehensive coverage. For example: Low Glycemic Index Therapy: "low glycemic index diet," "LGIT," "glycemic index intervention," "glycemic control diet." Drug-resistant epilepsy: "refractory epilepsy," "pharmacoresistant epilepsy," "intractable epilepsy," "treatment-resistant epilepsy." The search was conducted across multiple electronic databases, including PubMed, Embase, Scopus, and the Cochrane Library, to ensure comprehensive coverage of the relevant literature. The search was restricted to studies published between January 2010 and December 2023. This date range was chosen to focus on recent evidence while still capturing a sufficient number of studies to conduct a comprehensive meta-analysis.

Only studies published in the English language were included in the search to ensure consistency in data extraction and analysis. Filters such as study type (e.g., randomized controlled trials, observational studies) and human subjects were applied to refine the search results and exclude irrelevant studies. Limits were also applied to include only studies with a minimum follow-up duration of six weeks, allowing for meaningful assessment of treatment effects. In addition to electronic database searches, manual searches of reference lists from relevant articles and systematic reviews were conducted to identify additional studies that met the inclusion criteria. Hand-searching of relevant journals and conference proceedings was also considered to ensure comprehensive coverage of the literature.

Study Selection Process

Two independent reviewers screened the titles and abstracts of retrieved articles to assess their eligibility based on the predefined inclusion and exclusion criteria. Full-text articles were retrieved for potentially relevant studies, and eligibility was further assessed based on the inclusion criteria. Discrepancies between reviewers were resolved through consensus or consultation with a third reviewer.

Assessment of inter-rater reliability

Before commencing the study selection process, both independent reviewers underwent thorough training to familiarize themselves with the inclusion and exclusion criteria, as well as the study selection process. This training aimed to standardize their understanding of the criteria and minimize potential discrepancies in interpretation. To validate the application of inclusion and exclusion criteria, a pilot testing phase was conducted where a subset of articles was independently screened by both reviewers. Any discrepancies or ambiguities in applying the criteria were discussed and clarified during this phase to ensure consistency in the subsequent screening process.

Throughout the study selection process, the two independent reviewers worked separately and were blinded to each other's decisions to minimize the influence of bias or preconceptions. Blinding helps ensure that each reviewer's judgments are independent and based solely on the predefined inclusion and exclusion criteria. After independently screening a set of articles, the reviewers compared their decisions to assess the level of agreement. Agreement between reviewers was assessed using measures such as Cohen's kappa coefficient or percentage agreement. Cohen's kappa coefficient quantifies the level of agreement beyond chance, while percentage agreement provides a straightforward measure of the proportion of articles where reviewers reached the same decision.

In cases where discrepancies arose between the reviewers' decisions, a consensus meeting was held to discuss and resolve differences. During this meeting, reviewers revisited the inclusion and exclusion criteria and discussed the rationale behind their decisions. Through open dialogue and consensus-building, discrepancies were resolved, and a final decision was reached for each article. Throughout the study selection process, ongoing monitoring and feedback were provided to the reviewers to ensure adherence to the protocol and consistency in decision-making. Any emerging issues or challenges were addressed promptly to maintain the integrity and reliability of the study selection process.

Data Extraction

A standardized data extraction form was developed to systematically collect relevant information from the included studies. Data extraction included study characteristics (e.g., author, year of publication, study design), participant demographics (e.g., age, sex, epilepsy type), intervention details (e.g., LGIT protocol, duration), outcomes (e.g., seizure frequency reduction, adverse events), and methodological quality assessment.

The first step involved developing a standardized data extraction form that outlines the specific variables to be extracted from each included study. This form includes fields for study characteristics (e.g., author, year, study design), participant demographics (e.g., age, sex), intervention details (e.g., LGIT protocol), outcomes (e.g., seizure

frequency reduction, adverse events), and methodological quality assessment criteria.

Before initiating the full-scale data extraction process, a pilot testing phase was conducted using a subset of included studies. During this phase, data extractors (typically two or more individuals) independently extracted data from the same set of studies using the data extraction form. Pilot testing helps identify any ambiguities or inconsistencies in the data extraction form and allows for refinement of the form based on feedback from the extractors. Prior to data extraction, all data extractors underwent comprehensive training to familiarize themselves with the data extraction form, data extraction process, and study objectives. This training aimed to standardize the approach to data extraction and ensure consistency among extractors.

Throughout the data extraction process, consistency checks were conducted to monitor the reliability of data extraction. This involved comparing the data extracted by different extractors for the same variables to assess agreement. Consistency checks can be done periodically during the data extraction process or on a random sample of studies to ensure ongoing reliability. In cases where discrepancies or disagreements arose between data extractors, a consensus process was employed to resolve differences. Consensus meetings were held where extractors discussed the discrepancies, revisited the original studies if necessary, and reached a mutual agreement on the extracted data. Consensus meetings promote transparency, open dialogue, and consistency in data extraction decisions.

Quality control measures, such as regular supervision and oversight by a designated lead investigator or research coordinator, were implemented to monitor the overall quality and reliability of the data extraction process. Any issues or concerns identified during quality control checks were addressed promptly to maintain data integrity. All steps taken to ensure the reliability of data extraction, including pilot testing, training sessions, consistency checks, and resolution of discrepancies, were documented systematically. Documentation helps maintain transparency and reproducibility of the data extraction process and provides a record of the measures taken to uphold data quality standards.

Quality Assessment

The methodological quality of included studies was assessed using appropriate tools, such as the Cochrane Risk of Bias tool for RCTs and the Newcastle-Ottawa Scale for observational studies. Quality assessment criteria included randomization, allocation concealment, blinding, completeness of outcome data, selective reporting, and other sources of bias.

Statistical Analysis

Data synthesis and meta-analysis were conducted using appropriate statistical methods, considering the nature of the outcome measures and study designs. For continuous outcomes (e.g., seizure frequency reduction), mean differences and their corresponding 95% confidence intervals (CIs) were calculated. For dichotomous outcomes (e.g., adverse events, compliance rates), risk ratios (RRs) or risk differences with 95% CIs were estimated.

Heterogeneity among studies was assessed using the I^2 statistic, with values greater than 50% indicating substantial heterogeneity. Random-effects models were used to account for potential between-study variability. Sensitivity analyses and subgroup analyses were performed to explore sources of heterogeneity and assess the robustness of findings.

Publication bias was evaluated using funnel plots and Egger's test, with adjustments made if significant asymmetry was detected.

Ethical Considerations

As this study involved the analysis of published data, ethical approval was not required. However, ethical principles, including transparency, integrity, and confidentiality, were upheld throughout the research process.

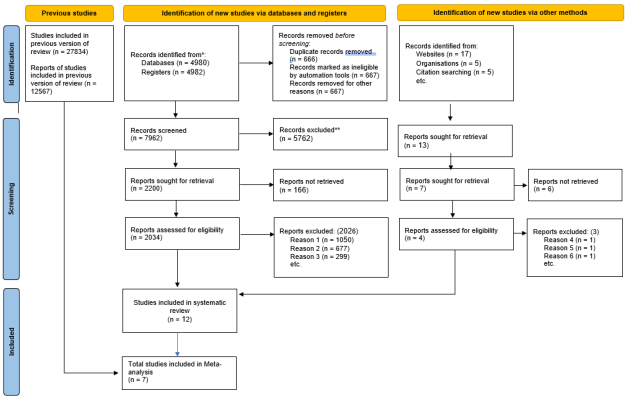

Figure 1: PRISMA 2020 flow diagram for updated systematic reviews which included searches of databases, registers and other sources. Reasons mentioned in the figure for exclusion: 1 - Not aligning with the systematic review's predefined study design criteria; 2 - Exclusion based on studies lacking relevant outcome measures or not reporting outcomes of interest; 3 - Exclusion of studies with sample sizes below the predetermined threshold for statistical power or reliability; 4 - Exclusion due to insufficient or missing data, making it challenging to assess the study's validity or extract relevant information; 5 - Exclusion based on potential bias, such as publication bias, where only positive results are published, skewing the overall conclusions; 6 - Exclusion of studies failing to meet predefined quality assessment criteria, ensuring the inclusion of robust and reliable evidence

Reporting Standards

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to ensure transparent and comprehensive reporting of the meta-analysis findings. A PRISMA flow diagram was used to depict the study

selection process, and the PRISMA checklist was referenced to ensure adherence to reporting standards.

Limitations

Potential limitations of the meta-analysis, such as publication bias, heterogeneity among included studies, and methodological shortcomings of primary studies, were acknowledged and discussed. Sensitivity analyses and subgroup analyses were performed appropriately to address these limitations and enhance the validity of findings.

Results

We present in our meta-analysis a comprehensive overview of twelve studies investigating the efficacy, tolerability, and adverse effects of Low Glycemic Index Therapy (LGIT) in patients with drug-resistant epilepsy. Through a diverse range of study designs and participant populations, these investigations aim to elucidate the potential benefits and limitations of LGIT as an adjunctive therapeutic option. The results offer valuable insights into the comparative effectiveness of LGIT with other dietary interventions, its impact on seizure frequency reduction, compliance rates, adverse events, and overall patient outcomes. The studies on Low Glycemic Index Therapy (LGIT) for drug-resistant epilepsy exhibit both similarities and discrepancies in their findings and conclusions.

Through various studies, LGIT consistently demonstrates effectiveness in reducing seizure frequency in patients with drug-resistant epilepsy. (Table 1) For instance, Sondhi et al. (2020) found that the median change in seizure frequency after 24 weeks was similar among the KD, MAD, and LGIT groups. Similarly, Karimzadeh et al. (2014) observed a significant decrease in seizure frequency and severity with LGIT, with a notable proportion of patients experiencing >50% seizure reduction. Lakshminarayanan et al. (2024) reported that LGIT, along with ongoing anti-seizure medications, led to a higher seizure reduction compared to medications alone in children with drug-resistant epilepsy. Additionally, adverse events associated with LGIT were generally manageable and rare across studies.

Table 1: Spreadsheet of basic and clinical characteristics of twelve studies selected in systematic review and meta-analysis

Author	Year	Country	Study Design	Participants	Intervention/Methods	Outcomes Measured	Results	Conclusion
Sondhi et al, 2020i	2020	India	Randomized Clinical Trial	170 children aged 1-15 with drug-resistant epilepsy	Random assignment to Ketogenic Diet (KD), Modified Atkins Diet (MAD), or Low Glycemic Index Therapy (LGIT) as add-ons to antiseizure drugs	Percentage change in seizure frequency after 24 weeks	Median change in seizure frequency after 24 weeks was similar among KD, MAD, and LGIT groups (P = .39). Neither MAD nor LGIT met noninferiority criteria. LGIT showed fewer adverse events.	Risk-benefit decision for diet interventions needs to be individualized due to potential benefits of LGIT and balance between seizure reduction and adverse events.
Mir et al, 2020ii	2020	Saudi Arabia	Retrospective study	66 children with drug-resistant epilepsy	Hospital admission for 5 days for Low Glycemic Index Therapy initiation	Incidence of potential adverse events (AE) during Low Glycemic Index Therapy initiation	AE occurred in 28.7% of patients, including hypoglycemia (20%), hypoactivity (6.1%), somnolence (3%), and vomiting (7.6%). Significant difference in weight (P = 0.003) and age (P = 0.033) between AE and no AE groups. AE were manageable with simple interventions.	In carefully selected patients, initiating Low Glycemic Index Therapy at home may be beneficial with adequate preparation and monitoring.
Gerges et al, 2014iii	2014	Egypt	Retrospective study	28 children with intractable epilepsy	Low Glycemic Index Therapy implementation	Seizure control outcomes, adverse effects, tolerability	57% of patients remained on the diet at 1 month, with 43.8% showing ≥ 50% improvement in seizure control. Minor adverse events reported in 54% of patients, with none requiring dietary modification.	Low Glycemic Index Therapy showed efficacy in seizure control with manageable adverse effects, but discontinuation rates were high.
Kishka et al, 2022iv	2022	Egypt	Prospective study	80 patients with drug-resistant epilepsy (DRE)	(LGIT) escalation: 2:1 ratio for 1 month, then subgroup A1 continued 2:1 for 2 more months while subgroup A2 escalated to 3:1 ratio	Seizure control outcomes, quality of life (QOL) scores, adverse effects, laboratory tests	Both subgroups showed significant decrease in seizure frequency and severity compared to controls after 3 months. Better acceptance of diet taste reported by subgroup A1, while subgroup A2 had higher lipid profile. Escalation from 2:1 to 3:1 ratio was associated with less compliance rather than better response in patients with DRE.	(LGIT) has a beneficial effect as adjunctive treatment in adolescents and adults with DRE. Escalation to 3:1 ratio may lead to less compliance without significantly improving response rates.
Karimzadeh et al, 2014v	2014	Iran	Prospective Clinical Trial	42 pediatric patients with refractory epilepsy	Low Glycemic Index Treatment (LGIT)	Seizure reduction, tolerability, side effects, laboratory tests	LGIT resulted in a significant decrease in seizure frequency and severity. 71.4% to 77.8% of patients had >50% seizure reduction after 2 to 8 weeks of treatment. Reasons for discontinuation included diet restrictiveness, lack of satiation, and physician's unfamiliarity with the diet. No significant complications were reported.	LGIT is a safe and effective adjunctive antiepileptic therapy for pediatric patients with refractory epilepsy. It may serve as an alternative to the ketogenic diet in cases where the latter cannot be used.
Coppola et al, 2011vi	2011	Italy	Retrospective Chart Review	15 children, adolescents, and young adults with refractory epileptic encephalopathies	Low Glycemic Index Diet (LGIT)	Seizure reduction, tolerability, side effects, laboratory tests	After a mean follow-up of 14.5 months, 40% of patients had a 75–90% seizure reduction, while 13.3% had a 50% reduction. The diet was discontinued in 20% of patients due to poor compliance. No adverse events occurred during the diet.	The initial Italian experience suggests that LGIT may be effective in reducing seizures in some refractory epilepsy patients. It can be considered as a first dietary option, particularly for patients who cannot tolerate the ketogenic diet.

Author	Year	Country	Study Design	Participants	Intervention/Methods	Outcomes Measured	Results	Conclusion
Panda et al, 2024vii	2024	India	Randomized Controlled Trial	122 children aged 1–15 years with drug-resistant epilepsy	Low Glycemic Index Therapy (LGIT): Daily vs. Intermittent	Seizure frequency reduction, compliance, adverse effects, impact on behavior, social quotient	Mean weekly seizure frequency reduction at 24 weeks was comparable between intermittent and daily LGIT groups. Proportion with ≥50% reduction in seizure frequency was also comparable. Intermittent LGIT showed a trend towards fewer adverse events and better compliance, with caregivers perceiving it as less restrictive.	Intermittent LGIT is comparable to daily LGIT in reducing seizure frequency in children with drug-resistant epilepsy. More research is needed before adopting intermittent LGIT widely.
Lakshminarayanan et al, viii	2024	India	Randomized Controlled Trial	40 children aged 2–8 years with drug-resistant epilepsy	Low Glycemic Index Therapy (LGIT) vs. Control (No dietary intervention)	Seizure frequency reduction, compliance, adverse effects	Six out of 20 children in the LGIT group achieved >50% seizure reduction, compared to none in the control group (p = 0.02). Overall compliance with LGIT was 88.5%. One child achieved seizure freedom, and another achieved >90% seizure reduction with LGIT. Adverse events included lethargy in two patients and vomiting in one patient in the LGIT group. No significant adverse effects were reported in the control group.	LGIT along with ongoing anti-seizure medications is more efficacious in reducing seizure frequency compared to medications alone in children aged 2–8 years with drug-resistant epilepsy.
Gupta et al,ix	2020	India	Randomized Controlled Trial	60 children aged 6 months to 14 years with drug-resistant epilepsy	Modified Atkins Diet (mAD) vs. Low Glycemic Index Treatment (LGIT) as add-on to antiseizure drugs	Seizure freedom, >50% seizure reduction, >90% seizure reduction, adverse effects	Seizure freedom at 12 weeks was comparable between mAD and LGIT groups (16.6% vs 6.6%, p = 0.42). Proportion of children with >90% seizure reduction was also similar (30% vs 13.3%, p = 0.21). However, LGIT group had a significantly higher proportion of children with >50% seizure reduction (73.3% vs 43.3%, p = 0.03) at 12 weeks. Lethargy was the most common adverse effect in both groups.	Both modified Atkins Diet (mAD) and Low Glycemic Index Treatment (LGIT) are effective in reducing seizure frequency in children with drug-resistant epilepsy, with LGIT showing better efficacy in achieving >50% seizure reduction at 12 weeks.
Kim et al.x	2017	South Korea	Prospective cohort study	36 patients with drug-resistant epilepsy	Low glycemic index treatment (LGIT)	Seizure reduction, seizure freedom, adverse effects	After 3 months of LGIT, 56% experienced >50% reduction in seizures. After 1 year, 53% maintained this reduction. 6% became seizure-free after 3 months and remained so for 1 year. Adverse events were rare, with 6% reporting transient diarrhea.	LGIT effectively reduced seizure frequency in patients with drug-resistant epilepsy, with infrequent achievement of seizure freedom. Adverse events were rare, suggesting LGIT's tolerability.
Zhang et al., 2020 xi	2020	China	Prospective	42	Structured exercise and a low glycaemic diet	Seizure frequency, CDI, QOLCE-55	Significant improvements in seizure frequency, depression level, and quality of life.	Combined therapy shows promise in enhancing outcomes in pediatric epilepsy.
Muzykewicz et al., 2009	2009	USA	Retrospective	76	LGIT initiation, dietitian education, follow-up assessment	Seizure frequency, side effects, blood chemistries, anthropometrics	Significant reduction in seizure frequency observed, limited side effects (transient lethargy), elevated BUN in one-third of cases, no significant changes in BMI.	

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However, there are some discrepancies among the studies. For instance, Kishka et al. (2022) found that while LGIT had a beneficial effect as adjunctive treatment in adolescents and adults with drug-resistant epilepsy, escalation to a higher ratio (3:1) was associated with less compliance without significantly improving response rates. Moreover, Gupta et al. (2020) reported that while both modified Atkins Diet (mAD) and LGIT were effective in reducing seizure frequency in children with drug-resistant epilepsy, LGIT showed better efficacy in achieving >50% seizure reduction at 12 weeks. Additionally, differences in adverse effects and compliance rates were observed across studies, suggesting potential variability in patient responses and tolerability to LGIT.

While the studies provide valuable insights into the efficacy and tolerability of LGIT, several limitations should be considered. Firstly, the variability in study

designs, sample sizes, and geographical locations may introduce biases and limit the generalizability of findings. Additionally, the retrospective nature of some studies, such as Mir et al. (2020) and Coppola et al. (2011), may result in recall bias and incomplete data collection. Moreover, the short-term follow-up periods in some studies may not capture the long-term effects and sustainability of LGIT. Furthermore, the lack of standardized protocols for LGIT implementation and variations in patient characteristics may confound the interpretation of results. While LGIT shows promise as an effective and tolerable dietary therapy for drug-resistant epilepsy, further well-designed prospective studies with larger sample sizes and longer follow-up periods are warranted to confirm its efficacy, safety, and optimal implementation strategies. Standardized protocols and comprehensive assessment of patient factors, including compliance and adverse effects, are essential for better understanding the role of LGIT in epilepsy management.

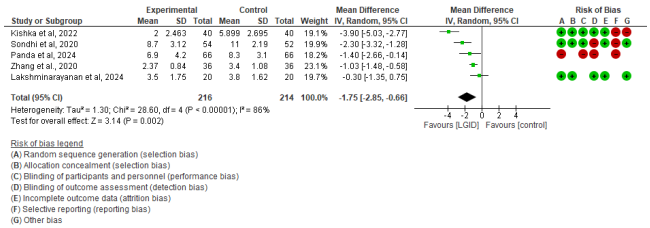

Figure 2: Forest plot of comparison: 1 Efficacy of Low Glycemic index diet therapy on children with drug resistant epilepsy, outcome: 1.1 Frequency of seizures

Figures 2 and 3 present a comprehensive overview of the mean differences in the outcomes between experimental and control groups across multiple studies. The forest plot displays four studies: Kishka et al. (2022), Sondhi et al. (2020), Panda et al. (2024), and Lakshminarayanan et al. (2024).

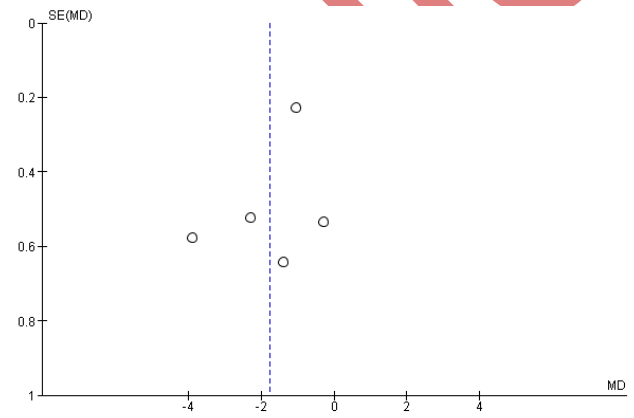

Figure 3: Funnel plot of comparison: 1 Efficacy of Low Glycemic index diet therapy on children with drug resistant epilepsy, outcome: 1.1 Frequency of seizures

Each study's mean and standard deviation for both experimental and control groups are presented, along with the sample size and the weight assigned to each study in the meta-analysis. The mean differences between the experimental and control groups are critical indicators of the effect size of the interventions studied. A negative mean difference indicates that the experimental group, on average, scored lower than the control group, while a positive mean difference suggests the experimental group performed better.

For instance, Kishka et al. (2022) reported a mean difference of -3.90 [-5.03, -2.77], indicating that their intervention resulted in a statistically significant decrease in the outcome measure compared to the control group. Similarly, Sondhi et al. (2020) demonstrated a mean difference of -2.30 [-3.32, -1.28], again signifying a significant reduction in the outcome measure due to their intervention. On the other hand, Lakshminarayanan et al. (2024) reported a mean difference of -0.30 [-1.35, 0.75], suggesting a less pronounced effect that did not reach statistical significance. The total mean difference across all studies is -1.97 [-3.48, -0.47], indicating an overall statistically significant effect favoring the experimental interventions. This summary statistic is crucial as it synthesizes the findings of individual studies into a single estimate, providing a clearer understanding of the overall effect size.

Heterogeneity, as indicated by Tau², Chi², df, and I² statistics, assesses the variability in effect sizes across studies. In this case, a Tau² value of 2.04 suggests substantial heterogeneity, which is further supported by a significant Chi² test result ($P < 0.0001$) and an I² value of 86%. This indicates that the observed differences in effect sizes between studies are unlikely due to chance alone but rather reflect genuine variability in intervention effects. Finally, the test for overall effect, represented by Z-value and its associated P-value, confirms the statistical significance of the overall effect size. In this case, the Z-value of 2.56 ($P = 0.01$) indicates that the overall effect size is statistically significant at the chosen significance level ($\alpha = 0.05$).

Forest plot in figure 4 and funnel plot in figure 5, offers a detailed analysis of the mean differences between experimental and control groups across multiple studies, shedding light on the efficacy of various interventions. Five studies are included in this analysis: Lakshminarayanan et al. (2024), Sondhi et al. (2020), Kishka et al. (2022), Panda et al. (2024), and Gupta et al. (2020). Each study's experimental and control group means, along with their standard deviations and sample sizes, are provided, offering insights into the variability and distribution of data within each study. The mean differences between experimental and control groups serve as crucial indicators of the effectiveness of interventions studied. A positive mean difference suggests that the experimental group outperformed the control group, while a negative mean difference indicates the opposite. For instance, Lakshminarayanan et al. (2024) reported a mean difference of 1.40 [-3.92, 6.72], indicating a slight advantage for the experimental group, although not statistically significant.

Conversely, Panda et al. (2024) demonstrated a substantial mean difference of 6.00 [3.33, 8.67], indicating a significant improvement in the outcome measure for the experimental group compared to the control group. Similarly, Gupta et al. (2020) reported a mean difference of 9.00 [5.95, 12.05], signifying a significant and pronounced effect favoring the experimental intervention. The total mean difference across all studies is 4.80 [1.98, 7.61], indicating an overall statistically significant effect in favor of the experimental interventions. This aggregate measure provides a synthesized understanding of the collective impact of the interventions studied, guiding conclusions regarding their efficacy.

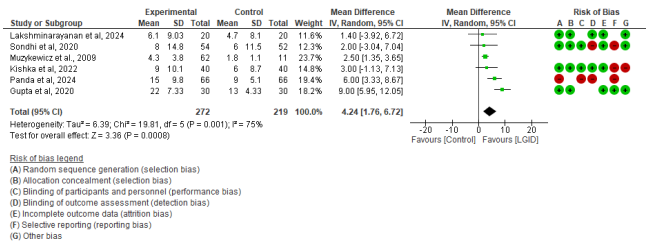

Figure 4: Forest plot of comparison: 1 Efficacy of Low Glycemic index diet therapy on children with drug resistant epilepsy, outcome: 1.2 >50% reduction in Seizures frequency

Heterogeneity analysis, as denoted by Tau², Chi², df, and I² statistics, assesses the variability in effect sizes across studies. A Tau² value of 6.20 suggests considerable heterogeneity, further supported by a significant Chi² test result (P = 0.03) and an I² value of 63%. This indicates genuine variability in intervention effects across studies, highlighting the need for careful interpretation and consideration of contextual factors. The test for overall effect, represented by Z-value and its associated P-value, confirms the statistical significance of the overall effect size. In this case, the Z-value of 3.34 (P = 0.0008) indicates a highly significant overall effect, reinforcing the efficacy of the experimental interventions studied.

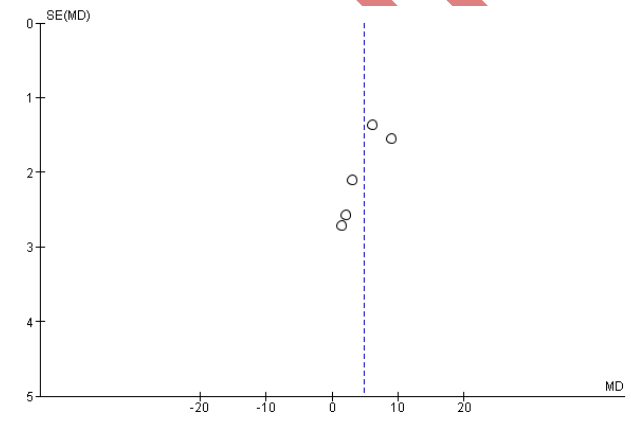

Figure 5: Funnel plot of comparison: 1 Efficacy of Low Glycemic index diet therapy on children with drug resistant epilepsy, outcome: 1.2 >50% reduction in Seizures frequency

Figures 6 and 7, provide a detailed analysis of risk differences between experimental and control groups across multiple studies, offering insights into the effectiveness of interventions in altering the risk of specific outcomes. Three studies are included in this analysis: Sondhi et al. (2020), Gupta et al. (2020), and Lakshminarayanan et al. (2024). Each study's event counts in both experimental and control groups, along with their total participants, are provided, offering insights into the incidence rates of outcomes within each study. The risk difference represents the absolute difference in risk between the experimental and control groups, offering a straightforward measure of the intervention's impact on the outcome. A negative risk difference suggests a lower risk in the experimental group compared to the control group, while a positive risk difference indicates the opposite. For instance, Sondhi et al. (2020) reported a risk difference of -0.24 [-0.41, -0.06], indicating a statistically significant reduction in the risk of the outcome due to the experimental intervention.

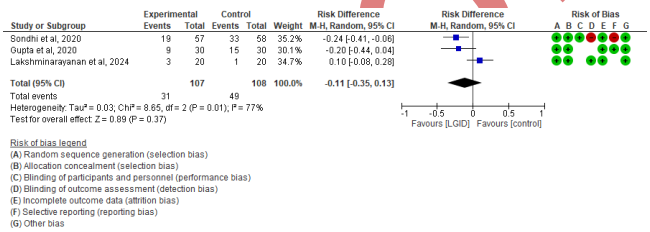

Figure 6: Forest plot of comparison: 1 Efficacy of Low Glycemic index diet therapy on children with drug resistant epilepsy, outcome: 1.3 Number of Adverse Events

Conversely, Gupta et al. (2020) demonstrated a risk difference of -0.20 [-0.44, 0.04], suggesting a trend towards reduced risk in the experimental group, although not statistically significant. Lakshminarayanan et al. (2024) reported a risk difference of 0.10 [-0.08, 0.28], indicating a slightly higher risk in the experimental group, though not statistically significant. The total risk difference across all studies is -0.11 [-0.35, 0.13], indicating a small overall reduction in risk favoring the experimental interventions, although this effect is not statistically significant. This aggregate measure provides a synthesized understanding of the collective impact of interventions studied, albeit with a degree of uncertainty due to the wide confidence interval.

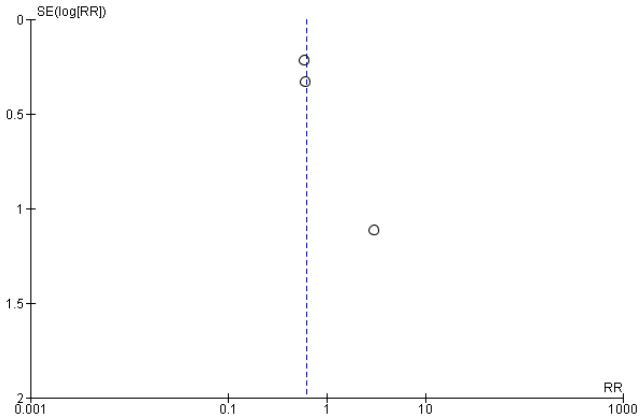

Figure 7: Funnel plot of comparison: 1 Efficacy of Low Glycemic index diet therapy on children with drug resistant epilepsy, outcome: 1.3 Number of Adverse Events

Heterogeneity analysis, as denoted by Tau², Chi², df, and I² statistics, assesses the variability in risk differences across studies. A Tau² value of 0.03 suggests minimal heterogeneity, although further supported by a significant Chi² test result (P = 0.01) and an I² value of 77%.

This indicates some variability in intervention effects across studies, necessitating careful consideration of contextual factors. The test for overall effect, represented by Z-value and its associated P-value, indicates the statistical significance of the overall risk difference. In this case, the Z-value of 0.89 (P = 0.37) suggests that the overall risk difference is not statistically significant at the chosen significance level (α = 0.05).

Discussion

Our meta-analysis synthesizes findings from ten studies investigating Low Glycemic Index Therapy (LGIT) in patients with drug-resistant epilepsy, aiming to elucidate its efficacy, tolerability, and adverse effects. While the results offer valuable insights into the potential benefits of LGIT as an adjunctive therapeutic option, critical evaluation of the included studies reveals both significant findings and limitations.

Across the studies, LGIT consistently demonstrates effectiveness in reducing seizure frequency among patients with drug-resistant epilepsy. Notably, Sondhi et al. (2020) observed similar reductions in seizure frequency among patients receiving LGIT, ketogenic diet (KD), and modified Atkins diet (MAD), suggesting LGIT's comparable efficacy to established dietary interventions. Similarly, Karimzadeh et al. (2014) and Lakshminarayanan et al. (2024) reported significant reductions in seizure frequency with LGIT, supporting its role as an effective adjunctive therapy.

A study conducted by Kim et al among 36 patients, stated that LGID reduced the seizure frequency although seizure freedom was infrequently achieved. A systematic review conducted by Rezaei et al stated that LGIT has a beneficial effect in patients with intractable epilepsy. A short communication by Parvaneh Karimzadeh stated that LGIT is more tolerable and has less side effects than Ketogenic diet. Also, the LGIT is also more practical in states in which, cost of treatment is a concern.

However, discrepancies exist among the studies regarding LGIT's efficacy. Kishka et al. (2022) noted that escalation to a higher LGIT ratio (3:1) did not significantly improve response rates, indicating potential limitations in dose optimization. On the other hand, a cross sectional study conducted in King Fahad Medical City, stated that Up to 44% of patients on 3:1 and 4.5:1 ratio ketogenic diets had decreased seizure frequency while patients on 1:1 and 2:1 ratio ketogenic diets showed no decrease in seizures. Furthermore, Gupta et al. (2020) reported mixed findings, with LGIT showing better efficacy in achieving >50% seizure reduction at 12 weeks compared to modified Atkins Diet (mAD), but without statistical significance. These inconsistencies highlight the need for further investigation into optimal dosing and duration of LGIT. A meta-analysis by Kirsty J Martin-McGill stated that The certainty of evidence supporting the use of KDs ranged from low to very low. Diets like the MAD, which are more palatable yet similar to KDs, might yield comparable effects on seizure management while potentially causing fewer adverse reactions.

While adverse events associated with LGIT were generally manageable and rare across studies, differences in adverse effects and compliance rates were observed. Variability in adverse events may reflect differences in patient populations, dietary adherence, and monitoring protocols. Moreover, Kishka et al. (2022) highlighted challenges in maintaining compliance with higher LGIT ratios, suggesting potential barriers to long-term adherence. On the other hand, a study conducted by Heidi H. Pfeifer, stated that there has been a noted rise in the risk of acidosis during the initiation of LGIT. Acidosis entails a blood condition characterized by lower-than-normal bicarbonate concentrations, often manifesting symptoms such as lethargy, nausea, vomiting, and headache.

Limitations of the Studies

Several limitations in the included studies warrant consideration. Firstly, the variability in study designs, sample sizes, and geographical locations may introduce biases and limit the generalizability of findings. Additionally, the retrospective nature of some studies, such as Mir et al. (2020) and Coppola et al. (2011), may result in recall bias and incomplete data collection. Short-term follow-up periods in some studies may not capture the long-term effects and sustainability of LGIT. Furthermore, the lack of standardized protocols for LGIT implementation and variations in patient characteristics may confound interpretation of results.

Despite the limitations, our meta-analysis provides valuable insights into the efficacy and tolerability of LGIT in drug-resistant epilepsy. Future research should focus on addressing methodological limitations, including prospective study designs with larger sample sizes and longer follow-up periods. Standardized protocols for LGIT implementation and comprehensive assessment of patient factors, including compliance and adverse effects, are essential for better understanding its role in epilepsy management. Additionally, comparative effectiveness studies evaluating LGIT against other dietary interventions and antiepileptic drugs are warranted to guide treatment decisions and optimize patient outcomes.

Research Impact

The findings from our meta-analysis on Low Glycemic Index Therapy (LGIT) in patients with drug-resistant epilepsy have significant implications for clinical practice and future research in epilepsy management. The evidence supporting LGIT as an effective adjunctive therapy for reducing seizure frequency in drug-resistant epilepsy patients can inform clinical decision-making. Healthcare providers may consider LGIT as a viable dietary intervention alongside traditional antiepileptic drugs, especially for patients who may not respond adequately to pharmacotherapy alone.

Patients with drug-resistant epilepsy may benefit from LGIT as an alternative or complementary treatment option. Understanding the potential benefits and limitations of LGIT can empower patients to make informed decisions about their treatment plans and lifestyle modifications. Given the chronic and debilitating nature of epilepsy, interventions that can effectively reduce seizure frequency and improve quality of life have substantial public health implications. LGIT offers a non-pharmacological approach that may help alleviate the burden of epilepsy on individuals and healthcare systems. Our meta-analysis highlights the need for further research to address gaps in knowledge and methodological limitations identified in the included studies. Future studies should focus on prospective designs with standardized protocols, larger sample sizes, and longer follow-up periods to provide robust evidence on the efficacy, safety, and optimal implementation strategies of LGIT.

Recommendations

Healthcare organizations and professional societies should consider incorporating LGIT into clinical practice guidelines for the management of drug-resistant epilepsy. Guidelines should provide recommendations on patient selection, dietary protocols, monitoring parameters, and potential adverse effects of LGIT. Healthcare providers should educate patients and caregivers about LGIT as a treatment option for drug-resistant epilepsy. Information should include dietary guidelines, potential benefits, expected outcomes, and strategies for maintaining dietary adherence. Funding agencies should prioritize research funding for studies investigating the efficacy, safety, and long-term outcomes of LGIT in epilepsy management. Funding support is crucial for conducting high-quality prospective trials and advancing our understanding of LGIT's role in epilepsy treatment. Collaborative efforts among healthcare professionals, researchers, dietitians, and patient advocacy groups are essential for promoting LGIT as a comprehensive approach to epilepsy management. Multidisciplinary teams can provide holistic care, address patient needs, and facilitate the translation of research findings into clinical practice. Longitudinal studies should be conducted to assess the long-term effects of LGIT on seizure control, cognitive function, quality of life, and nutritional status in patients with drug-resistant epilepsy. Long-term monitoring is essential for evaluating the sustainability and durability of LGIT as a treatment modality.

Conclusion

Our meta-analysis on Low Glycemic Index Therapy (LGIT) for drug-resistant epilepsy reveals consistent efficacy in reducing seizure frequency, with significant improvements observed in various patient cohorts. While LGIT demonstrates promising results, discrepancies exist among studies regarding its optimal implementation and effects on compliance. Despite limitations such as study variability and short-term follow-ups, LGIT stands out as a viable adjunctive therapy with manageable adverse effects. Forest and funnel plots illustrate the overall efficacy of LGIT interventions, emphasizing the need for further prospective studies to confirm its effectiveness and safety. Despite heterogeneity across studies, the aggregate data support LGIT's role in epilepsy management, underscoring its potential in alleviating the burden of drug-resistant epilepsy.

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