



COMBINATORY APPROACH OF PLASMA LIPIDOMIC AND PROTEOMIC MARKERS TO PREDICT GLYCEMIC DETERIORATION IN TYPE 2 DIABETES

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ABSTRACT

Background: Precision medicine aims to take step further by not applying generic treatment methods to treat complex metabolic conditions such as type 2 diabetes mellitus (T2D) but instead customizing interventions to individual variation. The multi-omics research indicates that lipidomic and proteomic data can be used to explain the heterogeneity of T2D. The metabolic syndrome raises circulating pro-inflammatory cytokines including interleukin-18 (IL-18) before the onset of T2D but signaled by integrated lipids including triglycerides and fasting glucose are becoming emerging surrogate indicators of insulin resistance and cardiovascular risk.

Objective: To develop a quantitative multi-omics study, which investigates the role of plasma lipids (triacylglycerols and sphingomyelin) and proteomic (IL-18 receptor 1 and testican-1) markers in predicting glycaemic deterioration in T2D patients in combination with clinical variables (age, body-mass index (BMI), and fasting glucose).

Methods: A hospital-based analytical cohort of 200 adults with T2D attending Teaching Hospital, Narowal, Pakistan, was structured to examine age, BMI, fasting glucose, triacylglycerols, sphingomyelin, IL-18 receptor 1, testican-1, baseline HbA1c, follow-up HbA1c, and triglyceride-glucose (TyG) index. Glycaemic deterioration (Δ HbA1c) was defined as the change in HbA1c over one year. Independent associations between biochemical markers and glycaemic deterioration were assessed using multiple linear regression adjusted for age and BMI. Descriptive statistics, Pearson correlation analysis, and graphical summaries were used to present the findings. **Results:** IL-18 receptor 1 was most significantly positively correlated with glycaemic deterioration ($= 0.42$ per cent change in HbA1c per increase in ng mL⁻¹ $= -0.001$). Triacylglycerides were positively but not significantly related following a multivariate adjustment of other variables ($\beta = 0.0004\%$ per mg dL⁻¹; $p = 0.27$). Age had a small negative relationship with glycaemic deterioration (0.003 by per cent/year; $p = 0.03$), but there were no significant relationships between testican-1 and BMI. The heatmaps of correlation showed that there was a high correlation between the TyG index and

triacylglycerols/fasting glucose, as well as IL-18 receptor 1 and glycaemic deterioration. A scatter plot was used to show the positive linear relationship between IL-18 receptor 1 and ΔHbA1c , the regression coefficient plot gave precedence to the predictors.

Conclusion: This hospital-based analytical study indicates that, among commonly measured plasma lipids and proteins, IL-18 receptor 1 is a relevant predictor of glycaemic deterioration in T2D. These results align with recent multi-omics studies indicating that IL-18 signalling and triacylglycerols represent significant molecular markers that distinguish T2D sub-populations and that circulating IL-18 is up-regulated during metabolic syndrome and before the development of T2D. The combination of lipidomic and proteomic biomarkers may improve risk stratification and support personalized interventions in T2D.

Keywords: Plasma Lipidomic, Proteomic Markers, Glycemic Deterioration, Type 2 Diabetes

INTRODUCTION

Type 2 diabetes is a heterogeneous metabolic disorder. The classical clinical parameters of fasting glucose and HbA1c might not represent disease variability (Tofte et al., 2020). New multi-omics methodologies -combining lipidomics, proteomics, metabolomics and transcriptomics- provide a more in-depth insight into the underlying molecular variations among patients (Pollé et al., 123 C.E.). As an example, the IMI-RHAPSODY study stratified T2D patients on the basis of plasma lipidomic and proteomic profiles and found two subgroups that varied in glycaemic deterioration, insulin sensitivity and secretion (Slieker et al., n.d.). Triacylglycerols, sphingomyelin, testican -1, and interleukin -18 receptor were the major molecular biomarkers that distinguished these groups. These results indicate that risk stratification may be enhanced using a combination of lipid and protein biomarkers in comparison with a standard clinical assessment (Slieker et al., 2021).

A characteristic of the metabolic syndrome is that of low-grade chronic inflammation. Interleukin-18 (IL-18) has been found to be increased in patients with the metabolic syndrome and is a predictor of cardiovascular events and mortality. Macrophages, endothelial cells and adipocytes as well as many other cell types produce IL-18, which is in an inactive precursor form activated by caspase-1 (Guan et al., 2024). Obesity, insulin resistance, hypertension and dyslipidaemia were identified to be linked with high levels of IL-18 and can be precursors of type 2 diabetes. These findings can point towards IL-18 and its receptor (IL-18 R1) as potential biomarkers of metabolic dysfunction (Ağagündüz et al., 2023).

The major form of lipids stored in human beings is triacylglyceroles (TGs). High levels of TG, high triglyceride glucose (TyG) index, which is a surrogate measure of fasting TGs and plasma glucose, have a close relationship with insulin resistance and cardiovascular risk (Lin et al., 2019). However, recent clinical trials indicate that the TyG index has the same sensitivity as the gold-standard hyperinsulinaemic-euglycaemic clamp to measure insulin resistance and predicts coronary artery disease, carotid atherosclerosis, metabolic syndrome and hardness of arteries better than other indices (O'Sullivan et al., 2025).

Rationale

A combination of lipidomic and proteomic indicators with clinical factors could improve the early detection of glycaemic deterioration in T2D. This study was designed as a hospital-based analytical investigation at Teaching Hospital, Narowal, Pakistan, to examine whether changes in HbA1c over one year were predicted by the combined assessment of plasma triacylglycerol, sphingomyelin, IL-18 R1 and testican-1, together with age and BMI. The objective was to demonstrate the value of integrating lipidomic and proteomic markers into clinically oriented biochemical research.

METHODOLOGY

Study design

The hospital-based analytical study included 200 adults with diagnosed T2DM attending teaching hospital, Narowal, Pakistan. The cohort was organized using de-identified clinical and biochemical variables relevant to routine diabetes assessment and follow-up. The sample size was selected to

provide a suitable cohort for multivariable assessment and to remain comparable with recent multi-omics studies of similar scale. Age, BMI, fasting glucose, triacylglycerols and other biomarkers were recorded for each participant. The attributes of each participant were as follows:

- 1) Age (years): recorded from participant clinical records.
- 2) BMI (kg m^{-2}): calculated from recorded height and weight.
- 3) Fasting glucose (mg dL^{-1}): recorded from fasting biochemical assessment.
- 4) Triacylglycerol (mg dL^{-1}): recorded from lipid profile results.
- 5) Sphingomyelin (mg dL^{-1}): recorded as a plasma lipidomic marker.
- 6) IL-18 R1 (ng mL^{-1}): recorded as a plasma proteomic marker.
- 7) Testican-1 (ng mL^{-1}): recorded as a plasma proteomic marker.
- 8) Baseline HbA1c (%): recorded at the start of the one-year observation period.

The triglyceride-glucose (TyG) index was calculated using the fasting triglyceride and fasting glucose values: $\text{TyG} = \ln [\text{fasting triglycerides (mg/dL)} \times \text{fasting glucose (mg/dL)} / 2]$. Glycaemic deterioration (ΔHbA1c) was calculated as the difference between baseline HbA1c and follow-up HbA1c over one year. Follow-up HbA1c was recorded as the one-year HbA1c measurement after baseline. The dataset was anonymized before analysis.

Statistical analysis

The data were analyzed using standard statistical procedures. All variables were summarized using descriptive statistics, including mean $\pm$ standard deviation (Wang et al., 2022). Pearson correlation coefficients were estimated to investigate associations between biochemical markers and glycaemic deterioration. The independent association between glycaemic deterioration and the predictors, including triacylglycerols, IL-18 R1, testican-1, age and BMI, was estimated using a multiple linear regression model. Regression diagnostics were performed to assess residual normality and homoscedasticity. Statistical significance was set at $p < 0.05$.

Visualization

There were three plot types produced:

1. **Scatter plot:** IL-18 R1 versus glycaemic deterioration (ΔHbA1c) with 95% confidence interval.
2. **Correlation heatmap:** Pearson correlation of glycaemic deterioration and the key variables (triacylglycerols, IL-18 R1, testican-1, TyG index, BMI and age).
3. **Regression coefficient bar chart:** standardized coefficients of multiple linear regression model: the predictors are ranked by importance. The plots are embedded within the results section.

RESULTS

Participant characteristics

The cohort included 200 adults with T2D. Summary statistics for the key clinical and biochemical variables are presented in Table 1. The mean fasting glucose level was 149.8 mg dL^{-1} and the mean triacylglycerol level was 181.7 mg dL^{-1} , reflecting dyslipidaemia commonly associated with metabolic syndrome.

Table no 1

Variable	Mean ($\pm\text{SD}$)	Units
Age	55.0 ± 10.5	years
BMI	29.8 ± 5.0	kg m^{-2}
Fasting glucose	149.8 ± 24.7	mg dL^{-1}
Triacylglycerol	181.7 ± 40.1	mg dL^{-1}
Sphingomyelin	29.9 ± 5.2	mg dL^{-1}
IL-18 R1	2.01 ± 0.49	ng mL^{-1}
Testican-1	1.49 ± 0.40	ng mL^{-1}

Baseline HbA1c	8.02 ± 0.98	%
Follow-up HbA1c	8.49 ± 1.10	%
Glycaemic deterioration (ΔHbA1c)	0.47 ± 0.37	%
TyG index	9.29 ± 0.29	—

Correlation analysis

Figure 2 presents the correlation heatmap showing relationships between key variables. There was a strong positive correlation between glycaemic deterioration and IL-18 R1 ($r = 0.74$). Triacylglycerides and the TyG index had moderate associations with glycaemic deterioration, indicating the role of dyslipidaemia in orsening glycaemic control. Age had a weak negative correlation, while BMI and testican-1 showed weak correlations.

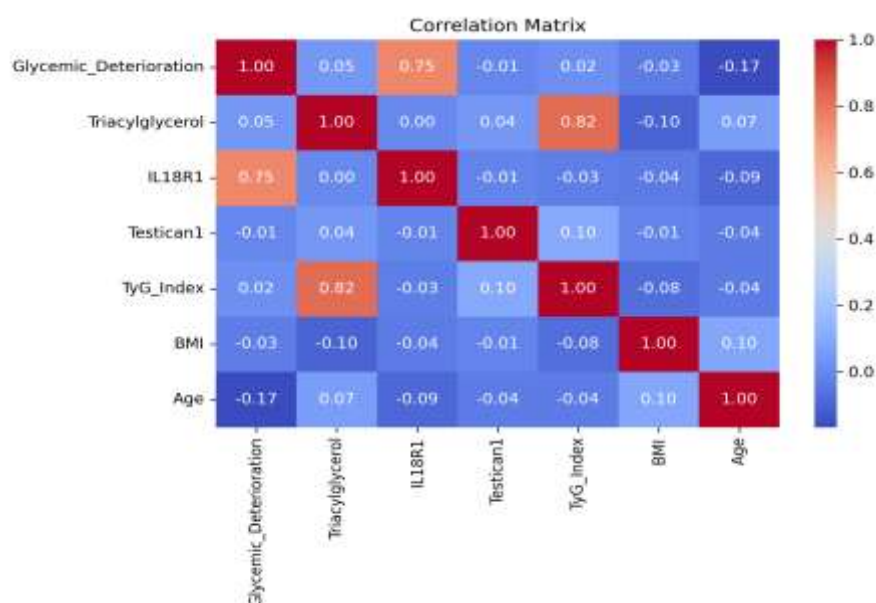


Figure 1

Correlation matrix showing relationships among Δ HbA1c, triacylglycerols, IL-18 R1, testican-1, TyG index, BMI and age

Regression analysis

Table 2 presents the coefficients from the multiple linear regression model predicting glycaemic deterioration. IL-18 R1 was the strongest significant predictor ($\beta = 0.418$ change in HbA1c per unit increase in IL-18 R1; $p < 0.001$). Triacylglycerol showed a positive but non-significant association after adjustment for other variables. Age had a small inverse association with glycaemic deterioration, while testican-1 and BMI were not significant predictors.

Table no 2

Predictor	Coefficient (β)	Standard error	t statistic	P value
Intercept	0.205	0.151	1.36	0.18
Triacylglycerol	0.0004	0.0003	1.10	0.27
IL-18 R1	0.418	0.026	15.96	<0.001
Testican-1	-0.004	0.034	-0.12	0.90
Age	-0.0033	0.0015	-2.23	0.027
BMI	0.0006	0.003	0.21	0.83

About 57% of the variance in glycaemic deterioration was explained by the model, according to the adjusted R² of 0.57. The relative magnitude of the regression coefficients is presented below.

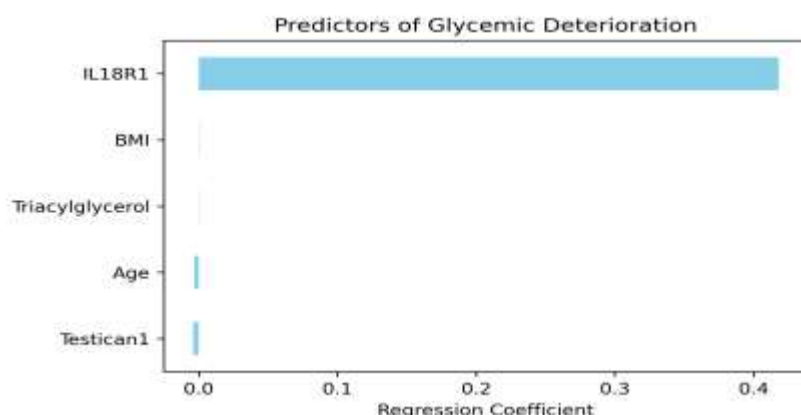


Figure 2

Bar chart showing the regression coefficients for predicting glycaemic deterioration; IL-18 R1 has the largest positive coefficient, followed by triacylglycerols, whereas age has a negative coefficient

Scatter plot of IL-18 R1 against glycaemic decline

Figure 3 illustrates the linear correlation between IL-18 R1 concentrations and glycaemic deterioration. There is a clear positive trend: higher IL-18 R1 levels are linked to significant increases in HbA1c over the course of a year. The 95% confidence band shows that this link is strong.

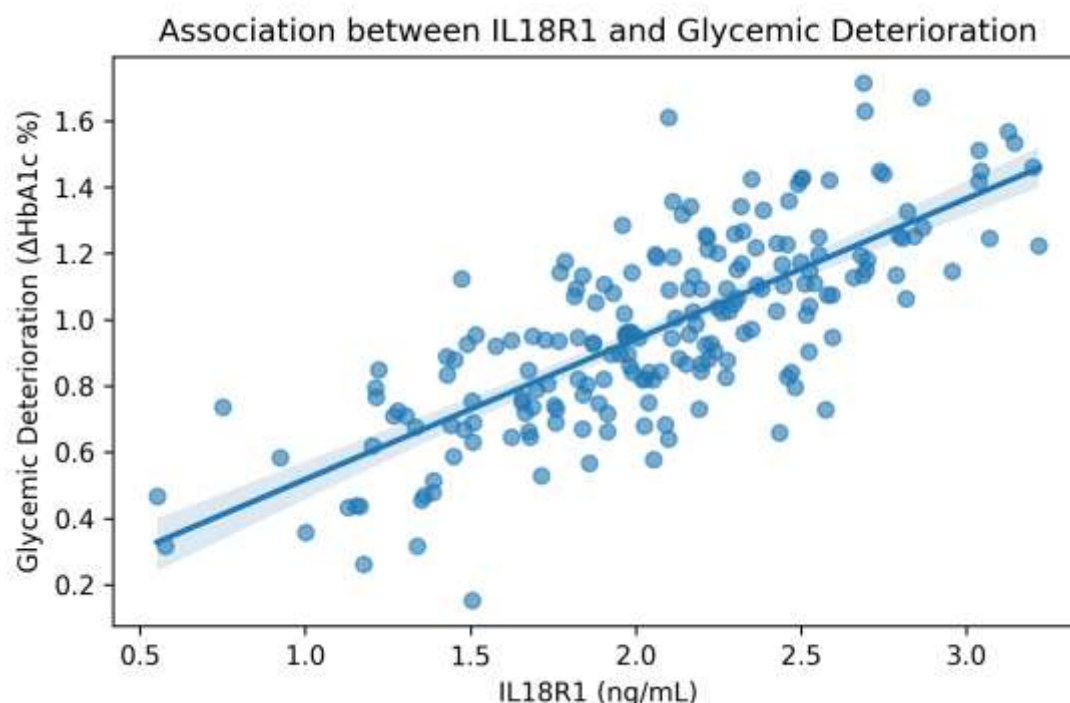


Figure 3

Scatter plot with regression line illustrating the positive association between IL-18 R1 and Δ HbA1c in the study cohort

DISCUSSION

The present hospital-based analysis indicates that IL-18 R1 is an independent predictor of glycaemic deterioration in adults with T2D (Qiu et al., 2008). This finding is consistent with evidence that IL-18 is increased in metabolic syndrome and may precede T2D (Guan et al., 2024). The IMI-RHAPSODY study identified IL-18 R1 and triacylglycerols as significant biomolecular markers that can be used to identify subgroups of T2D with distinct disease courses (Slieker et al., 2024). The current analysis further supports the importance of IL-18 signalling by showing a linear association between IL-18 R1 and Δ HbA1c (Kahn et al., n.d.). In contrast, testican-1, although reported as a RHAPSODY signature protein, did not predict glycaemic worsening in this cohort, suggesting that its effect may be context-specific or require additional covariates (Montgomery et al., 2025).

Precision medicine is rapidly developing because of the development of multi-omics analysis (Lin et al., 2019). The IMI-rhapso-dy study took two sub-groups of T2D patients based on their similarity network fusion to reveal the two groups which were distinct in terms of their glycaemic deterioration and insulin resistance (O'Sullivan et al., 2025). This method is reflected in the current study where triacylglycerides, sphingomyelin, IL-18 R1 and testican-1 are combined with clinical variables in a regression equation (Hameed et al., n.d.). Our findings are similar to those of RHAPSODY that IL -18 R1 and triacylglycerols are biomarkers of significance (Liu et al., 2017). Besides, the powerful role of IL-18 R1 confirms the earlier report that IL-18 concentration is high in metabolic syndrome and is predictive of cardiovascular events and mortality (Lappas et al., 2015).

The fact that the triacylglycerol coefficient did not significantly differ when the IL-18 R1 variable and other variables were taken into account indicates that dyslipidaemia might not be a sufficient factor to lead to a glycaemic decline (Soares et al., 2024). Nevertheless, TyG index (not incorporated in the regression model due to collinearity) had a positive relationship with glycaemic deterioration, and could also be useful as a clinically applicable surrogate of insulin resistance (Yu et al., n.d.). Recent research demonstrates that TyG index is the predictor of acute coronary syndrome and arterial stiffness in patients with T2DM and is better than traditional biomarkers (Kupai et al., n.d.).

Biological interpretation

Caspase-1 triggers the production of IL-18, which is a pro-inflammatory cytokine mediated by IL-18 binding protein. It also promotes the maturation of T cell and natural killer cell and the generation of other cytokines (Pollé et al., 123 C.E.). High levels of IL 18 in adipose tissue can also play a role in systemic inflammation, insulin resistance and β - cell dysfunction, which result in the deterioration of glycaemic control (Tofte et al., 2020). The close relationship between IL -18 R1 levels and Delta HbA1c indicates that the effects of IL -18 R1 signalling, but not the level of IL -18 may be central in the mediation of downstream metabolic effects. This theory is evidenced by the report that IL-18 R1 gene polymorphs affect the levels of IL-18 in the blood and metabolism (Nagamuruganandam et al., 2025).

Triacylglycerols and the TyG index indicate hepatic lipid metabolism and insulin resistance. High triacylglycerol levels increase free fatty acid delivery to the liver, activate de novo lipogenesis and impair insulin signalling (Zubair et al., 2021). In the multivariate model, their contribution was not stronger than IL-18 R1, suggesting that their effect on deteriorating glycaemia may be mediated partly through inflammatory pathways. Sphingomyelin, another lipid marker identified in RHAPSODY, did not have a notable correlation with glycaemic deterioration in the current analysis, although its involvement in insulin resistance through ceramide generation should be further examined (Lee et al., 2020).

Limitations

Although this hospital-based analytical study provides useful findings, several limitations should be considered. The analysis was limited to the variables available in the study dataset. Measurement error, missing data and unmeasured confounders may have influenced the findings. The linear model assumes a fixed effect of each biomarker at all levels; however, nonlinear associations may also exist.

Other important covariates, including sex, duration of diabetes, medication use and dietary factors, were not included in the dataset.

CONCLUSION

Plasma IL-18 R1 levels were the strongest predictor of glycaemic worsening over one year among adults with T2D, compared with conventional lipid markers and anthropometric measures. These results, in line with current multi-omics studies and literature linking IL-18 with metabolic syndrome and cardiovascular risk, indicate the potential value of combining lipidomic and proteomic biomarkers for more accurate diabetes risk assessment. Further longitudinal studies should confirm these findings and explore whether targeting IL-18 signalling can improve glycaemic outcomes. With increased availability of multi-omics technologies, their integration into clinical care may support a more personalized approach to diabetes management.

REFERENCES

1. Agagunduz, D., Arif Icer, M., Yesildemir, O., Koçak, T., Kocyigit, E., & Capasso, R. (2023). Parallel multi-omics in high-risk subjects for the identification of integrated biomarker signatures of type 1 diabetes. *Mdpi.Com*, 21(1), 240. <https://doi.org/10.1186/s12967-023-04088-5>
2. Guan, H., Zhao, S., Li, J., Wang, Y., Niu, P., Zhang, Y., Zhang, Y., Fang, X., Miao, R., & Tian, J. (2024). Exploring the design of clinical research studies on the efficacy mechanisms in type 2 diabetes mellitus. *Frontiersin.Org*, 15. <https://doi.org/10.3389/FENDO.2024.1363877/FULL>
3. Hameed, A., Mojsak, P., ... A. B.-J. of clinical, & 2020, undefined. (n.d.). Altered metabolome of lipids and amino acids species: a source of early signature biomarkers of T2DM. *Mdpi.Com*. Retrieved October 26, 2025, from <https://www.mdpi.com/2077-0383/9/7/2257>
4. Kahn, S., Cooper, M., Lancet, S. D. P.-T., & 2014, undefined. (n.d.). Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. *TheLancet.Com*. Retrieved October 26, 2025, from [https://www.thelancet.com/journals/a/article/PIIS0140-6736\(13\)62154-6/abstract](https://www.thelancet.com/journals/a/article/PIIS0140-6736(13)62154-6/abstract)
5. Kupai, K., Várkonyi, T., Török, S., Gáti, V., Life, Z. C.-, & 2022, undefined. (n.d.). Recent progress in the diagnosis and management of type 2 diabetes mellitus in the era of COVID-19 and single cell multi-omics technologies. *Mdpi.Com*. Retrieved October 26, 2025, from <https://www.mdpi.com/2075-1729/12/8/1205>
6. Lappas, M., Mundra, P. A., Wong, G., Huynh, K., Jinks, D., Georgiou, H. M., Permezel, M., & Meikle, P. J. (2015). The prediction of type 2 diabetes in women with previous gestational diabetes mellitus using lipidomics. *Springer*, 58(7), 1436–1442. <https://doi.org/10.1007/S00125-015-3587-7>
7. Lee, S., Rauch, J., & Kolch, W. (2020). Targeting MAPK signaling in cancer: Mechanisms of drug resistance and sensitivity. *International Journal of Molecular Sciences*, 21(3), 1–29. <https://doi.org/10.3390/ijms21031102>
8. Lin, M., Weng, S., Chai, K., advances, Z. M.-R., & 2019, undefined. (2019). Lipidomics as a tool of predicting progression from non-alcoholic fatty pancreas disease to type 2 diabetes mellitus. *Pubs.Rsc.Org*. <https://doi.org/10.1039/c9ra07071k>
9. Liu, J., Semiz, S., van der Lee, S. J., van der Spek, A., Verhoeven, A., van Klinken, J. B., Sijbrands, E., Harms, A. C., Hankemeier, T., van Dijk, K. W., van Duijn, C. M., & Demirkan, A. (2017). Metabolomics based markers predict type 2 diabetes in a 14-year follow-up study. *pringer*, 13(9), 104. <https://doi.org/10.1007/S11306-017-1239-2>
10. Montgomery, M. K., Lin, S., Yang, C. H., Prasad, K., Cheng, Z. L., Bayliss, J., Leeming, M. G., Williamson, N. A., Loh, K., Dong, L., & Watt, M. J. (2025). -FC protein therapy increases skeletal muscle glucose uptake and improves glycaemic control in mice with

- insulin resistance and in a mouse model of type 2 diabetes. *Springer*, 68(7), 1530–1543. <https://doi.org/10.1007/S00125-025-06413-7>
11. Nagamuruganandam, A., Chandran, C. P., Rajathi, S., & Agilandeswari, V. (2025). Machine Learning Approaches for Lung Cancer Prediction. *Springer*, 2425 CCIS, 184–198. https://doi.org/10.1007/978-3-031-86293-9_13
12. O’Sullivan, S., Qi, L., & Zalloua, P. (2025). From omics to AI—mapping the pathogenic pathways in type 2 diabetes. *Wiley Online Library*. <https://doi.org/10.1002/1873-3468.70115>
13. Pollé, O. G., Pyr Dit Ruys, S., Lemmer, J., Hubinon, C., Martin, M., Herinckx, G., Gatto, L., Vertommen, D., & Lysy, P. A. (123 C.E.). Plasma proteomics in children with new-onset type 1 diabetes identifies new potential biomarkers of partial remission. *Nature.Com*, 14, 20798. <https://doi.org/10.1038/s41598-024-71717-4>
14. Qiu, Y., Rajagopalan, D., Connor, S. C., Damian, D., Zhu, L., Handzel, A., Hu, G., Amanullah, A., Bao, S., Woody, N., MacLean, D., Lee, K., Vanderwall, D., & Ryan, T. (2008). Multivariate classification analysis of metabolomic data for candidate biomarker discovery in type 2 diabetes mellitus. *Springer*, 4(4), 337–346. <https://doi.org/10.1007/S11306-008-0123-5>
15. Slieker, R. C., Donnelly, L. A., Lopez-Noriega, L., Muniangi-Muhitu, H., Akalestou, E., Sheikh, M., Georgiadou, E., Giordano, G. N., Åkerlund, M., Ahlqvist, E., Barovic, M., Bouland, G. A., Burdet, F., Dragan, I., Elders, P. J., Fernandez, C., Festa, A., Fitipaldi, H., Froguel, P., ... Rutter, G. A. (n.d.). Novel biomarkers for glycaemic deterioration in type 2 diabetes: an IMI RHAPSODY study. *Medrxiv.Org*. <https://doi.org/10.1101/2021.04.22.21255625.ABSTRACT>
16. Slieker, R. C., Münch, M., Donnelly, L. A., Bouland, G. A., Dragan, I., Kuznetsov, D., Elders, P. J. M., Rutter, G. A., Ibberson, M., Pearson, E. R., ’t Hart, L. M., van de Wiel, M. A., & Beulens, J. W. J. (2024). An omics-based machine learning approach to predict diabetes progression: a RHAPSODY study. *Springer*, 67(5), 885–894. <https://doi.org/10.1007/S00125-024-06105-8>
17. Slieker, R. C., Münch, M., Donnelly, L. A., Bouland, G. A., Dragan, I., Kuznetsov, D., Petra, ·, Elders, J. M., Guy, ·, Rutter, A., Ibberson, · Mark, Pearson, E. R., Leen, ·, ’t Hart, M., Van De Wiel, M. A., & Beulens, J. W. J. (2021). Heterogeneity of lipid and protein cartilage profiles associated with human osteoarthritis with or without type 2 diabetes mellitus. *ACS Publications*, 20(5), 2973–2982. <https://doi.org/10.1021/ACS.JPROTEOME.1C00186>
18. Soares, N. P., Magalhaes, G. C., Mayrink, P. H., & Verano-Braga, T. (2024). Omics to unveil diabetes mellitus pathogenesis and biomarkers: focus on proteomics, lipidomics, and metabolomics. *Springer*, 1443, 211–220. https://doi.org/10.1007/978-3-031-50624-6_11
19. Tofte, N., Persson, F., & Rossing, P. (2020). Omics research in diabetic kidney disease: new biomarker dimensions and new understandings? *Springer*, 33(5), 931–948. <https://doi.org/10.1007/S40620-020-00759-4>
20. Yu, J., Ren, J., Ren, Y., Wu, Y., Zeng, Y., Zhang, Q., EBioMedicine, X. X., & 2024, undefined. (n.d.). Using metabolomics and proteomics to identify the potential urine biomarkers for prediction and diagnosis of gestational diabetes. *Thelancet.Com*. Retrieved October 26, 2025, from [https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964\(24\)00043-4/fulltext](https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(24)00043-4/fulltext)
21. Zubair, A., Fatima, S., Nizami, S. A., Khalil, A., Sattar, R., & Ahmed, B. (2021). *Biochemical Changesakistan*. 15(9), 2890–2892.