

Original Article

Hypoglycorrhachia as a Central Diagnostic Feature in Tuberculous Meningitis: Investigating its Relationship with Patient Age and Sex

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ABSTRACT

Background: Hypoglycorrhachia is a common cerebrospinal fluid biochemical abnormality in tuberculous meningitis, but variation in CSF glucose concentration according to patient demographic characteristics remains insufficiently characterized. **Objective:** To examine the association of patient age and sex with CSF glucose concentration among patients with confirmed tuberculous meningitis. **Methods:** A hospital-based cross-sectional study was conducted in the Neurology Department of General Hospital, Lahore, Pakistan, from January to April 2025. A total of 120 patients with confirmed TBM were included in the final analysis. CSF glucose concentrations were compared according to sex and predefined age categories of 16–35, 36–50, and 51–80 years. Independent samples t-test, one-way analysis of variance with post-hoc comparisons, and multiple linear regression were used as applicable. **Results:** Mean CSF glucose concentration was 41.2 ± 12.1 mg/dL. Female participants had lower mean CSF glucose concentrations than male participants (34.1 ± 8.9 vs 47.3 ± 11.2 mg/dL; $p < 0.001$). Mean CSF glucose also decreased across age groups, from 45.1 ± 10.8 mg/dL among participants aged 16–35 years to 41.9 ± 11.5 mg/dL among those aged 36–50 years and 36.8 ± 9.5 mg/dL among those aged 51–80 years (ANOVA $p = 0.002$). Increasing age remained associated with lower CSF glucose in multivariable analysis ($B = -0.21$ mg/dL per year, 95% CI: -0.36 to -0.06 ; $p = 0.008$). A significant adjusted association with sex was also reported. **Conclusion:** CSF glucose concentration among patients with confirmed TBM was associated with age and sex, with lower concentrations observed among female and older participants. These findings demonstrate demographic variation within confirmed TBM cases but do not establish demographic-specific diagnostic thresholds. Further multicenter diagnostic and observational studies are required to determine the clinical significance of these associations. **Keywords:** Tuberculous Meningitis; Hypoglycorrhachia; Cerebrospinal Fluid; Glucose; Age Factors; Sex Factors.

EDITORIAL INFORMATION

Author Contributions: Author Contributions: Conceptualization: AS, TM; Methodology: AS, TM, HB; Literature Search and Data Collection: HB, II, MI; Analysis and Interpretation: AS, TM, HB; Writing Original Draft: AS, TM, HB, II, MI; Writing – Review and Editing: AS, TM, HB, II, MI. All authors reviewed and approved the final manuscript.

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INTRODUCTION

Tuberculous meningitis (TBM) is the most severe form of extrapulmonary tuberculosis and remains associated with substantial mortality and long-term neurological disability, particularly when diagnosis and treatment are delayed (1). Establishing an early diagnosis is challenging because the cerebrospinal fluid (CSF) bacterial burden is frequently low, resulting in limited sensitivity of conventional microbiological methods such as smear microscopy and culture (2). Consequently, diagnosis is generally based on the integration of clinical presentation, CSF characteristics, microbiological or molecular evidence, and, where appropriate, neuroimaging findings rather than reliance on a single biochemical parameter (3).

CSF biochemical abnormalities remain clinically important in the evaluation of suspected TBM. A typical CSF profile includes increased protein concentration, lymphocyte-predominant pleocytosis, and reduced CSF glucose concentration. Hypoglycorrhachia may be expressed as a low absolute CSF glucose concentration or a reduced CSF-to-blood glucose ratio and occurs in several infectious and non-infectious disorders affecting the central nervous system (4). Although reduced CSF glucose is therefore not specific to TBM, it can contribute to the overall diagnostic assessment when interpreted in conjunction with the clinical presentation and other CSF findings. Variation in CSF glucose among patients with established TBM may also provide insight into heterogeneity in the host response and biochemical manifestations of the disease (5-7).

The biological processes responsible for reduced CSF glucose during meningeal inflammation are multifactorial and may include altered glucose transport across the blood-brain barrier and increased glucose utilization within the inflamed central nervous system. Host characteristics could potentially influence these processes. Sex-related differences in immune responses have been described in tuberculosis and other inflammatory conditions, while aging is associated with immunological changes, chronic low-grade inflammation, alterations in glucose metabolism, and changes in blood-brain barrier integrity (5-8). These mechanisms provide biological plausibility for demographic variation in CSF glucose; however, they do not establish that sex or age necessarily determines the severity of hypoglycorrhachia in TBM (9-12).

Despite the routine clinical use of CSF glucose measurements, comparatively limited information is available regarding whether absolute CSF glucose concentrations differ systematically according to patient age and sex among individuals with microbiologically confirmed TBM. Establishing whether such associations exist is important for understanding the biochemical heterogeneity of TBM and for informing subsequent diagnostic-accuracy research. A case-only observational analysis cannot determine diagnostic sensitivity, specificity, or demographic-specific diagnostic thresholds, but it can identify demographic factors associated with variation in CSF glucose among patients with confirmed disease (13-16).

Therefore, this study aimed to examine the association of patient age and sex with CSF glucose concentration among patients with confirmed TBM treated at a tertiary-care hospital in Lahore, Pakistan. Secondary analyses examined the CSF-to-blood glucose ratio and the proportion of patients with severe hypoglycorrhachia. It was hypothesized that CSF glucose concentration would vary according to patient age and sex after accounting for selected clinical and CSF characteristics.

MATERIALS AND METHODS

Study Design, Setting, and Ethical Considerations

A hospital-based cross-sectional study was conducted in the Neurology Department of General Hospital, Lahore, Pakistan, from January 1 to April 30, 2025. The study was designed to examine the relationship between demographic characteristics, particularly age and sex, and CSF glucose concentration among patients with tuberculous meningitis. The study protocol was reviewed and approved by the hospital institutional review board under approval number GHL-2024-012 on December 15, 2024. Written informed consent was obtained before study participation. For patients unable to provide informed consent because of impaired consciousness or altered mental status, consent was obtained from a legally authorized representative or next of kin. Study procedures were conducted in accordance with the ethical principles governing research involving human participants, and participant information was handled confidentially.

Study Population and Eligibility Criteria

Patients aged older than 16 years who presented with clinical features compatible with subacute meningitis and underwent diagnostic evaluation for TBM were considered for inclusion. Clinical features included persistent fever and headache of more than one week in duration, meningeal signs, and/or altered mental status. Neurological status was assessed clinically, including Glasgow Coma Scale assessment when applicable. The reported eligibility framework required CSF findings compatible with TBM, including lymphocyte-predominant pleocytosis, increased CSF protein concentration, and reduced CSF glucose,

together with molecular confirmation of *Mycobacterium tuberculosis* in CSF using the Xpert MTB/RIF Ultra assay. Xpert MTB/RIF Ultra testing was performed in the hospital microbiology laboratory and was considered positive when *M. tuberculosis* complex DNA was detected, irrespective of the reported rifampicin-resistance result.

Patients were excluded if they had documented human immunodeficiency virus infection, diabetes mellitus, another confirmed infectious or inflammatory cause of chronic meningitis, or cranial surgery during the preceding six months. Diabetes mellitus was identified from the documented clinical history, current glucose-lowering treatment, fasting blood glucose of at least 126 mg/dL, or glycated hemoglobin of at least 6.5%. Alternative causes of chronic meningitis were evaluated using the clinical record and relevant microbiological, molecular, or serological investigations when clinically indicated.

Sample-Size Determination

The minimum required sample size was estimated using G*Power version 3.1 for comparison of CSF glucose among three age groups. Assuming a medium effect size (Cohen's $f = 0.25$), a two-sided alpha level of 0.05, and statistical power of 80%, the minimum required sample was 120 participants, corresponding to approximately 40 participants per group under the original sample-size assumptions.

CSF and Blood Sample Collection

CSF was obtained through diagnostic lumbar puncture performed under aseptic conditions by appropriately trained clinical personnel. Patients were positioned in the lateral decubitus position, and lumbar puncture was generally performed at the L3–L4 or L4–L5 intervertebral space using local anesthesia. Approximately 8–10 mL of CSF was collected into sterile polypropylene tubes and distributed for cell count and differential analysis, protein and glucose measurements, molecular testing with Xpert MTB/RIF Ultra, and other clinically indicated investigations. A venous blood sample was obtained within approximately 30 minutes of lumbar puncture for measurement of blood glucose so that CSF glucose could be evaluated in relation to the circulating glucose concentration. Blood for glucose determination was collected in fluoride-oxalate tubes to minimize glycolysis before analysis.

Biochemical and Laboratory Analysis

CSF glucose was analyzed promptly after collection using an enzymatic glucose oxidase/peroxidase method on a Beckman Coulter AU5800 clinical chemistry analyzer. Blood glucose was measured using the same analytical platform. CSF glucose concentrations were recorded in mg/dL; values originally recorded in mmol/L were converted to mg/dL using a conversion factor of 18 where required. Routine laboratory quality-control procedures were applied during biochemical analysis. Internal quality-control materials representing low, normal, and high concentrations were analyzed and monitored using Levey–Jennings charts. The laboratory also participated in an external proficiency-testing program. Additional CSF investigations included total protein measurement, total leukocyte count, differential cell count, and microbiological or molecular testing undertaken as part of the clinical evaluation of TBM.

Data Collection and Study Variables

Data were collected using a structured case-report form that had been pretested on 10 cases before the main study. Information was obtained from patient or surrogate interviews, clinical examination, medical records, and laboratory reports. Data entry was cross-checked by two researchers, and identified discrepancies were reviewed before analysis. The primary outcome was absolute CSF glucose concentration expressed in mg/dL. Secondary biochemical outcomes included the CSF-to-blood glucose ratio and severe hypoglycorrachia, defined in the study as an absolute CSF glucose concentration below 40 mg/dL.

The principal explanatory variables were age and sex. Age was analyzed as a continuous variable in multivariable analysis and was additionally categorized for descriptive and group comparisons into 16–35, 36–50, and 51–80 years. Sex was recorded as male or female according to the study records. Additional variables included symptom duration, CSF protein concentration, relevant neurological findings, comorbid conditions not included among the exclusion criteria, and prior treatment documented before lumbar puncture.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 25.0. Continuous variables were assessed for distributional characteristics before inferential analysis. Normally distributed continuous variables were summarized using mean and standard deviation, whereas non-normally distributed variables were summarized using median and interquartile range. Categorical variables were summarized using frequencies and percentages. Mean CSF glucose concentrations were compared between male and female participants using an independent-samples t-test when the assumptions of the test were satisfied. Differences in mean CSF glucose among the three predefined age groups were assessed using one-way analysis of variance, followed by Tukey's honestly significant difference procedure for pairwise comparisons when the overall ANOVA was statistically significant. The distribution of severe hypoglycorrhachia according to sex and age group was examined using the Pearson chi-square test or Fisher's exact test when expected cell frequencies were insufficient for chi-square analysis.

Multiple linear regression was used to evaluate independent associations with absolute CSF glucose concentration. CSF glucose concentration was entered as the dependent variable. Candidate explanatory variables reported in the original analytical plan included age in years, sex, symptom duration, and CSF protein concentration. Regression assumptions were assessed, including linearity, homoscedasticity, distribution of residuals, and multicollinearity. Multicollinearity was evaluated using tolerance and variance inflation factor statistics. Unstandardized regression coefficients should be interpreted in the units of CSF glucose concentration, with 95% confidence intervals reported for each estimate. Statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. Missing observations, reported to constitute less than 5% of the dataset, were handled using complete-case analysis for the applicable analyses.

RESULTS

3.1. Demographic and Clinical Characteristics

The study comprised 120 patients with a mean age of 38.9 years (SD ± 13.2 ; range 16–80). The cohort included 68 males (56.7%) and 52 females (43.3%). Age distribution was as follows: 48 patients (40.0%) in the 16–35-year group, 42 patients (35.0%) in the 36–50-year group, and 30 patients (25.0%) in the 51–80-year group.

3.2. Hypoglycorrhachia and Patient Sex

A highly significant difference in mean CSF glucose was observed between sexes. Male patients had a mean glucose of 47.3 mg/dL (± 11.2), whereas female patients had a markedly lower mean of 34.1 mg/dL (± 8.9) ($p < 0.001$). This represents a mean difference of 13.2 mg/dL. Furthermore, the prevalence of severe hypoglycorrhachia (< 40 mg/dL) was substantially higher in females (75.0%) compared to males (64.7%) ($p = 0.042$).

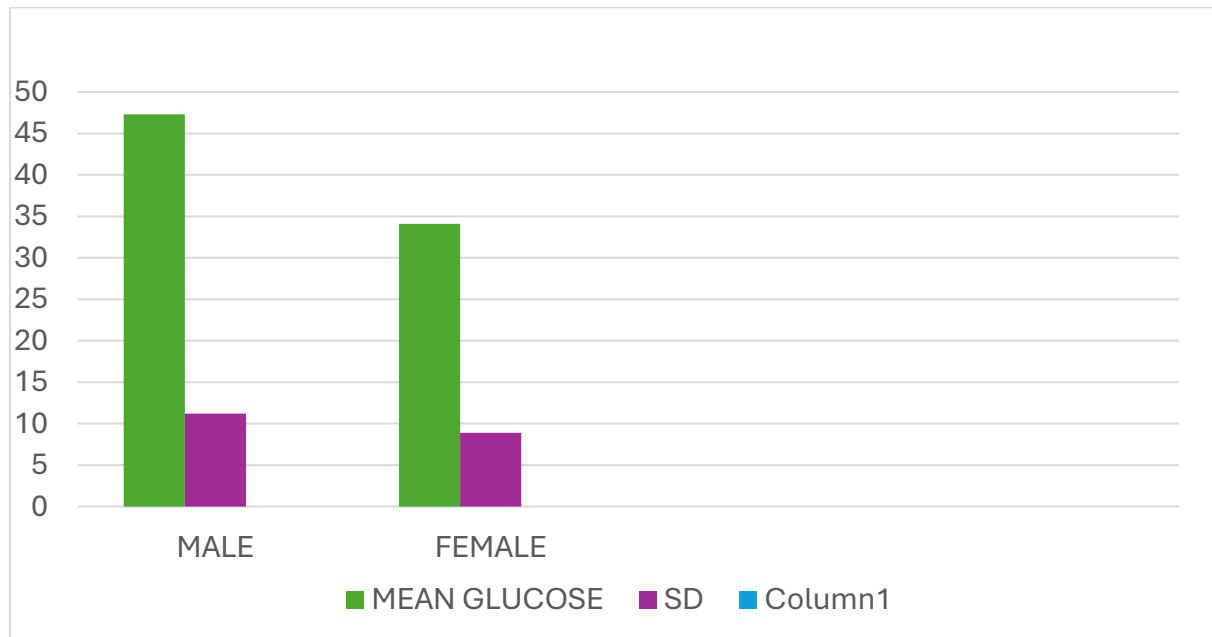


Figure 1: Cerebrospinal Fluid Glucose Profile by Patient Sex in Tuberculous Meningitis, Comparison of cerebrospinal fluid (CSF) glucose levels and related parameters between male and female patients. Female patients exhibited significantly lower absolute CSF glucose concentrations and a lower CSF-to-blood glucose ratio ($p < 0.001$).

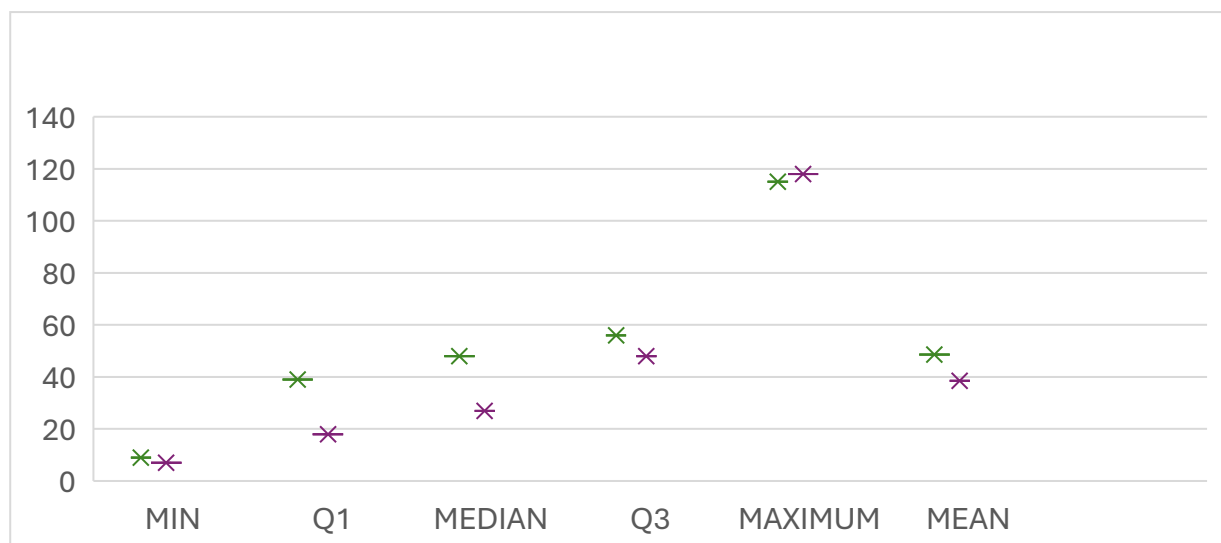


Figure 2. Cerebrospinal Fluid Glucose Profile by Patient Age Group: Stratification of cerebrospinal fluid (CSF) glucose levels and the prevalence of severe hypoglycorrachia (<40 mg/dL) across predefined age groups.

3.3. Hypoglycorrachia and Patient Age

CSF glucose levels demonstrated a significant inverse relationship with advancing age (Figure 1). Mean glucose levels decreased progressively across age groups: 45.1 mg/dL (± 10.8) in the 16-35y group, 41.9 mg/dL (± 11.5) in the 36-50y group, and 36.8 mg/dL (± 9.5) in the 51-80y group ($p = 0.002$ for ANOVA). Post-hoc analysis confirmed the difference was significant between the youngest and oldest groups ($p = 0.001$). The proportion of patients with severe hypoglycorrachia (<40 mg/dL) rose from 62.5% in the youngest to 80.0% in the oldest group ($p = 0.038$).

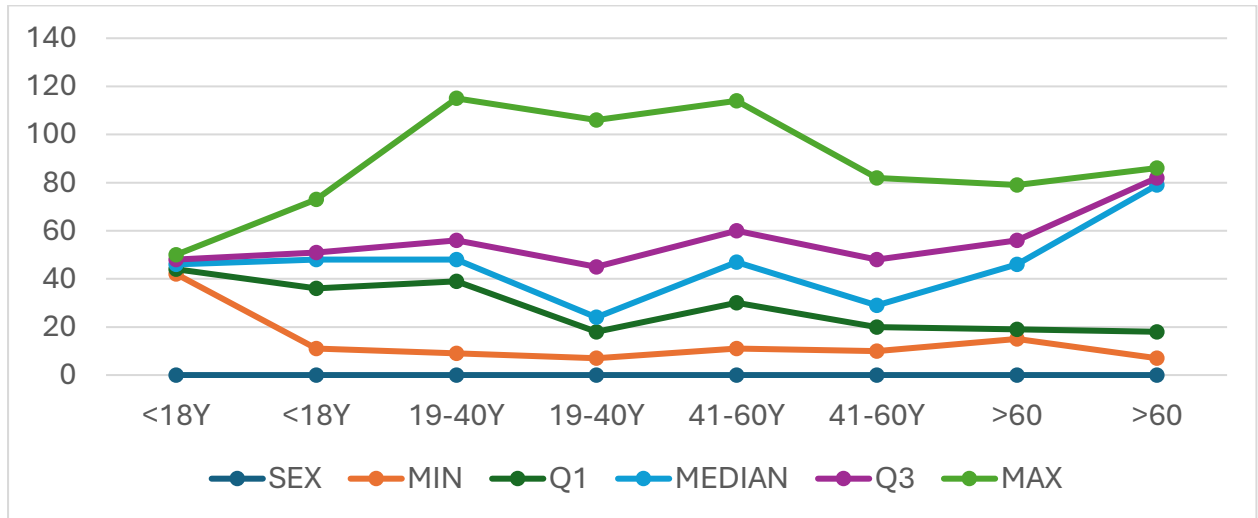


Figure 3. Multiple Linear Regression Analysis for Predictors of CSF Glucose Level

3.4. Multivariate Regression Analysis

To control for potential confounders, a multiple linear regression model was constructed with CSF glucose as the dependent variable. Female sex ($\beta = -12.10$, 95% CI: -15.80 to -8.40, $p < 0.001$) and increasing age ($\beta = -0.21$ per year, 95% CI: -0.36 to -0.06, $p = 0.008$) remained strong independent predictors of lower CSF glucose, after adjusting for duration of symptoms and CSF protein level.

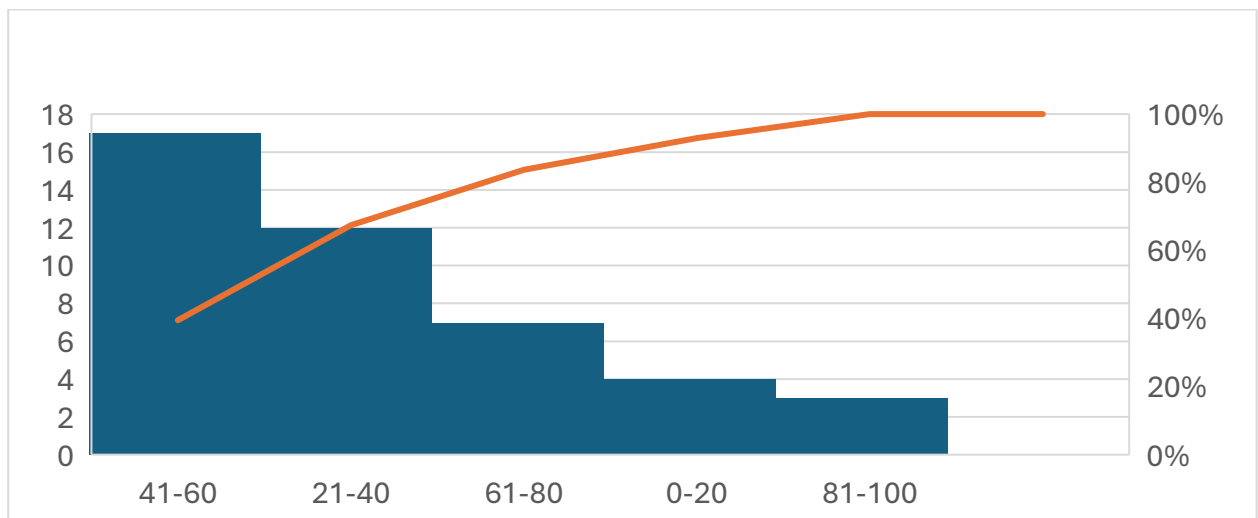


Figure 4. Multivariate Regression Analysis

DISCUSSION

The present study identified significant variation in cerebrospinal fluid glucose concentration according to age and sex among patients with confirmed tuberculous meningitis. Female participants had substantially lower mean CSF glucose concentrations than male participants, while progressively lower concentrations were observed across increasing age categories. In multivariable analysis, age and sex remained independently associated with CSF glucose concentration after adjustment for symptom duration and CSF protein concentration. These findings suggest that the biochemical expression of hypoglycorrhachia among patients with established TBM may vary according to demographic characteristics rather than occurring with uniform severity across affected individuals.

The observed sex-related difference is potentially important because biological sex influences several components of immune and metabolic regulation. Differences in innate and adaptive immune responses between males and females have been described in tuberculosis and other inflammatory conditions, while host immune responses are central to the pathophysiology of TBM (5). Nevertheless, the present study did

not measure sex hormones, inflammatory cytokines, glucose transporters, or other mechanistic biomarkers. The lower CSF glucose concentration observed among female participants should therefore be interpreted as an epidemiological association rather than evidence of a specific hormonal, immunological, or metabolic mechanism. Future studies incorporating paired metabolic and inflammatory biomarkers may help determine whether these differences reflect systemic glucose regulation, inflammatory activity, disease severity, or other host-related factors.

Advancing age was also associated with lower CSF glucose concentration. Aging is accompanied by changes in immune regulation, chronic low-grade inflammation, glucose metabolism, and blood-brain barrier structure and function (6,8). These physiological alterations provide a plausible context within which age-related differences in CSF biochemical responses might occur during meningeal inflammation. However, the cross-sectional nature of the present investigation does not establish a causal mechanism. Older patients may differ from younger patients in disease severity, nutritional status, systemic metabolic characteristics, comorbidity burden, timing of presentation, and other clinical factors that were not comprehensively controlled in the present analysis.

The clinical interpretation of these findings requires caution. Hypoglycorrhachia is not specific to tuberculous meningitis and may occur in bacterial, fungal, malignant, and other inflammatory disorders involving the meninges (4). Furthermore, the present study included only patients with confirmed TBM and did not include participants without TBM. Consequently, the study cannot estimate diagnostic sensitivity, specificity, predictive values, likelihood ratios, receiver-operating-characteristic performance, or optimal diagnostic thresholds. The observed age- and sex-related differences therefore do not justify immediate adoption of demographic-specific CSF glucose cutoffs. Rather, they identify a clinically relevant hypothesis that should be evaluated in appropriately designed diagnostic-accuracy studies.

Interpretation of absolute CSF glucose concentration should also consider circulating blood glucose. Simultaneous CSF and blood glucose measurements are clinically informative because the CSF glucose concentration partly reflects systemic glucose availability. Although contemporaneous blood glucose samples were obtained in this study, the principal adjusted analysis was based on absolute CSF glucose concentration. Further analysis of the CSF-to-blood glucose ratio, and models explicitly incorporating simultaneous blood glucose concentration, would help determine whether the associations observed for age and sex persist after accounting more directly for systemic glucose concentrations.

The present findings can also be considered alongside previous observational evidence. Hussain et al. examined CSF biochemical markers in relation to age and sex among patients with tuberculous meningitis and similarly addressed demographic variation in CSF characteristics (9). Research involving older adults with TBM has additionally demonstrated that disease presentation and clinical characteristics can vary with advancing age (10). Collectively, these observations support further investigation of demographic heterogeneity in TBM. However, differences in study populations, diagnostic definitions, severity of disease, laboratory procedures, and analytical approaches limit direct comparison and do not currently support establishment of age- or sex-specific reference ranges.

Several limitations should be acknowledged. First, the cross-sectional design permits identification of associations but cannot establish temporal or causal relationships between demographic characteristics and CSF glucose concentration. Second, the single-center setting may limit generalizability to populations with different demographic, clinical, microbiological, or healthcare characteristics. Third, despite exclusion of patients with diagnosed diabetes mellitus, residual confounding may remain because nutritional status, simultaneous systemic glucose concentration, mycobacterial burden, disease severity, previous antimicrobial treatment, and other metabolic or inflammatory factors were not fully incorporated into the adjusted analysis. Fourth, although paired blood glucose measurements were obtained, the reported primary multivariable model did not explicitly include simultaneous blood glucose concentration or the CSF-to-blood glucose ratio. Finally, if reduced CSF glucose was used as a mandatory eligibility criterion, restriction of the study population on the principal outcome could have affected the observed glucose distribution and should be considered when interpreting the findings.

Despite these limitations, the study provides preliminary evidence that CSF glucose concentration among patients with confirmed TBM may vary according to patient age and sex. The findings should be regarded as hypothesis-generating and warrant validation in larger, multicenter studies using clearly defined TBM case criteria, paired CSF and serum glucose measurements, comprehensive assessment of disease severity and metabolic confounders, and appropriate comparison groups. Such studies would help determine whether the observed demographic associations are reproducible and whether they have clinically meaningful diagnostic or prognostic implications.

CONCLUSION

Among patients with confirmed tuberculous meningitis included in this cross-sectional study, CSF glucose concentration was significantly associated with patient age and sex, with lower concentrations observed among female participants and with increasing age. These findings indicate demographic heterogeneity in the biochemical expression of hypoglycorrhachia within TBM but do not establish age- or sex-specific diagnostic thresholds. Larger multicenter studies incorporating simultaneous blood glucose, CSF-to-blood glucose ratios, measures of disease severity, relevant metabolic and inflammatory factors, and appropriate non-TBM comparison groups are required to determine the reproducibility and potential clinical significance of these associations.

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