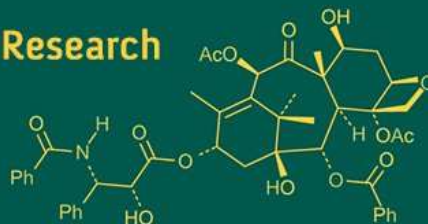
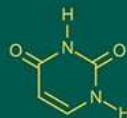
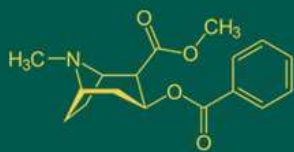


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Wafaa Mohammed Jaber
 Department of Biochemistry,
 College of Medicine, University
 of Basrah, Basrah, Iraq

Salman Kadhum Ajlan
 Department of Biochemistry,
 College of Medicine, University
 of Basrah, Basrah, Iraq

Haider Ayad Alidrisi
 Department of Medicine,
 College of Medicine, University
 of Basrah, Basrah, Iraq

Glycemic control measured by fructosamine versus glycated hemoglobin among patients with type 2 diabetes

Wafaa Mohammed Jaber, Salman Kadhum Ajlan and Haider Ayad Alidrisi

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Abstract

Background: Glycemic control is a crucial aspect of Type 2 Diabetes (T2D) management. Fructosamine (FA) is a good substitute to glycated hemoglobin (HbA1c) in certain clinical settings because its readings indicate the average glucose levels during 2-3 weeks.

Objective: The aim of the study was to compare glycemic control between FA and HbA1c, and to determine the difference in the utility of FA in comparison with predictive reliability of FA as an alternative biomarker.

Methodology: A control study was carried out between December 2024 and June 2025 where 90 T2D patients were matched with 90 controls. Parameters included HbA1c, FA and random plasma glucose (RPG) which were measured using independent t-tests, ANOVA and Pearson correlation ($p < 0.05$).

Results: A statistically significant increase in serum FA was found patients with T2D ($264.94 \pm 55.52 \mu\text{mol/L}$) than controls ($227.77 \pm 23.42 \mu\text{mol/L}$) ($p < 0.01$). Moreover, the level of fructosamine was significantly difference level of glycemic control; measured by HbA1c where patients with poor glycemic control ($\text{HbA1c} > 8\%$) had significantly higher mean FA ($273.55 \pm 58.06 \mu\text{mol/L}$) than patients with optimal glycemic control ($\text{HbA1c} < 7\%$; 238.57) ($P < 0.05$).

Conclusion: FA is potentially a strong indicator of short-term glycemic variations, particularly when HbA1C is not reliable. Its clinical integration may offer a useful alternative tool for management of T2D.

Keywords: Type 2 Diabetes, glycemic control, fructosamine, glycated hemoglobin

Introduction

Type 2 diabetes (T2D) is a growing global health issue that requires accurate and consistent blood glucose level measurements, aimed at preventing or postponing the development of chronic complications. The cornerstone of the contemporary therapeutic approach is optimal glycemic control. Major clinical trials have proven that proper maintenance of glucose levels near the normal range significantly reduces the risk of diabetic retinopathy, nephropathy, and neuropathy [1]. In this regard, glycated hemoglobin (HbA1c) has become the established gold standard in assessing the long-term glycemic control, which indicates average glucose levels throughout the lifespan of red blood cells, over the average three-month lifespan of erythrocytes [2]. Nonetheless, HbA1c alone can be limited in clinical applications in some contexts, necessitating the exploration of alternative or complementary biomarkers that offer a more representative view or a better time scale. Fructosamine (FA) is a known alternative biomarker. It is the result of the interaction of glucose with serum proteins, mainly albumin, via non-enzymatic glycation (the Maillard reaction). FA concentration represents the mean level of glycemic control within a two-to-three week window due to the short half-life of albumin compared to red blood cells [3]. This time disparity makes FA useful in cases where timely monitoring of therapeutic interventions is essential, or in cases where there are circumstances that impair the reliability of HbA1c measurements, (e.g. hemolytic anemia), hemoglobinopathies, or pregnancy, wherein the red blood cell turnover rate is greatly distorted [4]. Emerging evidence suggests that FA may outperform in predicting some acute and chronic clinical outcomes than HbA1c. As an example, research carried out on patients

Corresponding Author:
Wafaa Mohammed Jaber
 Department of Biochemistry,
 College of Medicine, University
 of Basrah, Basrah, Iraq`

undergoing major surgical operations, including joint replacement, has revealed that FA levels before surgery serves as a superior predictor of postoperative complications compared to HbA1c [5]. This is because the FA can indicate the level of glycemic condition of the patient in the few weeks before the surgery a critical period for assessing the risk of infection and poor wound healing [6]. Moreover, the so-called glycation gap, i.e. the difference between the fructosamine-predicted levels of HbA1c and the measured levels is under increasing interest. This gap has been established to be the possible cause of the development of renal complications in patients with diabetes [7].

The pathophysiological mechanism of FA formation differs from HbA1c in the nature of the targeted proteins. Whereas HbA1c is based on the glycation of hemoglobin in red blood cells, fructosamine is based on the circulation of plasma proteins. This difference means that it can be influenced by other factors that may affect the serum protein levels, including liver diseases or nephrotic syndrome, which lead to protein loss, which may influence the results of FA testing [8]. However, when such disorders are not present, fructosamine is a reliable indicator of glycemic fluctuations that may be obscured by HbA1c because of the long-time interval it measures [9]. Clinical guidelines introduced nowadays underline the importance of customizing monitoring tools according to the profile and the clinical condition of a particular patient, instead of using one standard to all patients [10].

The aim of the study was to provide a thorough comparative analysis of glycemic control in patients with T2D by measuring FA and HbA1c levels, to explore scenarios where significant discrepancies between these markers arise, and to evaluate fructosamine's predictive capability as a valid alternative to HbA1c in contexts with specific diagnostic limitations.

Patients and methods

Design of study

This is a case-control study conducted from December 2024 throughout June, 2025. The study included of 90 patients with T2D, 40 (44.4%) males and 50 (55.5%) females, aged 35 to 65 years. They were diagnosed by Consultant Endocrinologists at Al-Faihaa Specialized Diabetes, Endocrine and Metabolism Center – (FDEMC) in Basrah, Iraq, diagnosed them. The study also included 90 matched control participants, for both age and sex.

Study population

Patients with T2D were diagnosed according the American Diabetes Association (ADA) guideline for diagnosis of diabetes as following; “a FPG level of ≥ 126 mg/dL (7.0 mmol/L)”, or “a 2-h BG level ≥ 200 mg/dL (11.1 mmol/L) during a 75g OGTT”, or “HbA1c level $\geq 6.5\%$ or “RPG ≥ 200 mg/dL (11.1 mmol/L)” in symptomatic patients, with an age range between (35-65) years. A total of 90 participants matched for both age and sex with cases were selected as the control group who were apparently healthy subjects with no history of diabetes and proved to be in a good health state, by careful clinical examination and biochemical laboratory test, agreed to participate and consented to this study.

Exclusion criteria

The study excluded participants in cases where they had been diagnosed with diabetes other than T2D, pregnant or lactating women, those having chronic or acute diseases of the liver or kidneys affecting the functionality of these

organs and those who had a history of malignant tumours. Moreover, people taking certain drugs that are known to affect the metabolism of glucose or laboratory tests including Dexamethasone, Thiazides, Cyclosporine, and Olanzapine were also not included.

Blood sample

Random plasma glucose (RPG) samples were obtained from patients with T2D and the controls group by venipuncture using disposable syringe in the sitting position. Two ml was dispensed in an anticoagulant tube containing 1.5 mg/mL tri-potassium ethylene-diamine tetra acetic acid (K3EDTA) to be used in the measurement of HbA1c levels.

Biochemical determination

The level of FA was determined by ELISA using a kit provided by SunLong/ China. The reference range for FA: women = 186–248 $\mu\text{mol/L}$, and men = 196–269 $\mu\text{mol/L}$ [11].

In vitro test for the quantitative determination of RPG in serum, where RPG levels are determined by enzymatic reference method with hexokinase using a fully automated Glucose HK Gen.3. Cobas Integra 400 plus, Germany [12]. Expected Values: normal individual < 140 mg/dL (< 9.8 mmol/L), and patient with diabetes ≥ 200 mg/dL (≥ 11.1 mmol/L) [12].

In vitro test for the quantitative determination of mmol/mol hemoglobin A1c (IFCC) and % hemoglobin A1c (DCCT/NGSP) in whole blood on Roche clinical chemistry analyzers COBAS INTEGRA 400 plus [13]. In patients with diabetes, the glycemic control was categorized in to three categories based on HbA1c level: good glycemic control (HbA1c $< 7\%$), fair glycemic control (HbA1c 7-8%), and poor glycemic control (HbA1c $> 8\%$) [14].

Statistical Analysis

In this study, we employed the Statistical Package for Social Science (SPSS) program version 23 for data analysis. For determining statistical significance, a p-value of less than 0.05 was considered as the lowest limit for significance.

Ethical approval

The college council of the College of Medicine at the University of Basrah study clearance. Additionally, the hospital ethics board Basrah Health Directorate approved this study. All participants provided written informed consent after obtaining detailed information about the study's aims and methodologies.

Results

Characteristics of the study groups

(Table 1) demonstrates the demographic characteristics of patients with T2D and control groups. regarding the sex, more than half of the participants were females (60 % and 56.7 %) for patients and controls respectively, the difference between the two groups was statistically not significant ($p > 0.05$). The mean age of patients was (49.89 ± 9.00) years, while the mean age of controls was (49.17 ± 8.87) years and the difference was statistically not significant ($p > 0.05$). Furthermore, there was a nearly equal distribution of sex among the groups with no significant differences observed across all groups ($p > 0.05$). regarding to smoking, the most of patients' smoker among all groups as shown no significant difference, ($p > 0.05$).

Table 1: Characteristics of the patients with T2D and controls

Characteristics		Patient (n=90) (Mean ± SD)	Control (n=90) (Mean ± SD)	p-value
Sex	Male	36 (40%)	39 (43.3%)	0.625
	Female	54 (60%)	51 (56.7%)	
Age (years)		49.89 ± 9.00	49.17 ± 8.87	0.681
	<45	26 (28.9 %)	32 (35.6 %)	
	(45-54)	35 (38.9 %)	31 (34.4 %)	
	(55-64)	25 (27.8 %)	25 (27.8 %)	
	>65	4 (4.4 %)	2 (2.2 %)	
Smoking	Smoker	44 (48.9%)	45 (50%)	0.717
	Non-Smoker	27 (30%)	21 (23%)	
	Passive smoker	19 (21.1%)	24 (24%)	

Clinical characteristics of the study groups

The mean value of BMI for both diabetes patients and control revealed no significant differences ($p>0.05$) with regard to BP, SBP for the patients was significantly higher than control group ($p<0.01$), whereas the DBP for patients had slightly increased values than controls with no significant difference, ($P>0.05$). Additionally, the study shows that the mean of WC in patient of T2D was (95.76 ± 23.93 cm), whereas in controls it was (97.33 ± 10.93 cm) with no statistically significant difference ($p>0.05$) (Table 2).

Table 2: Characteristics of patients with T2D and controls

Characteristics		Patient (Mean ± SD)	Control (Mean ± SD)	p-value
BMI (Kg/m ²)		30.76 ± 5.03	29.71 ± 3.93	0.118
BP (mmHg)	SBP	140.47 ± 16.46	114.40 ± 8.21	0.001**
	DBP	84.94 ± 10.28	83.51 ± 3.76	0.217
WC (cm)		95.76 ± 23.93	97.33 ± 10.93	0.570

** Significant at 0.01 level

Glycemic parameters among patients with T2D and control subjects

Glycemic markers are presented in (Table 3). There was a significant increase in RPG and HbA1c in the T2D group in comparison to control group, ($p<0.001$). In additionally serum FA level was significantly higher in patients (264.94 ± 55.52 μmol/L) than in controls (227.77 ± 23.42 μmol/L), ($p<0.001$).

Table 3: Glycemic parameters of patients with T2D and controls

Parameters	Patient (Mean ± SD)	Control (Mean ± SD)	p-value
HbA1c (%)	9.40 ± 2.02	5.05 ± 0.53	0.001**
RPG (mg/dL)	284.94 ± 123.97	107.32 ± 13.54	0.001**
Fructosamine (μmol/L)	264.94 ± 55.52	227.77 ± 23.42	0.001**

** Significant at 0.01 level

Fructosamine levels in relation to status of glycemic control measured by HbA1c

The pattern of FA among patients with T2D according to glycemic control, measured by HbA1c is shown in (Table 4). Patients with poor glycemic control (HbA1c > 8%) had higher mean FA levels (273.55 ± 58.06 μmol/L) compared to patients with optimal and acceptable control (238.57 ± 39.23 μmol/L and 240.43 ± 39.28 μmol/L) respectively, ($p<0.05$).

Table 4: Distribution of diabetic patients according to glycated hemoglobin

HbA1c (%)	Fructosamine (Mean±SD) (μmol/L) Total (n= 90)
Optimal control <7	238.57 ± 39.23 (7)
Acceptable control 7–8	240.43 ± 39.28 (16)
Poor control >8	273.55 ± 58.06 (67)
p-value	0.041*

* Significant at 0.05 level

Discussion

The present study examined the effectiveness of FA, in terms of HbA1c as a biomarker of glycemic control in T2D patients. We found that there was a considerable increase in HbA1c, FA and RPG concentrations in the diabetic population compared to the healthy controls. In particular, the results revealed that the levels of FA were significantly increased in patients with poor glycemic control (HbA1c > 8%), which implies the high sensitivity of this method to short-term changes in glycemic levels. The findings highlight the clinical significance of FA as an adjunctive agent in the management of diabetes especially in situations where quick evaluation is necessary.

In compliance with the other reports, Ismail (2026) [15], performed a comparative study that points to the fact that, although HbA1c is still a leading parameter, FA offers crucial extended monitoring capabilities in patients with T2D irrespective of their BMI levels. This is also backed by the studies of Naik (2024) [16], who found that FA was significantly positively correlated with HbA1c, indicating that FA could be used as an effective alternative measure of glycemic control in routine clinical activity. The 2-3 week window indicated by FA provides a particular benefit compared to 3 months average of HbA1c particularly at times of intensive treatment change.

FA has a specific clinical utility in a situation where HbA1c might not be reliable. Hassan (2025) [17], claims that FA levels do not vary under different hematological variations, and consequently, is a better option in glycemic evaluation in patients with conditions such as hemoglobinopathies, which interfere with the HbA1c assays. This view is supported by Mahmoud (2024) [18], whose systematic review identified that FA is more specific in identifying blood glucose intolerance and more sensitive in identifying diabetes in some high-risk groups than HbA1c.

Moreover, the predictive value of FA has also been highlighted in the recent report on the outcomes of surgery. Regmi (2026) [19], showed that preoperative FA can be equivalent to HbA1c as a short-term glycemic parameter to predict the occurrence of postoperative complications in orthopedic surgery implying that the latest glycemic status is a crucial predictor of surgical success. Also, Ha (2024) [20], discussed the idea of using the fructosamine-albumin ratio, which gives evidence that this refined measure can help to make glycemics monitoring more accurate in patients with T2D by considering the rates of protein turnover.

The association between FA and the chronic complications of diabetes is also a major area of concern. Arjunan (2025) [21], pointed out that impaired glucose intolerance (IGT) is linked to high FA levels, alongside HbA1c, but they pointed out that a combination of these markers with FPG is most accurate to diagnose IGT. In the same way, Al-Yasiri and Hassan (2026) [22], study established that FA enables the earlier detection of therapeutic effects or dietary changes

than HbA1c, enabling more timely interventions in the treatment of diabetes.

Furthermore, the so-called HbA1c-glycemia mismatch or glycation gap is becoming a new issue in the personalized diabetes care. According to Sureshkumar (2026) ^[23], the discordance between HbA1c and other glycemic parameters is far too different depending on the population characteristics, which validates the need to use other biomarkers such as FA to close these gaps in diagnosis. This is especially applicable to diabetic retinopathy, where the albumin-corrected FA has been reported to have significant correlation with the presence and severity of the disease based on recent clinical studies ^[24].

Recent logistic regression models also assessed the role of FA as a new biomarker in the early diagnosis of diabetes, and concluded that high FA levels are independently linked to an increased risk of developing T2D ^[25]. This indicates that FA might be more significantly involved in screening programs. Besides, the 2026 Standards of Care in Diabetes by the ADA recognize the usefulness of FA as a supplementary monitoring tool, especially when HbA1c fails to provide an accurate representation of the glycemic status of a patient ^[26].

FA has also been incorporated in the digital health framework through technological innovations. Chandran (2024) ^[27], found a high correlation between FA and continuous glucose monitoring (CGM) measures in the Southeast Asian populations, indicating that it is an effective means of intermediate glycemic control. Moreover, Raza *et al.* (2026) ^[28], offered both biochemical explanations of how widely used drugs such as metformin can shield human insulin against fructosylation, consequently modulating FA concentrations and lowering long-term issues. Lastly, Entuc *et al.* (2026) ^[29] noted that new biomarkers such as FA are critical to the development of precision care in T2D, which offers a more metabolic picture than conventional markers.

Conclusion

FA is an important marker of glycemic control and especially in cases where the HbA1c measurement cannot be relied upon to determine whether patients with T2D is under good glycemic control or not. Incorporating the use of FA into clinical practice in conjunction with HbA1c can be used to offer a more comprehensive and accurate assessment of glycemic control with subsequent resultant improvement of the management of T2D patients. More research is required to set reference values of FA in different populations and to verify its implication in the development of certain chronic complications.

Author contributions

W.M.J, S.K.A and H.A.A. were responsible for the conception, design, data collection, analysis, and manuscript preparation. F.D.E.M.C provided the patient samples and contributed to data acquisition.

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References

1. Selvin E, Rawlings AM, Grams M, *et al.* Fructosamine and glycated albumin for risk stratification and prediction of incident diabetes and microvascular complications: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study. *Lancet Diabetes Endocrinol.* 2014;2(4):279-288.
2. Nathan DM, Kuenen J, Borg R, *et al.* Translating the A1C assay into estimated average glucose values. *Diabetes Care.* 2008;31(8):1473-1478.
3. Danese E, Montagnana M, Nouvenne A, Lippi G. Advantages and pitfalls of fructosamine and glycated albumin in the diagnosis and treatment of diabetes. *J Diabetes Sci Technol.* 2015;9(2):169-176.
4. Hivre M, Holkar S, Vaishnav D, Surkar P. Beyond HbA1c: alternative glycemic biomarkers in hemoglobinopathies, malignancy, and special clinical populations - a review. *Int J Med Res Health Sci.* 2023;12(5):45-58.
5. Shohat N, Tarabichi M, Tan TL, *et al.* Fructosamine is a better glycaemic marker compared with glycated haemoglobin (HbA1c) in predicting adverse outcomes following total knee arthroplasty. *Bone Joint J.* 2019;101-B(7):3-9.
6. Shohat N, Goswami K, Breckenridge L, *et al.* Fructosamine is a valuable marker for glycemic control and predicting adverse outcomes following total hip arthroplasty: a prospective multi-institutional investigation. *Sci Rep.* 2021;11(1):2343.
7. Cohen RM, Holmes YR, Chenier TC, Joiner CH. Discordance between HbA1c and fructosamine: evidence for a glycosylation gap and its relation to diabetic nephropathy. *Diabetes Care.* 2003;26(1):163-167.
8. Malmström H, Walldius G, Grill V, *et al.* Fructosamine is a useful indicator of hyperglycaemia and risk of type 2 diabetes in a large population-based cohort. *J Intern Med.* 2014;276(3):280-290.
9. Jurascheck SP, Steffes MW, Miller ER, *et al.* Alternative markers of glycemia (fructosamine and glycated albumin) and risk of coronary heart disease in the Atherosclerosis Risk in Communities Study. *Diabetes Care.* 2012;35(11):2265-2270.
10. American Diabetes Association Professional Practice Committee. 6. Glycemic targets: standards of care in diabetes—2024. *Diabetes Care.* 2024;47(Suppl 1):S111-S125.
11. Roche Diagnostics. COBAS INTEGRA 400 Plus Analyzer Operator's Manual. Version 12.0. Mannheim: Roche Diagnostics GmbH; 2023.
12. American Diabetes Association Professional Practice Committee. 2. Diagnosis and classification of diabetes: standards of care in diabetes—2024. *Diabetes Care.* 2024;47(Suppl 1):S20-S42.
13. American Diabetes Association Professional Practice Committee. 6. Glycemic goals and hypoglycemia: standards of care in diabetes—2024. *Diabetes Care.* 2024;47(Suppl 1):S111-S125.
14. ElSayed NA, Aleppo G, Aroda VR, *et al.* Glycemic targets: standards of care in diabetes—2023. *Diabetes Care.* 2023;46(Suppl 1):S97-S110.
15. Ismail M. A comparative analysis of HbA1c and fructosamine as indicators of glycemic control across

- body mass index in type 2 diabetes. *Georgian Med News*. 2026;370(1). Available from: <https://pubmed.ncbi.nlm.nih.gov/41804151/>
16. Naik SR. Comparative evaluation of fructosamine and glycated haemoglobin as a marker of glycaemic control in type 2 diabetes mellitus. *J Diabetes Allied Pract*. 2024;1(2):6. Available from: https://journals.lww.com/jdap/fulltext/2024/01020/comparative_evaluation_of_fructosamine_and.6.aspx
 17. Hassan T. Hemoglobin A1c or fructosamine as a measurement related to glycemic control in diabetic patients with Hb Louisville. *Blood*. 2025;146(Suppl 1). Available from: <https://ashpublications.org/blood/article/146/Supplement%201/1128/550284/>
 18. Mahmoud AA. HbA1c or fructosamine on evaluating glucose intolerance: a systematic review and meta-analysis. *Pediatr Res*. 2024. <https://doi.org/10.1038/s41390-024-03146-y>
 19. Regmi A. Preoperative fructosamine is comparable to HbA1c as a short-term glycemic marker for predicting postoperative complications in orthopaedic surgery. *J Clin Orthop Trauma*. 2026. Available from: <https://www.sciencedirect.com/science/article/pii/S0972978X26000498>
 20. Ha MT. Assessing fructosamine and fructosamine-albumin ratio in type 2 diabetes patients: a cross-sectional study. *Diabetes Metab Syndr*. 2024;18(2). Available from: <https://www.sciencedirect.com/science/article/pii/S2666396124000190>
 21. Arjunan D. The utility of HbA1c and fructosamine in evaluating glucose intolerance in diverse populations. *Cureus*. 2025;17(3). Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC12768318/>
 22. Al-Yasiri EF, Hassan JK. The effect of herbal interventions on advanced glycation end products and fructosamine levels in patients with type 2 diabetes. *Palest Med Pharm J*. 2026;11(1). Available from: <https://journals.najah.edu/journal/pmpj/first-online/article/2782/>
 23. Sureshkumar P. A comprehensive review of HbA1c-glycemia mismatch in clinical practice. *Diabetes Res Clin Pract*. 2026. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S016882272600135X>
 24. Wiley OL. A study of the relationship between serum albumin-corrected fructosamine levels and diabetic retinopathy. *J Diabetes Res*. 2026. Available from: <https://onlinelibrary.wiley.com/doi/10.1155/jdr/9275699>
 25. ResearchGate. Evaluation of fructosamine as a new biomarker in the diagnosis of diabetes mellitus. 2025. Available from: <https://www.researchgate.net/publication/396439037>
 26. American Diabetes Association. 2. Diagnosis and classification of diabetes: standards of care in diabetes—2026. *Diabetes Care*. 2026;49(Suppl 1). Available from: https://diabetesjournals.org/care/article/49/Supplement_1/S27/163926/
 27. Chandran K. Fructosamine and HbA1c: a correlational study in a Southeast Asian population. *Cureus*. 2024;16(4). Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC11163312/>
 28. Raza A, Habib S, Noor S, Ahmad A. Metformin protects human insulin from fructosylation: an in vitro biochemical study. *Curr Med Chem*. 2026. Available from: <https://www.benthamdirect.com/content/journals/cmc/10.2174/0109298673397564250529061139>
 29. Entuc AM, Bogdan M, Boboc IKS, Tartau LM. Selected emerging biomarkers in type 2 diabetes mellitus: clinical insights and implications for precision care. *Medicina*. 2026;62(1). Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC12843815/>
 - 30.