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Serum CA 19-9 as a potential biomarker for diabetic neuropathy: a comparative study among diabetic patients and healthy controls

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ABSTRACT

This study investigated the potential of serum carbohydrate antigen 19-9 (CA 19-9) as a biomarker for diabetic neuropathy (NP) by comparing its levels among patients with diabetes mellitus (DM) and NP, patients with DM without NP, and healthy controls. Participants were recruited between February and August 2022 at the Center of Diabetes, Merjan Medical City, Babil Province, Iraq. A total of 220 subjects were analysed. Serum CA 19-9 concentrations were significantly higher in the DM with NP group (21.99 ± 5.23 U/mL) compared to the DM without NP group (20.29 ± 4.67 U/mL) and healthy controls (9.65 ± 3.12 U/mL). Correlation analysis revealed a strong positive association between CA 19-9 and glycated haemoglobin (HbA1c) levels (r=0.72, p<0.01). Receiver operating characteristic curve analysis demonstrated high diagnostic accuracy, with an area under the curve of 0.95 for distinguishing DM with NP from healthy subjects. Logistic regression analysis suggested a positive, though statistically non-significant, association between CA 19-9 and NP. These findings support the potential role of CA 19-9 as a biomarker for the early detection of diabetic NP, underscoring its relevance in clinical practice to enhance DM management and patient outcomes. Further research is warranted in order to elucidate the underlying mechanisms and validate these findings across diverse populations.

1. Introduction

Diabetic neuropathy (NP) is a common complication of diabetes mellitus (DM), characterized by neuronal damage resulting from prolonged

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hyperglycaemia. Diabetic NP affects approximately half of individuals with DM, contributing to significant morbidity and reduced quality of life[1]. Early diagnosis and intervention are essential to prevent irreversible tissue damage and associated complications, such as foot ulcers and amputations[2]. Current diagnostic approaches primarily rely on clinical assessments and nerve conduction studies; however, these methods can be invasive, time-consuming, and may not consistently yield prompt results[1].

Recent research has highlighted the potential utility of biomarkers in the early detection of DM-related complications. Among these, carbohydrate antigen 19-9 (CA 19-9) – a well-established marker of pancreatic malignancy[3] – has emerged as a promising candidate due to its association with various metabolic disorders linked to DM[2,4]. Elevated CA 19-9 levels have been observed in patients with DM, suggesting a connection to pancreatic inflammation or tissue injury, both of which are implicated in the pathophysiology of diabetic NP[5].

This study aimed to evaluate serum CA 19-9 concentrations in DM patients with NP compared to healthy controls, thereby assessing its potential as a biomarker for early diabetic NP detection. By elucidating the relationship between serum CA 19-9 levels and diabetic NP, the findings may inform improved screening strategies and therapeutic interventions in DM. These results could also support further investigation into CA 19-9 as a non-invasive biomarker to enhance clinical management of diabetic complications.

2. Methodology

This case-control study was conducted between February and August 2022 at the Center of Diabetes, Merjan Medical City, Babil Province, Iraq. Biochemical analyses were performed at the College of Pharmacy of the University of Babylon. A total of 220 participants were enrolled, comprising 160 patients with type II DM and 60 healthy individuals. Diabetic patients were divided into two groups: group 1 (N=80) included those with NP, and group 2 (N=80) included those without NP.

Participants aged 30–70 years were selected based on medical history, clinical presentation, and nerve conduction study results. Exclusion criteria included type I DM, gestational DM, hepatic disease, chronic cardiac conditions, endocrine disorders, and chronic kidney disease. All participants were sex-matched to ensure group comparability.

Demographic data – including age, sex, duration of DM (months), weight (kg), height (m), and body mass index (BMI) – were recorded. Blood samples were collected for biochemical evaluation, including measurements of glycated haemoglobin (HbA1c), CA 19-9, and vitamin D_2. HbA1c was quantified using high-performance liquid chromatography (HPLC), while vitamin D_2 levels were measured using enzyme-linked immunosorbent assay (ELISA) kits (Elabscience® Biotechnology Ltd, USA). The CA 19-9 concentrations were determined using a chemiluminescence autoanalyzer (Snibe® Maglumi 800, China).

Ethical approval was granted by the local ethics committees of the Merjan Hospital and the Babylon Health Directorate (IRB A0030) in January 2022. Informed verbal consent was obtained from all participants prior to sample collection.

Statistical analyses were performed using Microsoft Excel (2017) and the IBM SPSS Statistics for Windows (version 28) software. Data are presented as mean ± standard deviation, with statistical significance set at $p<0.05$. Analysis of variance (ANOVA) was used in order to detect differences among groups, while regression analysis assessed correlations. The Chi-square test evaluated categorical variables, and receiver operating characteristic (ROC) curve analysis was employed in order to further explore diagnostic performance.

3. Results and Discussion

This study assessed serum CA 19-9 concentrations as a potential biomarker for diabetic NP by comparing levels among patients with DM and NP, patients with DM without NP, and healthy controls. The data revealed significant differences in CA 19-9 levels across groups, as summarized in Table 1.

The DM with NP group exhibited a mean CA 19-9

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Table 1. Comprehensive analysis of metabolic and diagnostic insights regarding the carbohydrate antigen 19-9 (CA 19-9) levels in diabetic neuropathy. Abbreviations used: AUC, area-under-the-curve; BMI, body mass index; DM, diabetes mellitus; HbA1c, glycated haemoglobin; NP, neuropathy.

Category	Key insights
Descriptive statistics	CA 19-9 measures significantly higher in the subgroup of DM with NP (21.9 ± 5.2 U/mL), compared to the DM group without NP (20.3 ± 4.7 U/mL); the healthy group exhibited much lower concentrations (9.7 ± 3.1 U/mL)
Correlation analysis	CA 19-9 exhibited a robust direct correlation with HbA1c (r=0.72, p<0.01), signifying that increased CA 19-9 levels are related to poorer glycemic control; the correlation with BMI was weak but significant (r=0.15, p=0.02); additionally, CA 19-9 exhibited a moderate inverse correlation with vitamin D_2 (r=-0.601, p<0.01), highlighting a negative relationship
Comparative statistics	Analysis of variance revealed statistically significant differences in the CA 19-9 levels across the three groups (p<0.01); *post-hoc* testing showed that the most pronounced difference was between the DM with NP group and the control group
Receiver operating characteristic analysis	High diagnostic accuracy of CA 19-9 for DM with NP *vs.* the control: the AUC was 0.95 (95% CI: 0.92–0.98), with a cut-off value of 15.3 U/mL, giving a 91% sensitivity and a 93% specificity; for DM without NP *vs.* healthy control, the AUC was 0.85 (95% CI: 0.80–0.90) with a 14.8 U/mL value cut off, providing a 78% sensitivity and a 81% specificity; for all DM *vs.* the control, the AUC was 0.95 (95% CI: 0.92–0.98), with a cut-off value of 14.9 U/mL, yielding a sensitivity of 89% and a specificity of 90%
Logistic regression analysis	CA 19-9 had a positive coefficient (1.34), indicating a potential association with increased odds of neuropathy; however, the result was not statistically significant (p=0.329); other variables like HbA1c (p=0.364), BMI (p=0.423), and vitamin D_2 (p=0.657) also showed no significant associations with neuropathy in this analysis

level of 21.9 ± 5.2 U/mL, significantly higher than the DM without NP group (20.3 ± 4.7 U/mL). Healthy controls demonstrated markedly lower levels (9.7 ± 3.1 U/mL). Previous studies have reported elevated CA 19-9 levels in approximately 14% of DM patients with poor glycaemic control[4]. Diabetic NP is associated with increased oxidative stress and inflammatory markers, which may influence CA 19-9 concentrations[2].

Elevated CA 19-9 levels have been linked to the severity of diabetic complications, independent of malignancy[6]. The biomarker has also shown correlations with risk factors for diabetic retinopathy, suggesting a role in microvascular complications[7]. Additionally, high-normal serum carcinoembryonic antigen levels have been proposed as indicators of diabetic peripheral neuropathy, implying that CA 19-9 may similarly reflect neuropathic severity[8]. While advanced glycation end products are associated with diabetic complications, their relationship with diabetic NP appears distinct; CA 19-9 may offer clearer insights into the NP severity[9].

Correlation analyses confirmed a strong positive association between CA 19-9 and HbA1c levels (r=0.72, p<0.01), indicating that poorer glycaemic control is linked to elevated CA 19-9. This aligns with prior findings that inflammatory markers in DM are associated with reduced glycaemic control[1,4]. A weak but statistically significant correlation was observed between BMI and CA 19-9 (r=0.15, p=0.02).

A moderate inverse correlation was found between CA 19-9 and vitamin D_2 levels (r=-0.60, p<0.01), suggesting that vitamin D deficiency may be associated with metabolic dysregulation and heightened systemic inflammation[1,4,10].

ANOVA revealed significant differences in CA 19-9 levels among the three groups (p<0.01). *Post hoc* analysis confirmed a statistically significant difference between DM with NP and healthy controls, reinforcing the association between elevated CA 19-9 and diabetic NP. Prior studies have similarly reported increased inflammatory markers in patients with

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diabetic NP and diabetic retinopathy[7].

ROC curve analysis demonstrated high diagnostic accuracy for CA 19-9 in identifying diabetic NP. The area-under-the-curve (AUC) was 0.95 (95% CI: 0.92–0.98) for distinguishing DM with NP from healthy controls. A cutoff value of 15.3 U/mL yielded 91% sensitivity and 93% specificity. For DM without NP *versus* healthy controls, the AUC was 0.85 (95% CI: 0.80–0.90), with 78% sensitivity and 81% specificity at a cutoff of 14.8 U/mL. These findings affirm the diagnostic potential of CA 19-9 in diabetic NP, consistent with earlier research[6,7].

Logistic regression analysis yielded a coefficient of 1.34, suggesting a possible association between CA 19-9 and diabetic NP risk; however, this was not statistically significant (p=0.3). Elevated CA 19-9 levels were positively correlated with poor glycaemic control, including HbA1c and fasting plasma glucose[6]. Prior studies have linked increased CA 19-9 to diabetic retinopathy and nephropathy, supporting its role in risk stratification[1,7]. No significant associations were found between diabetic NP and HbA1c (p=0.4), BMI (p=0.4), or vitamin D_2 (p=0.7), possibly due to sample size limitations or residual confounding.

4. Conclusion

This study demonstrated elevated serum CA 19-9 levels in DM patients with NP, with a strong positive correlation to HbA1c, thereby suggesting its utility in identifying poorly controlled DM. ROC analysis confirmed CA 19-9 as a promising biomarker for early diabetic NP detection. Further research is warranted in order to clarify its role in screening and managing DM-related complications.

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Conflicts of interest

None exist.

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