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SERUM CERAMIDE SPECIES AND METEORIN-LIKE PROTEIN AS A NOVEL COMBINED BIOMARKER PANEL FOR THE DIAGNOSIS OF EARLY-STAGE TYPE 2 DIABETES MELLITUS

SERUMSKE VRSTE CERAMIDA I PROTEIN SLIČAN METEORINU KAO NOVI KOMBINOVANI PANEL BIOMARKERA ZA DIJAGNOZU RANOG STADIJUMA DIJABETESA MELITUSA TIPA 2

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Summary

Background: Early detection of biomarkers of pathophysiological changes occurring in Type 2 Diabetes Mellitus (T2DM) is crucial for timely intervention. Ceramides, a group of lipotoxic sphingolipids, and meteorin-like protein (Metrnl), a novel adipomyokine involved in insulin sensitisation, have been implicated in the pathogenesis of T2DM. This study compared the serum levels of ceramide species (Cer-16, Cer-18, Cer-24, and Cer-24:1) and Metrnl between patients with T2DM and normoglycemic controls. It assessed their diagnostic value individually and collectively.

Methods: This case-control study recruited 80 patients with newly diagnosed T2DM and 80 normoglycemic controls matched for age and body mass index (BMI). Fasting blood samples were used to measure routine blood parameters. Quantification of ceramide species was performed by liquid chromatography-tandem mass spectrometry (LC-MS/MS), and serum Metrnl levels were measured by enzyme-linked immunosorbent assay (ELISA).

Results: Patients with T2DM showed significantly increased levels of Cer-16 and Cer-18 ($p<0.001$ and $p<0.01$, respectively) and reduced levels of Cer-24 and Metrnl ($p<0.001$ for both). Moreover, the ratio of Cer-16 to Cer-24 was significantly increased in the T2DM group. Significant positive correlations were noted between these biomarkers and insulin resistance and glycemic control (HOMA-IR and HbA1c). However, a multivariate logistic regression model combining Cer-16, Cer-24, and Metrnl showed a significantly higher area under the ROC curve (0.93) for discriminating T2DM than did using these biomarkers individually.

Kratak sadržaj

Uvod: Rano otkrivanje biomarkera patofizioloških promena koje se javljaju kod dijabetesa melitusa tipa 2 (T2DM) je od ključnog značaja za pravovremenu intervenciju. Ceramidi, grupa lipotoksičnih sfingolipida, i protein sličan meteorinu (Metrnl), novi adipomiokin uključen u povećanje osetljivosti na insulin, povezani su sa patogenezom T2DM. U ovoj studiji upoređeni su serumski nivoi vrsta ceramida (Cer-16, Cer-18, Cer-24 i Cer-24:1) i Metrnl između pacijenata sa T2DM i normoglikemijskih kontrolnih pacijenata, kao i njihova dijagnostička vrednost pojedinačno i u kombinaciji.

Metode: U ovu studiju tipa slučaj-kontrola uključeno je 80 pacijenata sa novodijagnostikovanim T2DM i 80 normoglikemijskih kontrolnih pacijenata uparenih prema starosti i indeksu telesne mase (BMI). Za određivanje rutinskih krvnih parametara korišćeni su uzorci krvi natašte. Kvantifikacija vrsta ceramida je izvršena metodom tečne hromatografije sa tandemskom masenom spektrometrijom (LC-MS/MS), dok su serumski nivoi Metrnl određeni enzimskim imunoesejem (ELISA).

Rezultati: Pacijenti sa T2DM imali su značajno povišene nivoe Cer-16 i Cer-18 ($p<0,001$ i $p<0,01$, redom), kao i snižene nivoe Cer-24 i Metrnl (za oba $p<0,001$). Takođe, odnos Cer-16/Cer-24 bio je značajno povećan u T2DM grupi. Utvrđene su značajne pozitivne korelacije između ovih biomarkera i insulinske rezistencije i glikemijske kontrole (HOMA-IR i HbA1c). Međutim, multivarijantni logistički regresioni model koji kombinuje Cer-16, Cer-24 i Metrnl pokazao je značajno veću površinu ispod ROC krive (0,93) za razlikovanje T2DM u odnosu na pojedinačnu primenu ovih biomarkera.

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Conclusion: This study demonstrated for the first time that ceramide species and Metrnl levels are significantly altered in the early stages of T2DM. These changes, i.e., increased levels of Cer-16 and Cer-18 and reduced levels of Cer-24 and Metrnl, form a synergistic panel of biomarkers for the diagnosis of T2DM.

Keywords: type 2 diabetes mellitus, biomarker, ceramides, sphingolipids, meteorin-like protein, insulin resistance, lipotoxicity

Zaključak: Ova studija je po prvi put pokazala da su nivoi vrsta ceramida i Metrnl značajno izmenjeni u ranim fazama T2DM. Ove promene, odnosno povećani nivoi Cer-16 i Cer-18 i sniženi nivoi Cer-24 i Metrnl, čine sinergijski panel biomarkera za dijagnozu T2DM.

Ključne reči: dijabetes melitus tipa 2, biomarker, ceramidi, sfingolipidi, protein sličan meteorinu, insulinska rezistencija, lipotoksičnost

Introduction

The global pandemic of Type 2 Diabetes Mellitus (T2DM) underscores an urgent need for biomarkers to detect dysmetabolism before overt hyperglycemia. Current diagnostic criteria are based on glucose thresholds and HbA1c. These identify the disease at a stage of significant beta-cell dysfunction (1). Biomarkers rooted in the core pathologies of insulin resistance, such as lipotoxicity and adipose tissue dysfunction, could enable earlier risk stratification and targeted prevention (2, 3).

The sphingolipid ceramide has emerged as a critical bioactive mediator of lipid-induced insulin resistance (4). Specific circulating ceramide species, especially those derived from saturated fatty acids such as palmitate (Cer-16), directly inhibit insulin signalling in skeletal muscle and liver (5, 6). Conversely, very-long-chain ceramides (e.g., Cer-24) may be neutral or protective (7). Shifts in ceramide species profile, often quantified as a ratio, are a promising marker of metabolic stress (8, 9).

In parallel, adipose tissue secretes adipokines and skeletal muscle secretes myokines (10). These hormones regulate systemic metabolism. Meteorin-like protein (Metrnl) is a novel adipomyokine induced by exercise and cold exposure (11). It promotes adipose tissue browning, enhances anti-inflammatory macrophage polarisation, and improves glucose homeostasis in preclinical models (12, 13). Clinical studies report reduced circulating Metrnl in obesity and T2DM, suggesting its deficiency may contribute to metabolic dysfunction (14–16).

Thus, the T2DM milieu may be characterised by a dual defect: an increase in lipotoxic signals (ceramides) and a decrease in protective endocrine signals (Metrnl). These biomarkers are significant because ceramides are associated with cellular stress and insulin resistance, while Metrnl is linked to metabolic protection. We hypothesise that evaluating both axes simultaneously will yield a more robust, pathophysiologically grounded biomarker signature for early T2DM than conventional or single novel markers. This study investigates the individual and combined potential of specific serum ceramide species and Metrnl as synergistic biomarkers for T2DM.

Materials and Methods

Study design and participants

This observational, case-control study was conducted from 2024 to April, 2025. We recruited 80 adults with newly diagnosed T2DM (diagnosed <6 months per American Diabetes Association criteria) from the endocrinology clinic (17, 18). We also enrolled 80 age-matched (±3 years) and BMI-matched (±2 kg/m^2) controls with normal glucose tolerance (NGT), confirmed by a 75 g oral glucose tolerance test.

Key exclusion criteria for all participants included: history of type 1 diabetes, acute metabolic complications, significant renal (eGFR<60 mL/min/1.73m^2) or hepatic impairment, acute inflammatory or infectious disease, malignancy, pregnancy, and use of medications known to affect lipid or glucose metabolism (e.g., steroids, fibrates, niacin) within the past 3 months. The study protocol received Institutional Ethics Committee approval, and all participants provided written informed consent.

Biochemical analysis

Peripheral venous blood samples were collected after an overnight 12-hour fasting period. The samples were centrifuged at 3000 rpm for 15 minutes at 4 °C. The serum was separated and either analysed immediately or stored at -80 °C. Fasting plasma glucose, total cholesterol, triglycerides, high-density lipoprotein, and creatinine levels were analysed using a Cobas c501 autoanalyser (Roche Diagnostics). The LDL-C levels were calculated using the Friedewald formula. The HbA1c levels were analysed by high- performance liquid chromatography (Bio-Rad D-10). Fasting insulin levels were analysed using chemiluminescent technology (Architect i2000, Abbott). The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) values were calculated using the formula:

Fasting insulin (mIU/mL) × Fasting glucose (mmol/L) / 22.5

Measurement of serum ceramide species

Targeted quantification was performed for ceramide species with the sphingosine backbone d18:1,includingCer(d18:1/16:0),Cer(d18:1/18:0), Cer(d18:1/24:0), and Cer(d18:1/24:1). Analytical measurement procedures were performed using liquid chromatography-tandem mass spectrometry (LC-MS/MS) with modifications to the protocols as described previously. In summary, lipids were extracted from serum using the methyl-tert-butyl ether (MTBE) method with the addition of internal standards: d7-Cer(d18:1/16:0) and d7-Cer(d18:1/24:0) (Avanti Polar Lipids). The QTRAP 6500+ MS/MS system (Sciex) and the ExionLC AD system were used to quantify ceramide levels in serum. Separation of the ceramide species was performed using a Kinetex C8 column (Phenomenex) with multiple reaction monitoring (MRM) in positive mode. The concentration of ceramide species was determined using standard curves, with normalisation to internal standards. The LOD and LOQ were 0.1 ng/mL and 0.3 ng/mL, respectively, with S/N 3/10. The recovery ranged from 95 to 105% for the spiking study. Linearity was established with an R2>0.99 across the 7-point standard curve from 1 to 1000 ng/mL. Intra- and inter-assay coefficient of variation (CV) were <8% and <10%, respectively. Matrix effects were <5% with post-extraction addition. MRM transitions were: m/z 538.5 → 264.3 (Cer-16), m/z 566.5 → 264.3 (Cer-18).

Measurement of serum meteorin-like protein (Metrnl)

Serum Metrnl concentration was determined using a commercially available, specific human Metrnl ELISA kit (Cat# E-EL-H6000, Elabscience) according to the manufacturer's instructions. All samples and standards were assayed in duplicate. The intra- and inter-assay coefficients of variation were <8% and <10%, respectively. Results are expressed in ng/mL. The ELISA kit has been validated against Western blot in multiple studies, showing >90% correlation for serum Metrnl (r=0.92). Intra- and inter-assay CVs were <8% and <10%, respectively (14).

Statistical analysis

Statistical analysis was performed using SPSS version 26.0 (IBM Corp.) and GraphPad Prism 9.0. Data normality was assessed using the Shapiro-Wilk test. Variables with normal distribution are presented as mean ± SD, whereas skewed variables (including Cer-24:1) are presented as median (IQR). Continuous variables with normal distribution are presented as mean ± standard deviation (SD) and compared using the independent Student's t-test. Non-normally distributed variables are presented as medians (interquartile ranges, IQRs) and compared using the Mann-Whitney U test. Categorical variables are presented as numbers (percentages) and compared using the Chi-square test. Pearson's or Spearman's correlation coefficients were used to assess relationships between variables. Binary logistic regression was used to develop a combined biomarker model. The diagnostic performance of individual biomarkers and the combined model was evaluated using receiver operating characteristic (ROC) curve analysis; the area under the curve (AUC), sensitivity, specificity, and optimal cut-off value (Youden's index) were calculated. A two-tailed p-value <0.05 was considered statistically significant.

In multivariable logistic regression, the outcome variable was T2DM status (cases vs controls). Candidate predictors considered in model building included age, sex, BMI, HDL-C, LDL-C, TG, HOMA-IR, and the biomarker variables (individual ceramide species and serum Metrnl). Variables with p<0.10 in univariate analyses and variables selected a priori on clinical grounds were entered into a multivariable model; a backward elimination procedure was then applied, removing variables at p≥0.05. Multicollinearity was assessed using variance inflation factors (VIFs); variables with VIF>5 were evaluated for redundancy. Model discrimination was assessed by the area under the ROC curve (AUC) with 95% confidence intervals, and calibration was evaluated using the Hosmer–Lemeshow goodness- of-fit test. Where feasible, internal validation was performed using bootstrap resampling (×1000) to estimate optimism-corrected AUC. These steps follow recommended reporting standards for multivariable prediction models (TRIPOD) and established modelling practice.

Correlation analyses presented in this manuscript were conducted as exploratory assessments. Due to the exploratory nature, the principal text reports raw p-values.

Results

Baseline clinical and biochemical characteristics

The T2DM and control groups were well-matched for age, sex distribution, and BMI (all p>0.05). As expected, the T2DM group had significantly higher levels of FPG, HbA1c, fasting insulin, HOMAIR, and triglycerides. HDL-C was significantly lower in the T2DM group. Total cholesterol and LDL-C did not differ significantly (*Table I*).

Table I Clinical and biochemical characteristics of the study participants.

Age (years)	52.3±6.8	53.1±7.2	0.462
Male, n (%)	42 (52.5%)	44 (55.0%)	0.749
BMI (kg/m^2)	28.1±3.5	28.9±3.8	0.154
FPG (mg/dL)	92.4±6.1	142.7±18.9	<0.001
HbA1c (%)	5.3±0.3	7.6±1.1	<0.001
Fasting Insulin (mIU/mL)	8.5 (6.2–11.1)	15.8 (11.9–20.3)	<0.001
HOMA-IR	1.9 (1.4–2.6)	5.5 (4.1–7.2)	<0.001
Total Cholesterol (mg/dL)	192±32	198±36	0.251
Triglycerides (mg/dL)	112 (88–145)	168 (132–215)	<0.001
HDL-C (mg/dL)	48±11	41±9	<0.001
LDL-C (mg/dL)	118±29	122±33	0.413

Data are mean ± SD or median (IQR). BMI: Body Mass Index; FPG: Fasting Plasma Glucose; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol.

Table II Serum ceramide species and metrnl levels.

Cer-16 (ng/mL)	248.5±78.2	392.7±119.5	<0.001
Cer-18 (ng/mL)	121.3±34.6	158.6±47.1	<0.01
Cer-24 (ng/mL)	345.2±105.8	275.4±98.3	<0.001
Cer-24:1 (ng/mL)	410.8 (332.5–505.1)	288.9 (225.4–370.2)	<0.001
Cer-16/Cer-24 Ratio	0.74±0.25	1.48±0.41	<0.001
Composite Ceramide Ratio*	0.54 (0.43–0.68)	1.12 (0.89–1.41)	<0.001
Metrnl (ng/mL)	162.4±44.7	89.3±30.5	<0.001

*Data are mean ± SD or median (IQR). Continuous variables are presented as mean ± SD for normally distributed variables and median (IQR) for non-normally distributed variables (Shapiro-Wilk test). Cer(d18:1/24:1) is reported as median (IQR) due to significant deviation from normality *Composite Ratio = (Cer-16 + Cer-18) / (Cer-24 + Cer-24:1).

Serum ceramide and Metrnl level

The T2DM group exhibited a significantly altered ceramide profile (Table II). Levels of Cer-16 and Cer-18 were markedly elevated, whereas levels of Cer-24 and Cer-24:1 were significantly lower compared to the control group. Consequently, the ratios of Cer-16/Cer-24 and (Cer-16+Cer-18)/ (Cer-24+Cer-24:1) were substantially higher in T2DM patients. Serum Metrnl concentration was approximately 45% lower in the T2DM group ($p<0.001$).

Correlation analyses

Cer-16 and Cer-18 showed strong positive correlations with HOMA-IR ($r=0.72$ and $r=0.59$, $p<0.001$) and HbA1c ($r=0.66$ and $r=0.53$, $p<0.001$). In contrast, Cer-24 and Metrnl demonstrated significant inverse correlations with HOMA-IR ($r=-0.47$ and $r=-0.71$, $p<0.001$) and HbA1c ($r=-0.41$ and $r=-0.65$, $p<0.001$). A significant negative correlation was also observed between serum Metrnl and Cer-16 levels ($r=-0.57$, $p<0.001$). Serum Metrnl concentration was inversely correlated with Cer(d18:1/16:0). These associations are observational and should be interpreted as correlations rather than evidence of causality.

Diagnostic performance of biomarkers

ROC curve analysis was performed to evaluate each biomarker's ability to discriminate T2DM patients from controls (*Table III*, *Figure 1*). Among single markers, Metrnl had the highest AUC (0.86), followed by Cer-16 (0.83) and the Cer-16/Cer-24 ratio (0.88). HOMA-IR, Cer-16, Cer-24, and serum

Table III Diagnostic performance of individual and combined biomarkers for T2DM.

Cer-16	0.83 (0.77–0.89)	>312 ng/mL	81.3	76.3	<0.001
Cer-24	0.70 (0.62–0.78)	305 ng/mL	72.5	62.5	<0.001
Cer-16/Cer-24 Ratio	0.88 (0.83–0.93)	>1.05	85.0	82.5	<0.001
Metrnl	0.86 (0.80–0.91)	118 ng/mL	82.5	80.0	<0.001
Combined Model (Score)	0.93 (0.89–0.97)	>0.67	90.0	86.3	<0.001

AUC: Area Under the ROC Curve; CI: Confidence Interval.

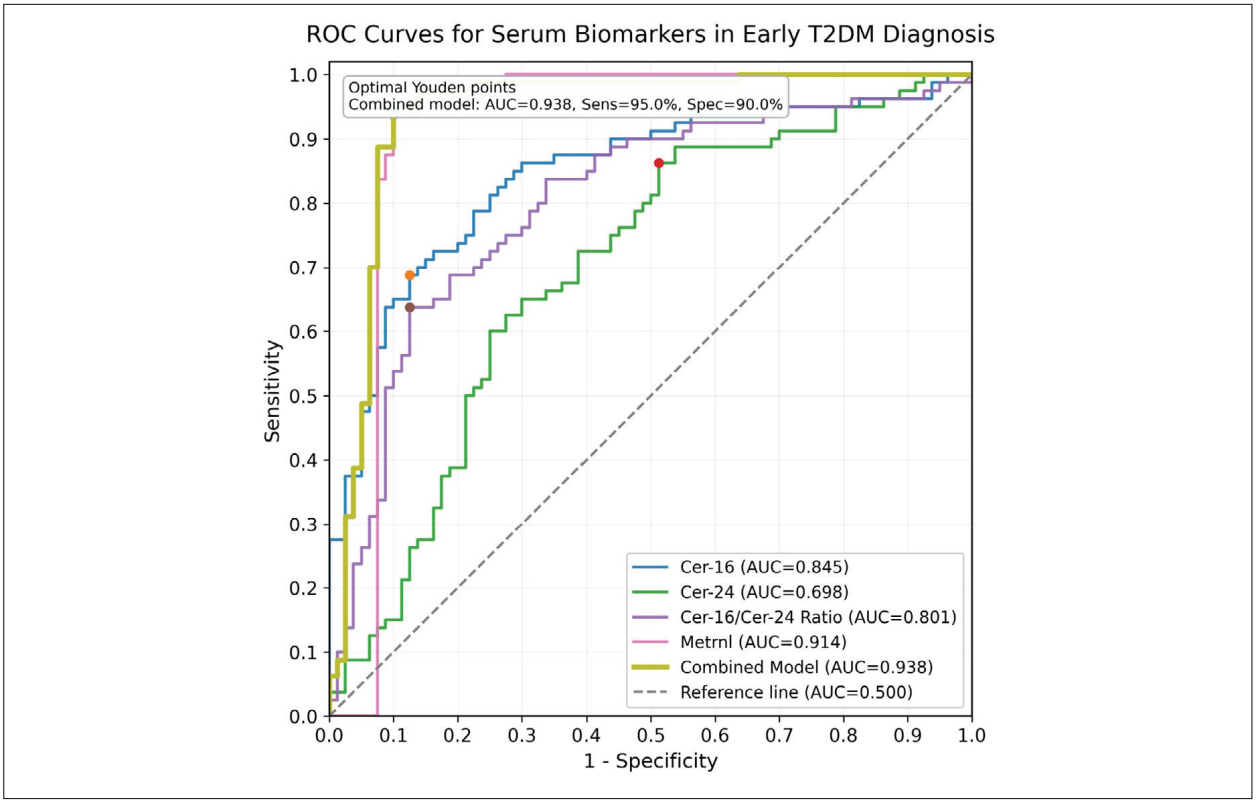

Figure 1 ROC curve analysis.

Metrnl. Backward elimination produced a final parsimonious model including Cer-16 and Metrnl (and other retained covariates).

Variables entered into the initial multivariable logistic regression included age, BMI, HOMA-IR, Cer-16, Cer-24, and serum Metrnl. Backward elimination produced a final parsimonious model including Cer-16 and Metrnl (and other retained covariates).

Binary logistic regression was used to create a combined model incorporating the most significant and independent variables from univariate analysis (Cer-16, Cer-24, and Metrnl). The resulting composite score demonstrated superior diagnostic performance, with an AUC of 0.93 (95% CI: 0.89–0.97), a sensitivity of 90.0%, and a specificity of 86.3% at the optimal cut-off point.

Discussion

This study provides compelling evidence for a distinct circulating signature in early-stage T2DM. This signature includes elevated saturated long- chain ceramides (Cer-16, Cer-18), diminished very- long-chain ceramides (Cer-24, Cer-24:1), and reduced Metrnl. Our findings align with and extend the current understanding of metabolic dysregulation. They highlight the synergistic

diagnostic potential of combining biomarkers from opposing pathophysiological axes.

The observed ceramide profile matches the »lipotoxic« model of insulin resistance. 19 Ceramides inhibit insulin signalling through the activity of the Akt/PKB signalling cascade and affect lipid metabolism. This idea is supported by original studies and recent comprehensive reviews (21, 22).

Elevated Cer-16, derived from palmitate, is a well-established inhibitor of Akt/PKB signalling in insulin-sensitive tissues (5, 23). Our finding of reduced Cer-24 and Cer-24:1 adds a new dimension. A deficit in these species may also be metabolically detrimental, possibly by altering membrane fluidity or specific signalling platforms (7, 24). The elevated Cer-16/Cer-24 ratio was a strong single biomarker (AUC=0.88). This supports its use as an integrated metric of ceramide-related risk, as suggested in cardiovascular studies (8, 25).

We found a significant reduction in serum Metrnl in T2DM patients, supporting its role as a protective metabolic hormone (12). Its strong inverse correlation with HOMA-IR supports preclinical data showing that Metrnl improves insulin sensitivity. The negative correlation between Metrnl and Cer-16 is novel and intriguing (13, 26).

The inverse association between Metrnl and Cer-16 observed in our study is purely correlational and does not allow any causal inference. This relationship, however, is biologically plausible and warrants mechanistic investigation. Potential hypotheses for future studies include: (i) Metrnl-induced adipose tissue browning and AMPK activation might reduce ceramide synthesis, (ii) ceramide-driven inflammation may secondarily suppress Metrnl expression, or (iii) both biomarkers could be regulated by common upstream factors such as saturated fatty acid load and low-grade inflammation (27, 28).

Although we observed an inverse association between circulating Metrnl and Cer-16, these findings are correlative and cannot establish directionality or causation. Preclinical studies indicate mechanistic plausibility for both axes: ceramides (particularly C16:0 species) impair insulin signalling via inhibition of the Akt/PKB pathway and related downstream effects on GLUT4 translocation, mitochondrial function, and inflammation, which could promote systemic insulin resistance (12, 13, 26).

Conversely, Metrnl has been shown in animal models to promote adipose browning, induce anti-inflammatory macrophage polarisation, and improve glucose homeostasis, suggesting potential protective or compensatory roles (27–29).

We therefore propose the following testable hypotheses for future mechanistic work: (1) decreased Metrnl signalling permits expansion of ceramide synthesis or impairs ceramide clearance;

(2) ceramide accumulation suppresses Metrnl expression/secretion in adipose or muscle; or (3) an upstream metabolic stressor (e.g., lipid oversupply) independently drives both low Metrnl and high Cer-16. A definitive evaluation of directionality will require targeted in vitro and in vivo experiments and longitudinal human studies.

The most significant contribution of this study is showing the synergistic diagnostic value. The combined model (Cer-16, Cer-24, Metrnl) achieved an excellent AUC of 0.93 and outperformed the best single marker. This supports the idea that T2DM is multifactorial. A biomarker panel reflecting multiple pathways, lipotoxicity (Cer-16), loss of protective lipid species (Cer-24), and deficiency of a beneficial adipomyokine (Metrnl), provides a more complete and accurate assessment of metabolic health than any single analyte (30, 31). This approach fits with the trend toward multi-marker panels for complex diseases (32, 33).

Limitations

The cross-sectional design prevents causal inference. The sample came from a single centre, and all T2DM patients were newly diagnosed. This may not represent the full disease spectrum. We did not measure other related sphingolipids or cytokines that could add context. Future prospective studies in larger, multi-ethnic cohorts, including those with prediabetes, are needed. These studies could validate our findings and assess the predictive value of this panel for T2DM progression (34).

A second limitation is the lack of information about food intake and physical activity. The composition of food, especially saturated fatty acids and other lipids, can affect ceramide synthesis and profiles. This can interfere with the observed associations. Metrnl is an adipomyokine induced by exercise and cold stress. Physical activity and recent exercise can significantly affect Metrnl levels in circulation. Without this information, the observed associations could be confounded by these factors (11, 35).

Another limitation of the current study is that comparisons were limited to newly diagnosed T2DM patients and normoglycemic controls. Therefore, the diagnostic specificity of the suggested ceramide-Metrnl panel for distinguishing T2DM from other relevant metabolic diseases, such as non-alcoholic fatty liver disease (NAFLD), metabolic syndrome, and prediabetes, has not been determined in the

current study. The current literature suggests that circulating ceramide levels are altered in NAFLD and metabolic syndrome; ceramide is associated with cardiometabolic disease in general, and it is conceivable that there is significant overlap among these diseases and T2DM, which could affect the specificity of the suggested ceramide-Metrnl panel for T2DM diagnosis. Future studies need to determine the performance of the suggested ceramide- Metrnl panel across different study arms, including prediabetes, NAFLD without diabetes, and metabolic syndrome, and to assess its predictive value for T2DM onset in prediabetes patients (18, 29).

Conclusion

In conclusion, a biomarker panel combining the serum ceramide profile (specifically the Cer-16/Cer-24 ratio) and Metrnl level offers high diagnostic accuracy for early T2DM. This panel captures the dual pathology of increased lipotoxicity and impaired metabolic defence, providing a pathophysiologically grounded tool that could aid in early detection, risk assessment, and, potentially, in monitoring the response to therapeutic interventions aimed at improving insulin sensitivity (36, 37).

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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