

Physical Activity, Myokine–Adipokine Signatures and Haemoglobin Glycation Index in Adults with Type 2 Diabetes

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Background: The Hemoglobin Glycation Index (HGI) reflects variability in hemoglobin glycation beyond ambient glycaemia and is a marker of metabolic heterogeneity, cardiovascular risk and treatment response in type 2 diabetes mellitus (T2DM). Whether circulating myokines and adipokines are related to HGI, or whether relationships differ across exercise modalities, is unclear.

Objective: To examine associations of circulating myokines (irisin, myostatin, myonectin, IL-6, IL-15) and adipokines (leptin, adiponectin) with HGI, and whether associations differ between physically active and sedentary individuals and across exercise modalities.

Methods: Cross-sectional study of 185 adults with T2DM recruited at Thumbay Hospital, Ajman, United Arab Emirates, classified as physically active (n=98) or sedentary (n=87), with active individuals sub-grouped by predominant modality: aerobic (70), resistance (11), combined (17). Measurements were obtained after an overnight fast. HGI was calculated as the residual of HbA1c regressed on fasting plasma glucose. Mann–Whitney U, Kruskal–Wallis, Spearman correlations with false discovery rate (FDR) correction and median regression adjusted for age, sex, BMI and fasting glucose were used.

Results: Active participants had lower HGI than sedentary participants (median -0.44 vs 0.12 ; $p = 0.001$), with lower BMI, fasting glucose and HbA1c. HGI differed by modality ($p < 0.001$), most favourable in the combined-training group and least favourable in the aerobic-only group. IL-6 was inversely correlated with HGI in active participants and leptin in sedentary participants (both FDR $p < 0.05$). Physical activity remained an independent predictor of lower HGI after adjustment for age, sex and BMI ($\beta = -0.65$; $p < 0.001$), and persisted after adjustment for IL-15 and leptin.

Conclusion: Precludes causal inference; if confirmed prospectively, associations may inform individualized exercise prescription and HGI-based risk stratification.

Distinct myokine–adipokine signatures were associated with glycation variability beyond mean glycaemia and combined aerobic-plus-resistance training with the most favourable HGI profile. The cross-sectional design precludes causal inference; if confirmed prospectively, associations may inform individualized exercise prescription and HGI-based risk stratification.

Keywords: type 2 diabetes, hemoglobin glycation index, myokines, adipokines, exercise modality

Introduction

Type 2 diabetes mellitus (T2DM) is a heterogeneous metabolic disorder characterised by insulin resistance, progressive β -cell dysfunction and chronic hyperglycaemia, affecting more than 537 million adults worldwide and projected to exceed 783 million by 2045.^{1,2} Glycated haemoglobin (HbA1c) is the cornerstone of long-term glycaemic monitoring and a key predictor of microvascular and macrovascular complications.^{3,4} Yet HbA1c is not solely determined by mean

Graphical Abstract



glycaemia: erythrocyte lifespan, intracellular glucose handling, oxidative stress and inter-individual differences in protein glycation kinetics all contribute to discordance between measured HbA1c and the value predicted from ambient glucose.^{5–7}

This biological discordance is captured by the Hemoglobin Glycation Index (HGI), originally proposed by Hempe and colleagues as the residual of HbA1c regressed on fasting plasma glucose (FPG).^{5,6} Individuals with a high HGI display higher HbA1c than expected for their glycaemia, whereas those with low HGI display lower HbA1c than expected. Beyond statistical curiosity, HGI tracks within individuals over time, is partially heritable and is associated with insulin resistance, carotid atherosclerosis and an excess of severe hypoglycemia and cardiovascular events under intensive glycaemic treatment in the ACCORD cohort.^{6–9} HGI is therefore increasingly viewed as a clinically meaningful marker of metabolic phenotype rather than a measurement artefact.

Clinically, HGI can be derived from routinely measured HbA1c and fasting glucose without additional testing, making it a low-cost candidate for flagging patients whose glycation propensity diverges from their mean glycaemia.

Skeletal muscle is now recognised as a major endocrine organ secreting myokines that act locally and systemically to regulate glucose, lipid and inflammatory pathways.^{10,11} Among these, irisin and IL-6 promote insulin sensitivity and glucose handling,^{12,13} IL-15 and myonectin coordinate muscle–fat metabolic coupling,^{14,15} and myostatin acts as a negative regulator of muscle mass whose elevation tracks insulin resistance and obesity.^{16,17} On the adipose side, leptin and adiponectin reflect, respectively, fat mass and insulin-sensitizing capacity, and both are remodeled by physical activity.^{18,19}

These seven biomarkers were prioritized because each offers a plausible mechanistic link between muscle–adipose signalling and the determinants of haemoglobin glycation including insulin sensitivity, oxidative stress and erythrocyte glucose handling rather than as an exhaustive survey of the secretome.

Exercise is a cornerstone non-pharmacological intervention in T2DM, lowering HbA1c, improving lipid profile and modifying body composition.^{20,21} Aerobic, resistance and combined modalities exert overlapping but distinct effects: aerobic training primarily enhances mitochondrial and oxidative capacity, resistance training increases muscle mass and insulin signalling, and combined training is hypothesized to engage both pathways simultaneously. Consistent with this, combined regimens have produced the largest HbA1c reductions in randomised trials,^{22,23} making them a plausible candidate for influencing glycation biology beyond single-modality exercise. However, it remains unknown whether HGI itself differs across exercise modalities, and whether circulating myokine–adipokine profiles track this glycation variability, in clinical T2DM populations. To our knowledge, no prior study has jointly examined exercise modality, muscle–adipose biomarkers and HGI in adults with T2DM, and none has done so in a Gulf population, where the burden of T2DM is among the highest globally.²⁴

In the United Arab Emirates, the burden of T2DM is among the highest globally, with the International Diabetes Federation reporting an adult diabetes prevalence of 16.3% in 2019,²⁴ underscoring the regional importance of identifying modifiable correlates of glycaemic risk.

Accordingly, the present cross-sectional study had three aims: (i) to compare HGI between physically active and sedentary adults with T2DM; (ii) to characterise myokine–adipokine differences across exercise modalities (aerobic, resistance, combined); and (iii) to test the association of irisin, myostatin, myonectin, IL-6, IL-15, leptin and adiponectin with HGI overall and within activity strata, using non-parametric and robust regression techniques.

The present study differs from earlier exercise–biomarker work in diabetes in four respects: it is set in a Gulf (UAE) T2DM population; it profiles myokines and adipokines simultaneously rather than in isolation; it uses HGI, rather than HbA1c, as the glycaemic outcome; and it stratifies associations by exercise modality. To our knowledge, this combination has not previously been examined.

We hypothesized that physical activity would be associated with lower HGI, that combined aerobic-plus-resistance training would show the most favourable HGI profile, and that the associations of myokines and adipokines with HGI would differ between active and sedentary individuals.

Materials and Methods

Study Design and Setting

This was a cross-sectional, observational study conducted between [15th January 2025] and [31st October 2025] at the diabetes outpatient clinic of Thumbay University Hospital, Ajman, United Arab Emirates, in collaboration with Thumbay Labs. The protocol was approved by the Institutional Review Board of Gulf Medical University (**Ref. no. IRB-COHS-STD-131-Dec-2024**) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent before enrolment.

Participants

Adults aged 18 years or older with a physician-confirmed diagnosis of T2DM (according to American Diabetes Association criteria)¹ were eligible. Exclusion criteria were type 1 diabetes; gestational diabetes or pregnancy; haemoglobinopathies, recent blood transfusion (within 3 months) or chronic anaemia, all of which can confound HbA1c interpretation; chronic kidney disease (eGFR < 30 mL/min/1.73 m²); chronic liver disease; active malignancy; ongoing systemic corticosteroid therapy; and physical disability precluding habitual exercise. After screening, 185 participants met the inclusion criteria and constituted the analytical sample.

The required sample size was estimated using G*Power 3.1.9.7. For a two-tailed Spearman rank correlation, assuming a medium effect size ($\rho = 0.3$), a significance level of $\alpha = 0.05$ and statistical power of 80%, a minimum of 85 participants was required (incorporating an upward adjustment relative to the Pearson model to account for the lower asymptotic efficiency of the Spearman coefficient). To accommodate stratified analyses by physical activity status, account for measurement variability and ensure robust subgroup comparisons, a target of 100–120 participants was considered appropriate. The final enrolled sample of 185 participants exceeded this target, providing adequate power to detect moderate correlations ($|\rho| \geq 0.28$) within each activity stratum (active $n = 98$; sedentary $n = 87$). Modality-stratified comparisons within the active group remained underpowered given the small resistance ($n = 11$) and combined-training ($n = 17$) subgroups and are therefore considered exploratory and hypothesis-generating.

Demographic and Anthropometric Assessment

Age, sex and current glucose-lowering therapy were recorded by structured interview. Body weight (kg) and height (m) were measured in light clothing without shoes using calibrated equipment. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²) and categorized per World Health Organization criteria.²⁵

Physical Activity Assessment

Habitual physical activity over the preceding three months was assessed using a standardised questionnaire adapted from the International Physical Activity Questionnaire (IPAQ) short form.²⁶ The IPAQ short form is a validated instrument, but no objective measure (eg, accelerometry) was used to corroborate self-reported activity in this cohort. Participants reporting at least 150 minutes per week of moderate-to-vigorous structured exercise on ≥ 3 days per week were classified as active; those below this threshold were classified as sedentary. Active participants were further classified by predominant exercise modality:

- Aerobic (eg, walking, jogging, cycling, swimming);
- Resistance (eg, weight training, resistance bands);
- Combined (regular practice of both aerobic and resistance modalities, ≥ 1 session per week of each).

Biochemical Analyses

Venous blood was collected after an overnight fast of at least 8 hours. Fasting plasma glucose (FPG; Ref. OSR6121) and HbA1c (HbA1c; Ref. B00389) were measured at Thumbay Labs using the hexokinase method and a turbidimetric immunoinhibition, respectively on the Beckman Coulter AU/DxC 700 platform. Serum was separated by centrifugation at $3000 \times g$ for 10 min and stored at -80°C until batch analysis.

A multiplex panel of five myokines interleukin-6 (IL-6), interleukin-15 (IL-15), irisin, myostatin, and myonectin and two adipokines leptin, adiponectin was quantified using commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kits, according to each manufacturer's protocol.

Myokines

IL-6 (Cat. No. ELK1156; ELK Biotechnology, Wuhan, China) selected as the most extensively characterized pleiotropic myokine, also secreted by adipose tissue, and a central mediator of the muscle–adipose inflammatory axis.

IL-15 (Cat. No. ELK1146; ELK Biotechnology, Wuhan, China) selected as a predominantly muscle-derived myokine implicated in skeletal muscle insulin sensitivity and muscle–adipose crosstalk.

Irisin (Cat. No. ELK6625; ELK Biotechnology, Wuhan, China) selected as an exercise-induced adipomyokine released from the proteolytic cleavage of FNDC5, implicated in white-adipose browning and glucose homeostasis.

Myostatin (Cat. No. ELK5288; ELK Biotechnology, Wuhan, China) selected as a TGF- β superfamily member and negative regulator of skeletal-muscle mass, whose elevation in T2DM is associated with insulin resistance.

Myonectin (CTRP15) (Cat. No. ELK7647; ELK Biotechnology, Wuhan, China) selected as a recently characterized myokine involved in fatty-acid uptake and metabolic coupling between muscle and adipose tissue.

Adipokines

Leptin (Cat. No. ELK1160; ELK Biotechnology, Wuhan, China) selected for its central role in energy homeostasis and its reciprocal relationship with adiposity and insulin resistance.

Adiponectin (Cat. No. ELK1233; ELK Biotechnology, Wuhan, China) selected as the principal insulin-sensitizing, anti-inflammatory adipokine, typically reduced in T2DM.

All assays standards were performed in duplicate along with samples from active and sedentary participants distributed evenly across plates to minimize batch effects.

Intra- and inter-assay coefficients of variation were consistent with manufacturer specifications. Quality control was maintained by including standard curves and control samples on every plate, averaging duplicate readings, blank-correcting, and re-analyzing any sample with optical density outside the calibration range at an adjusted dilution.

Washing steps were carried out on a semi-automated microplate washer (Tecan HydroFlex, Serial No. 12,050,000,331; Tecan Group Ltd., Männedorf, Switzerland) to ensure consistency and reduce background signal. Optical density was read at 450 nm on a TECAN Sunrise Basic microplate reader (Serial No. 1,205,000,443). Duplicate OD readings were averaged, blank-corrected, and fitted to a four- or five-parameter logistic standard curve using GainData (Arigo Biolaboratories), a web-based curve-fitting platform. Final concentrations were back-calculated using the appropriate dilution factor. Samples yielding OD values outside the calibration range were re-analyzed at an adjusted dilution.

Calculation of the Hemoglobin Glycation Index

HGI was calculated according to Hempe et al^{5,6} as the residual of HbA1c regressed on FPG within the present cohort:

$$\text{Predicted HbA1c}(\%) = a + b \times \text{FPG}(\text{mg/dL})$$

$$\text{HGI} = \text{Observed HbA1c} - \text{Predicted HbA1c}$$

Where the constants a and b were derived from linear regression of HbA1c on FPG using all 185 participants. Negative HGI values indicate lower-than-predicted HbA1c; positive values indicate higher-than-predicted HbA1c.

Statistical Analysis

Distribution of continuous variables was inspected using histograms and the Shapiro–Wilk test; non-Gaussian distributions were observed for the majority of biomarkers. Accordingly, continuous data are reported as median (interquartile range, IQR) and analyzed with non-parametric or robust methods. Categorical data are reported as frequency (percentage).

Median (quantile) regression was chosen in preference to ordinary least-squares linear regression because HGI was non-normally distributed and contained outliers. Quantile regression models the conditional median, is robust to non-normality and extreme values, and does not rely on the normality-of-residuals and homoscedasticity assumptions required by linear regression.

The resistance ($n = 11$) and combined ($n = 17$) subgroups were small and underpowered for modality comparisons and interaction terms, which are therefore considered exploratory and hypothesis-generating.

Two-group comparisons (active vs sedentary) used the Mann–Whitney U -test with rank-biserial correlation as effect size. Three-group comparisons (aerobic vs resistance vs combined) used the Kruskal–Wallis test with epsilon-squared (ϵ^2) as effect size; significant omnibus results were followed by Dunn's post-hoc test with Bonferroni correction. Spearman rank correlations were used to examine biomarker–HGI relationships, separately within active and sedentary strata. To account for multiple testing across biomarkers, the Benjamini–Hochberg false discovery rate (FDR) procedure was applied within each analytical family.

The comparison of HGI between active and sedentary participants and the multivariable median regression of activity status on HGI were pre-specified as the primary analyses; biomarker–HGI correlations and modality subgroup comparisons were exploratory and hypothesis-generating.

Multivariable quantile (median) regression was used to model HGI given its non-normal distribution and to limit the influence of extreme values. Seven nested models were fitted: (Model 1) physical activity status only; (Model 2) adjusted for age, sex and BMI; (Model 3) Model 2 plus FPG; (Model 4) Model 2 plus selected biomarkers (IL-6, IL-15, leptin); and Models 5–7 testing activity $\times$ biomarker interactions for IL-15, leptin and IL-6, respectively.

The biomarkers entered in Model 4 (IL-6, IL-15 and leptin) were pre-selected on mechanistic grounds and because they showed the strongest stratum-specific associations with HGI in bivariate analysis.

A two-sided p -value < 0.05 was considered statistically significant. Analyses were performed in Python (v3.11) using the pandas, scipy, statsmodels and pingouin libraries, and SPSS v30 (IBM Corp., Armonk, NY, USA).

Results

Demographic and Clinical Characteristics

A total of 185 adults with T2DM were analyzed. The cohort was predominantly male (124/185, 67%) with a median age in the 45–59 year category (88/185, 47.6%); 53 participants (28.6%) were younger than 45 years and 44 (23.8%) were older than 60 years. Excess adiposity was prevalent: 38.9% of participants were overweight, and 32.9% met criteria for obesity (Class I 21.6%, Class II 8.1%, Class III 3.2%), while 25.9% had normal BMI and 2.2% were underweight. Ninety-eight participants (53%) were classified as physically active and 87 (47%) as sedentary; among active participants, aerobic exercise was the most common modality (70/98, 71.4%), followed by combined (17/98, 17.3%) and resistance training (11/98, 11.2%) (Table 1). Glucose-lowering therapy consisted predominantly of metformin monotherapy, with smaller proportions on combination oral therapy including DPP-4 inhibitors and/or sulfonylureas; medication distributions were broadly comparable between active and sedentary participants.

Metabolic and Biomarker Profiles by Physical Activity Status

Active participants exhibited significantly more favourable glycaemic and anthropometric profiles than sedentary participants (Table 2). Active participants had lower fasting glucose (median 127, IQR 119–153 vs 150, IQR 130–200 mg/dL; $p < 0.001$, $r = -0.35$), HbA1c (6.84%, IQR 6.49–8.04 vs 8.07%, IQR 7.14–9.61; $p < 0.001$, $r = -0.42$) and BMI (26.0, IQR 23.7–30.3 vs 28.7, IQR 26.5–33.5 kg/m²; $p < 0.001$, $r = -0.34$), with medium-to-large effect sizes. All three differences remained significant after FDR adjustment.

Among myokines and adipokines, myostatin (median 7.13 vs 7.90 ng/mL; $p = 0.030$) and adiponectin (median 14.4 vs 15.4 ng/mL; $p = 0.017$) differed significantly between groups. After FDR correction, adiponectin remained higher in sedentary participants (FDR $p = 0.039$), whereas the myostatin difference became borderline (FDR $p = 0.062$). Irisin, myonectin, IL-6, IL-15 and leptin did not differ significantly between activity strata before or after FDR correction (Table 3).

Table 1 Demographic and Anthropometric Characteristics of the Study Population (n = 185)

Variable	Group	n	%
Age group (WHO)	<45	53	28.6
	45–59	88	47.6
	>60	44	23.8
Gender	Female	61	33.0
	Male	124	67.0
BMI (WHO)	Underweight	4	2.2
	Normal	48	25.9
	Overweight	72	38.9
	Obesity Class I	40	21.6
	Obesity Class II	15	8.1
	Obesity Class III	6	3.2
Physical activity status	Active	98	53.0
	Sedentary	87	47.0
Exercise subgroup ^a	Aerobic	70	71.4
	Resistance	11	11.2
	Combined	17	17.3

Notes: Age and BMI categories follow WHO criteria. Data are presented as frequency (n) and percentage (%). ^aExercise-subgroup percentages are expressed relative to the 98 physically active participants (aerobic, resistance, and combined aerobic–resistance training).

Abbreviations: BMI, body mass index; WHO, World Health Organization.

Table 2 Metabolic and Anthropometric Parameters in Active vs Sedentary Participants

Variable	Active (n = 98) Median (IQR)	Sedentary (n = 87) Median (IQR)	p	Effect Size r
Fasting glucose (mg/dL)	127 (119–153)	150 (130–200)	<0.001	–0.35
HbA1c (%)	6.84 (6.49–8.04)	8.07 (7.14–9.61)	<0.001	–0.42
BMI (kg/m ²)	26.0 (23.7–30.3)	28.7 (26.5–33.5)	<0.001	–0.34
Weight (kg)	80.0 (68.5–85.0)	82.0 (72.1–96.5)	0.068	–0.16

Notes: Data are median (IQR). Comparisons used the Mann–Whitney U-test; $r = Z/\sqrt{N}$ (values of ≈0.1, 0.3 and 0.5 denote small, medium and large effects). Negative r indicates lower values in the active group. Highlighted rows are significant at $p < 0.05$.

Abbreviations: HbA1c, glycated haemoglobin; BMI, body mass index; IQR, interquartile range.

Table 3 Myokines and Adipokines in Active vs Sedentary Participants

Variable	Active Median (IQR)	Sedentary Median (IQR)	p	FDR p
Adiponectin (ng/mL)	14.4 (10.7–17.0)	15.4 (13.1–18.9)	0.017	0.039
Myostatin (ng/mL)	7.13 (5.13–9.08)	7.90 (6.35–10.73)	0.030	0.062
Myonectin (ng/mL)	3.54 (2.55–5.81)	3.47 (2.19–4.27)	0.127	0.205
IL-6 (pg/mL)	7.10 (4.86–9.42)	7.81 (5.12–12.16)	0.175	0.263
Leptin (ng/mL)	0.05 (0.02–0.16)	0.09 (0.02–0.25)	0.417	0.515
IL-15 (pg/mL)	105.0 (72.4–213.2)	111.9 (74.0–173.0)	0.795	0.879
Irisin (pg/mL)	116.8 (100.2–131.6)	114.1 (103.5–129.7)	0.900	0.945

Notes: Data are median (IQR). Comparisons used the Mann–Whitney U-test; FDR p adjusted by the Benjamini–Hochberg procedure. Highlighted rows remained significant after FDR correction (FDR $p < 0.05$).

Abbreviations: IQR, interquartile range; FDR, false discovery rate; IL-6, interleukin-6; IL-15, interleukin-15.

Differences Across Exercise Modalities

Among 98 active participants, several parameters differed significantly across aerobic, resistance and combined modalities (Table 4). BMI was lowest in the combined modality group (median 23.0 kg/m²) compared with aerobic (26.8 kg/m²) and resistance (29.1 kg/m²) groups ($p < 0.001$; $\epsilon^2 = 0.23$). HbA1c followed the same pattern (combined 6.41%, aerobic 7.39%, resistance 7.05%; $p < 0.001$; $\epsilon^2 = 0.15$). Among biomarkers, IL-15 differed significantly (combined 71.7 pg/mL vs aerobic 125.6 vs resistance 133.9 pg/mL; $p = 0.009$; $\epsilon^2 = 0.08$), with combined-training participants showing a 43–46% lower median IL-15 than the other groups. Irisin ($p = 0.065$) and leptin ($p = 0.058$) showed borderline differences. No significant differences were detected for fasting glucose, myostatin, myonectin, IL-6 or adiponectin.

Dunn–Bonferroni post-hoc testing localised the principal differences to comparisons involving the combined-modality group. Specifically, BMI, weight and HbA1c each differed significantly between aerobic and combined participants (all Bonferroni-adjusted $p < 0.001$), and IL-15 was significantly lower in combined vs aerobic participants (adjusted $p = 0.007$). HGI differed most strongly between aerobic and combined participants ($z = 4.90$; adjusted $p < 0.001$).

Hemoglobin Glycation Index by Activity Status and Modality

Active participants demonstrated substantially lower and more negative HGI values than sedentary participants (median -0.44 , IQR -0.83 to -0.07 vs 0.12 , IQR -0.50 to 0.81 ; Mann–Whitney U $p = 0.001$; rank-biserial $r = -0.28$) (Table 5 and

Table 4 Metabolic and Biomarker Parameters by Exercise Modality Among Active Participants ($n = 98$)

Parameter	Aerobic ($n = 70$) Median (IQR)	Resistance ($n = 11$) Median (IQR)	Combined ($n = 17$) Median (IQR)	P	ϵ^2
<i>Metabolic and anthropometric parameters</i>					
Weight (kg)	80.0 (73.2–85.8)	86.3 (79.5–98.0)	66.5 (62.0–68.0)	<0.001	0.17
BMI (kg/m²)	26.8 (24.7–30.5)	29.1 (27.2–32.7)	23.0 (19.7–23.7)	<0.001	0.23
Fasting glucose (mg/dL)	128 (119–159)	127 (113–167)	123 (122–138)	0.715	<0.01
HbA1c (%)	7.39 (6.62–8.50)	7.05 (6.49–7.60)	6.41 (6.41–6.70)	<0.001	0.15
<i>Myokines and adipokines</i>					
IL-15 (pg/mL)	125.6 (84.0–222.8)	133.9 (60.7–228.1)	71.7 (52.2–93.6)	0.009	0.08
Leptin (ng/mL)	0.05 (0.02–0.16)	0.024 (0.014–0.031)	0.10 (0.011–0.23)	0.058	0.04
Irisin (pg/mL)	119.2 (102.0–135.0)	116.9 (110.1–122.5)	111.7 (95.1–115.0)	0.065	0.04
Myonectin (ng/mL)	3.61 (2.55–5.12)	4.95 (3.51–5.89)	2.60 (0.49–6.14)	0.114	0.03
IL-6 (pg/mL)	6.86 (4.46–8.68)	9.42 (5.62–11.40)	8.62 (5.88–9.42)	0.106	0.03
Adiponectin (ng/mL)	14.7 (10.7–17.5)	12.9 (9.86–14.7)	13.6 (12.6–15.3)	0.339	<0.01
Myostatin (ng/mL)	6.73 (5.00–9.37)	7.91 (5.58–10.30)	7.39 (5.74–9.03)	0.643	<0.01

Notes: Data are median (IQR). Comparisons used the Kruskal–Wallis test; ϵ^2 values of ≈ 0.01 , 0.06 and 0.14 denote small, medium and large effects. Highlighted rows are significant at $p < 0.05$. The resistance ($n = 11$) and combined ($n = 17$) subgroups are small, so modality comparisons are exploratory.

Abbreviations: IQR, interquartile range; BMI, body mass index; HbA1c, glycated haemoglobin; IL-6, interleukin-6; IL-15, interleukin-15; ϵ^2 , epsilon-squared.

Table 5 Hemoglobin Glycation Index by Physical Activity Status

Group	n	Median HGI	IQR	IQR Width	P
Active	98	−0.44	−0.83 to −0.07	0.76	0.001
Sedentary	87	0.12	−0.50 to 0.81	1.30	

Notes: HGI was calculated as the difference between measured HbA1c and HbA1c predicted from fasting plasma glucose; negative values indicate lower-than-predicted HbA1c. Comparison used the Mann–Whitney U -test.

Abbreviations: HGI, Hemoglobin Glycation Index; IQR, interquartile range.

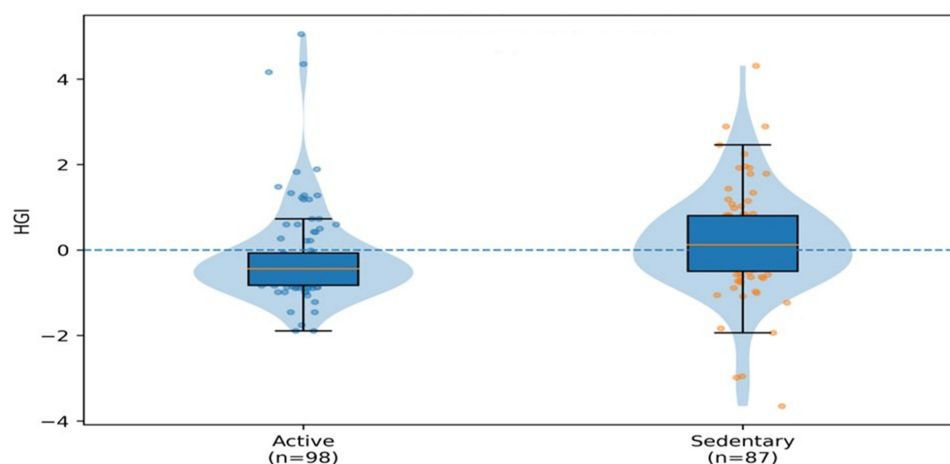


Figure 1 Distribution of the hemoglobin glycation index (HGI) in physically active ($n = 98$) vs sedentary ($n = 87$) adults with type 2 diabetes. Violins show the kernel density of the distribution; the embedded box shows the median (orange line) and interquartile range, with whiskers extending to $1.5 \times \text{IQR}$; points are individual participants. The dashed line marks $\text{HGI} = 0$ (observed HbA1c equal to predicted). Active participants had significantly lower and less dispersed HGI (Mann–Whitney U -test, $p = 0.001$). **Abbreviations:** HbA1c, glycated haemoglobin; IQR, interquartile range.

Figure 1). The IQR width was also markedly greater in the sedentary group (1.30 vs 0.76), indicating greater inter-individual heterogeneity in glycation behaviour among inactive patients.

Among active participants, HGI varied significantly across exercise modalities (Kruskal–Wallis $p < 0.001$; $\epsilon^2 = 0.25$), describing a hierarchical pattern in which combined training was associated with the most favourable (most negative) HGI, followed by resistance and then aerobic exercise (Table 6 and Figure 2). Dunn–Bonferroni post-hoc testing confirmed that the difference was driven principally by the combined-vs-aerobic contrast ($z = 4.90$; adjusted $p < 0.001$), with smaller, non-significant differences between aerobic and resistance and between resistance and combined.

Spearman Correlations Between Biomarkers and HGI

Spearman correlations between HGI and circulating myokines/adipokines are summarised in (Table 7 and Figure 3). In active participants, IL-6 was inversely correlated with HGI ($\rho = -0.32$, 95% CI -0.48 to -0.12 ; raw $p = 0.002$), and this association remained significant after FDR correction (FDR $p = 0.015$). IL-15 showed a positive correlation with HGI ($\rho = 0.20$; raw $p = 0.048$) but did not survive FDR adjustment (FDR $p = 0.191$). Irisin, myostatin, myonectin, leptin and adiponectin were not significantly associated with HGI in active participants.

In sedentary participants, leptin was inversely correlated with HGI ($\rho = -0.37$, 95% CI -0.53 to -0.17 ; raw $p < 0.001$), remaining the most robust association after FDR correction (FDR $p = 0.004$). IL-15 also showed an inverse correlation ($\rho = -0.22$; raw $p = 0.037$) that did not retain significance after FDR adjustment (FDR $p = 0.150$). No other biomarker reached significance in this stratum.

Table 6 Hemoglobin Glycation Index by Exercise Modality Among Active Participants

Modality	N	Median HGI	IQR	Overall p
Combined	17	−0.87	−0.90 to −0.72	<0.001
Resistance	11	−0.47	−0.85 to −0.28	
Aerobic	70	−0.22	−0.52 to 0.48	

Notes: Comparison used the Kruskal–Wallis test. The resistance and combined subgroups are small, so the modality ordering should be interpreted cautiously.

Abbreviations: HGI, Hemoglobin Glycation Index; IQR, interquartile range.

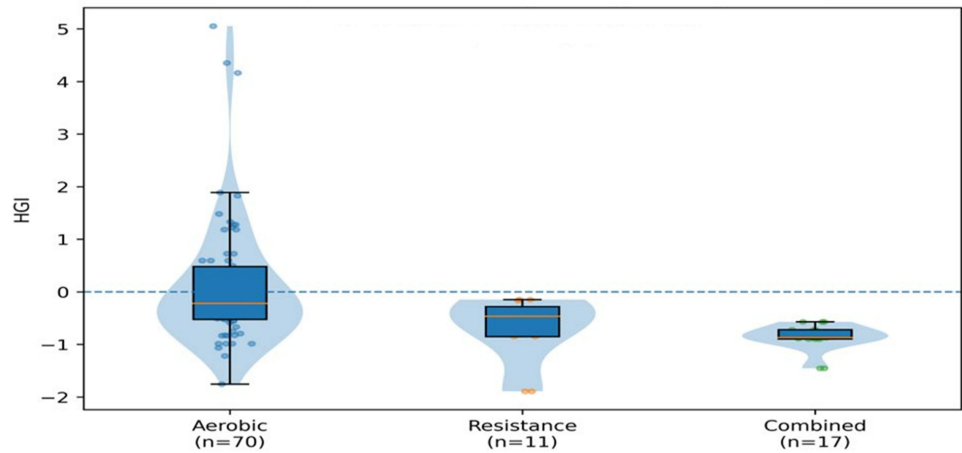


Figure 2 Distribution of HGI by predominant exercise modality among active participants: aerobic ($n = 70$), resistance ($n = 11$) and combined ($n = 17$). Violins show kernel density; boxes show median (orange line) and IQR; whiskers extend to $1.5 \times \text{IQR}$; the dashed line marks $\text{HGI} = 0$. HGI decreased from aerobic to resistance to combined training (Kruskal–Wallis $p < 0.001$; $\epsilon^2 = 0.25$). The resistance and combined subgroups are small, so these modality comparisons are exploratory and should be interpreted with caution.

Abbreviation: ϵ^2 , epsilon-squared.

Multivariable Median Regression of HGI

To assess the independent contribution of physical activity and biomarkers to HGI, seven nested median regression models were fitted (Table 8). In Model 1, active status was associated with a substantial median reduction in HGI of 0.56 units ($\beta = -0.56$, 95% CI -0.86 to -0.27 ; $p < 0.001$). After adjustment for age, sex and BMI (Model 2), the active-status coefficient strengthened slightly ($\beta = -0.65$, 95% CI -0.94 to -0.36 ; $p < 0.001$), with older age also independently associated with lower HGI ($\beta = -0.018$ per year; $p = 0.010$). Adding fasting glucose (Model 3) attenuated but did not abolish the activity coefficient ($\beta = -0.25$, 95% CI -0.51 to -0.003 ; $p = 0.048$), confirming that part of HGI's link to activity is mediated through glycaemia, with FPG itself emerging as an independent predictor ($\beta = 0.005$ per mg/dL; $p < 0.001$).

Table 7 Spearman Correlations of HGI with Biomarkers, Stratified by Activity Status

Stratum	Biomarker	ρ	95% CI	Raw p	FDR p
Active ($n = 98$)	Fasting glucose	0.16	−0.04 to 0.35	0.106	0.283
	Irisin	0.03	−0.17 to 0.23	0.772	0.909
	Myostatin	0.06	−0.14 to 0.25	0.578	0.909
	Myonectin	0.03	−0.17 to 0.22	0.796	0.909
	IL-6	−0.32	−0.48 to −0.12	0.002	0.015
	IL-15	0.20	0.00 to 0.38	0.048	0.191
	Leptin	0.01	−0.19 to 0.21	0.948	0.948
	Adiponectin	0.11	−0.09 to 0.31	0.262	0.525
	Fasting glucose	0.13	−0.08 to 0.33	0.234	0.597
	Irisin	0.11	−0.10 to 0.32	0.298	0.597
Sedentary ($n = 87$)	Myostatin	0.08	−0.13 to 0.29	0.459	0.612
	Myonectin	0.02	−0.20 to 0.23	0.888	0.888
	IL-6	−0.02	−0.23 to 0.19	0.870	0.888
	IL-15	−0.22	−0.42 to −0.01	0.037	0.150
	Leptin	−0.37	−0.53 to −0.17	<0.001	0.004
	Adiponectin	0.09	−0.13 to 0.29	0.431	0.612

Notes: FDR p adjusted by the Benjamini–Hochberg procedure within each stratum. Highlighted rows remained significant after FDR correction (FDR $p < 0.05$).

Abbreviations: HGI, Hemoglobin Glycation Index; ρ , Spearman correlation coefficient; CI, confidence interval; FDR, false discovery rate; IL-6, interleukin-6; IL-15, interleukin-15.

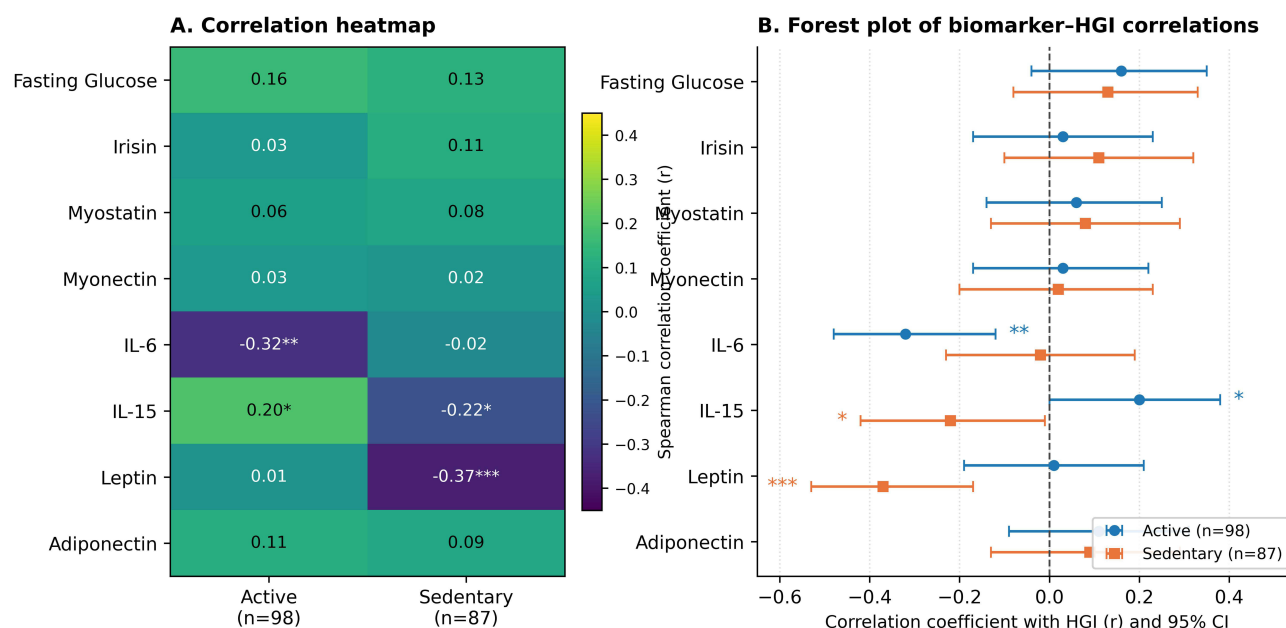


Figure 3 Associations between circulating biomarkers and HGI, stratified by activity status (active $n = 98$, sedentary $n = 87$). **(A)** Heatmap of Spearman correlation coefficients (ρ); colour indicates the direction and magnitude of ρ (scale at right). **(B)** Forest plot of the same correlations showing ρ (points) with 95% confidence intervals (horizontal lines); the vertical dashed line marks $\rho = 0$. Asterisks denote uncorrected significance: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. After Benjamini–Hochberg FDR correction, only the inverse associations of IL-6 in active participants and of leptin in sedentary participants remained significant (FDR $p < 0.05$); the IL-15 associations did not survive correction. ρ , Spearman correlation coefficient.

Abbreviations: CI, confidence interval; FDR, false discovery rate; IL-6, interleukin-6; IL-15, interleukin-15.

In Model 4, addition of selected biomarkers (IL-6, IL-15, leptin) to demographic adjustments left the activity association essentially unchanged ($\beta = -0.58$, 95% CI -0.86 to -0.31 ; $p < 0.001$), with IL-15 ($\beta = 0.001$ per pg/mL; $p = 0.004$) and leptin ($\beta = -0.56$ per ng/mL; $p = 0.037$) emerging as independent predictors of HGI. Models 5–7 tested formal activity $\times$ biomarker interactions; none reached statistical significance for IL-15, leptin or IL-6 (all $p > 0.20$), suggesting that although biomarker–HGI relationships differ in direction or magnitude between strata, the multiplicative interaction term was not detectable in this sample.

Table 8 Median (Quantile) Regression of HGI Across Nested Models

Model	Term	β	95% CI	P
Model 1: activity only	Active	-0.56	-0.86 to -0.27	<0.001
Model 2: + age, sex, BMI	Active	-0.65	-0.94 to -0.36	<0.001
	Age	-0.018	-0.032 to -0.004	0.010
	Male	-0.25	-0.57 to 0.08	0.133
	BMI	0.000	-0.026 to 0.026	1.000
Model 3: + FPG	Active	-0.25	-0.51 to -0.003	0.048
	FPG	0.005	0.003 to 0.008	<0.001
Model 4: + IL-6, IL-15, leptin	Active	-0.58	-0.86 to -0.31	<0.001
	IL-15	0.001	0.000 to 0.002	0.004
	Leptin	-0.56	-1.08 to -0.03	0.037
Model 5: activity $\times$ IL-15	Interaction	0.001	-0.001 to 0.003	0.212
Model 6: activity $\times$ leptin	Interaction	0.65	-0.39 to 1.69	0.217
Model 7: activity $\times$ IL-6	Interaction	0.001	-0.007 to 0.010	0.756

Notes: Each model is adjusted for the listed terms; Models 5–7 test activity $\times$ biomarker interactions. Highlighted rows are significant at $p < 0.05$.

Abbreviations: HGI, Hemoglobin Glycation Index; β , median (quantile) regression coefficient; CI, confidence interval; FPG, fasting plasma glucose; BMI, body mass index.

Discussion

In this cross-sectional study of 185 adults with T2DM, we examined whether circulating myokines and adipokines are associated with the Hemoglobin Glycation Index, and whether such associations differ between physically active and sedentary individuals and across exercise modalities. Three principal findings emerged. First, physical activity was associated with a substantial and statistically significant reduction in HGI, persisting in multivariable median regression after adjustment for age, sex, BMI and selected biomarkers. Second, HGI followed a clear modality-dependent gradient, with combined aerobic-plus-resistance training associated with the most negative HGI values, intermediate values for resistance and the least favourable values for aerobic-only training. Third, biomarker–HGI associations were stratum-specific, with IL-6 inversely correlated with HGI only in active participants, and leptin inversely correlated with HGI only in sedentary participants.

The biological meaning of HGI has been refined considerably since its original description.^{5,6} Within an individual, HGI is reproducible over years and only modestly attenuated by changes in mean glycaemia, supporting its interpretation as a stable trait reflecting both intracellular glucose handling and erythrocyte biology.⁷ High HGI has been linked to greater insulin resistance, subclinical atherosclerosis, microvascular complications and excess cardiovascular events under intensive treatment.^{8,9,27} Our finding that HGI is markedly lower (more negative) in physically active T2DM patients—even after adjustment for demographic factors and BMI suggests that physical activity is associated with not only lower mean glycaemia but also a lower propensity for haemoglobin glycation itself, potentially through reduced oxidative stress, improved erythrocyte turnover and altered intra-erythrocytic glucose flux.^{28,29} Because oxidative stress, erythrocyte turnover and intra-erythrocytic glucose handling were not directly measured, these proposed pathways remain inferential. The greater dispersion of HGI in the sedentary group (IQR width 1.30 vs 0.76) further supports the notion that inactivity unmasks inter-individual heterogeneity in glycation phenotypes, whereas exercise tends to homogenise glycation behaviour towards a more favourable profile.

The hierarchical modality pattern, with combined training showing the most favourable HGI, mirrors landmark trials in which combined aerobic-plus-resistance regimens produced the largest HbA1c reductions in T2DM.^{22,23} Importantly, our HGI findings extend these observations beyond mean glycaemia: combined training was associated not only with lower HbA1c, but also with a more negative residual after accounting for fasting glucose, suggesting that the benefit cannot be entirely explained by lower ambient glucose. Mechanisms may include enhanced muscle mass and insulin signalling from resistance components, improved mitochondrial function and oxidative defense from aerobic components, and a lower IL-15 milieu (43% lower in combined vs aerobic), which could indicate a transition toward a metabolically efficient muscle phenotype with reduced compensatory cytokine secretion.^{14,30} Conversely, the least favourable HGI profile in the aerobic-only group, despite the largest sample size, may partly reflect lower training intensity or less complete remodeling of muscle mass and insulin sensitivity in the absence of resistance loading.

These modality comparisons rest on small resistance ($n = 11$) and combined ($n = 17$) subgroups, so the corresponding estimates may be unstable and are at risk of overinterpretation. They should be regarded as preliminary, and replication in larger, balanced cohorts will be needed to confirm the observed modality gradient.

A notable observation in our data was the stratum-specific pattern of biomarker–HGI associations. In active individuals, IL-6 was inversely correlated with HGI after FDR correction. This is consistent with the dual physiology of IL-6, which acts as a contraction-induced, insulin-sensitizing myokine during exercise but as a chronic inflammatory cytokine in sedentary metabolic disease.^{13,31,32} The inverse association confined to active participants may capture this exercise-related protective signature, although the cross-sectional design cannot confirm it.

In sedentary individuals, leptin emerged as the strongest inverse correlate of HGI. This is biologically interesting because in obesity-driven T2DM, leptin levels are typically elevated alongside leptin resistance.³³ The inverse association observed here may indicate that, within the sedentary stratum where leptin distribution is wider and more reflective of adipose mass, individuals with relatively higher leptin signalling display lower-than-predicted HbA1c possibly via residual central effects on glucose disposal or appetite-related improvements in glycaemic excursions.³⁴ The specificity of this association to inactive participants suggests that, when exercise is absent, adipose-derived signalling becomes the

dominant modulator of glycation behaviour, whereas in active individuals, muscle-derived signalling (IL-6) takes precedence.

The mechanistic interpretations proposed above IL-6 as a protective contraction-induced myokine in active participants, and leptin as an inverse correlate of HGI in sedentary participants remain speculative. Because the data are cross-sectional and based on single fasting measurements, these explanations should be viewed as hypotheses to be tested directly rather than established mechanisms.

One finding ran counter to expectation: adiponectin was higher in sedentary than in active participants, whereas exercise and insulin sensitivity are typically associated with elevated adiponectin. Several explanations are plausible. Differences in glucose-lowering therapy may contribute, as certain agents (eg, thiazolidinediones) raise adiponectin independently of activity; differences in adiposity distribution and the wider BMI range of the sedentary group may also influence circulating levels; and a compensatory rise in adiponectin in the setting of greater insulin resistance cannot be excluded. Given the cross-sectional design, this observation should be interpreted cautiously and confirmed in future work.

Median regression analyses confirmed that physical activity is an independent predictor of lower HGI, with the coefficient remaining robust under demographic and biomarker adjustments. The marked attenuation observed in Model 3 after addition of fasting glucose (β reduced from -0.65 to -0.25) indicates that approximately 60% of the activity–HGI association is statistically accounted for by fasting glycaemia, while the remaining ~40% appears independent of fasting glucose; given the cross-sectional design, these proportions reflect statistical attenuation rather than formally established mediation. Independent contributions of IL-15 (positive) and leptin (inverse) in Model 4 reinforce a multifactorial interpretation in which both muscle and adipose endocrine signals shape inter-individual glycation. The non-significance of formal activity $\times$ biomarker interaction terms despite stratum-specific Spearman correlations suggests that interaction effects are subtle and may require larger samples to be detected at the multiplicative scale.

Alternative explanations should also be considered: medication use, diabetes duration, dietary patterns, body-composition differences and underlying inflammatory status may each contribute to the observed biomarker profiles and HGI variability, and the associations reported here may partly reflect these unmeasured factors rather than activity per se.

If HGI is confirmed prospectively as a predictor of vascular outcomes in T2DM beyond HbA1c, identifying behavioral and biochemical correlates of HGI becomes clinically relevant. Our findings raise the possibility that combined aerobic-plus-resistance training, rather than aerobic exercise alone, may be associated with benefits at the level of glycation biology, a hypothesis that requires prospective testing. Furthermore, the divergent biomarker signals (IL-6 in active, leptin in sedentary patients) hint at the possibility of activity-aware risk stratification: in active individuals, low IL-6 might flag a sub-optimal myokine response, while in sedentary individuals, low leptin (relative to adiposity) might identify a higher-glycator phenotype warranting more aggressive intervention.

Strengths and Limitations

Strengths include a clinically well-characterised cohort representative of the Gulf T2DM population, a comprehensive panel of myokines and adipokines, the use of robust non-parametric and quantile regression methods, and rigorous control of multiple testing through Benjamini–Hochberg FDR correction. Several limitations should be acknowledged. First, the cross-sectional design precludes causal inference; we cannot determine whether exercise lowers HGI or whether individuals with constitutionally low HGI are more able to maintain habitual activity. Second, sample sizes for resistance ($n = 11$) and combined ($n = 17$) modality subgroups were modest, reducing statistical power for modality-specific Spearman analyses and limiting precision of effect estimates; these results should be regarded as hypothesis-generating. Third, physical activity was assessed by self-report rather than by objective monitoring, introducing potential recall bias and misclassification of exercise intensity and modality; no independent validation of questionnaire responses was performed. Fourth, single fasting biomarker measurements may not capture the dynamic, exercise-induced fluctuations of myokines such as IL-6 and irisin. Fifth, the cohort was predominantly male and drawn from a single center, which may limit generalizability. Sixth, we did not measure red-cell turnover or markers of oxidative stress, which would help disentangle the erythrocyte and metabolic contributions to HGI. Seventh, Although Benjamini–Hochberg correction

was applied, the number of biomarkers and subgroup analyses means residual type I error cannot be excluded; the exploratory associations should be interpreted in that light. Finally, several potential confounders including diabetes duration, medication dosage, dietary habits, smoking status and comorbidities were not systematically captured. Antidiabetic therapy is a particular concern, as drug classes differ in their effects on the biomarkers studied: metformin can lower circulating IL-6 and other inflammatory markers, thiazolidinediones raise adiponectin, and incretin-based and sulfonylurea agents influence glycaemic indices through distinct mechanisms. Because medication class was recorded but not adjusted for, and dose and duration were not captured, residual confounding of the biomarker–HGI associations by treatment cannot be excluded.

Future Directions

Prospective studies linking baseline myokine–adipokine profiles, HGI trajectories and incident vascular outcomes are needed, alongside randomised trials comparing exercise modalities with HGI as a pre-specified outcome. Mechanistic work integrating erythrocyte glucose-handling assays, inflammatory profiling and dynamic myokine responses to acute exercise would clarify whether the IL-6 and leptin signals identified here represent causal mediators or downstream markers.

Conclusion

In adults with T2DM, the Hemoglobin Glycation Index was significantly lower in physically active individuals and showed a modality-dependent gradient, with the most favourable values observed in those undertaking combined aerobic-plus-resistance training. After multivariable adjustment, IL-6 was independently associated with HGI in active individuals and leptin in sedentary individuals, suggesting that distinct muscle- and adipose-derived signals are associated with glycation variability according to activity context. These findings position HGI as a candidate modifiable marker of metabolic phenotype in T2DM. However, as no longitudinal or interventional data were included, the results remain exploratory and require confirmation in prospective or randomized studies before any clinical application can be established. Future work should test these associations in longitudinal and mechanistic studies and evaluate whether modality-specific, personalized exercise strategies can favorably modify HGI as part of individualized T2DM management.

Data Sharing Statement

The de-identified datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study protocol was approved by the Institutional Review Board of Gulf Medical University, Ajman, UAE (Ref. no. IRB-COHS-STD-131-Dec-2024) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Specific contributions, following the CRediT taxonomy, are as follows:

Marwan Ismail: Conceptualization; Methodology; Investigation; Data curation; Formal analysis; Writing – original draft; Project administration.

Mutaz Ibrahim Hassan: Conceptualization; Methodology; Supervision; Validation; Writing – review & editing.

Akhtamova Shahzoda Fozilovna: Investigation; Resources; Data curation; Writing – review & editing.

Namoz Xalimovich Mavlonov: Investigation; Resources; Validation; Writing – review & editing.

Nuriddin Nuritdinov: Formal analysis; Software; Visualization; Writing – review & editing.

Elmotaz Abdelfatah: Investigation; Data curation; Visualization; Writing – review & editing.

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Disclosure

The authors declare that they have no competing interests.

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