haematologica
Journal of the Ferrata Storti Foundation

Diabetes mellitus and diabetes-related complications are common in patients with myelodysplastic syndromes but Hemoglobin A1C is an inadequate marker

by Ariel Israel, Roi Gat; Howard Oster, Yakir Moshe, Itamar Raz, Moshe Mittelman and Eugene Merzon

Received: October 8, 2025.
Accepted: January 12, 2026.

Citation: Ariel Israel, Roi Gat; Howard Oster, Yakir Moshe, Itamar Raz, Moshe Mittelman and Eugene Merzon. Diabetes mellitus and diabetes-related complications are common in patients with myelodysplastic syndromes but Hemoglobin A1C is an inadequate marker.
Haematologica. 2026 Jan 29. doi: 10.3324/haematol.2025.300022 [Epub ahead of print]

Diabetes mellitus and diabetes-related complications are common in patients with myelodysplastic syndromes but Hemoglobin A1C is an inadequate marker

Ariel Israel*[1], Roi Gat*[2,3], Howard Oster[3,4], Yakir Moshe[2,3], Itamar Raz[5,6], Moshe Mittelman**[2,3], Eugene Merzon**[1,7]

1. Leumit Health Services, Israel
2. Department of Hematology, Tel-Aviv Sourasky Medical Center, Tel-Aviv;
3. Faculty of Medicine, Tel-Aviv University; Tel-Aviv; Israel
4. Department of Medicine, Tel-Aviv Sourasky Medical Center, Tel-Aviv; Israel
5. Hadassah Medical Center, Jerusalem; Israel
6. Hebrew University, Jerusalem; Israel
7. Ariel University, Israel

* AI and RG contributed equally as co-first authors
** MM and EM contributed equally as co-senior authors

AI: Study conception, data access, cleaning and analysis, manuscript writing.

RG: Data analysis, literature review, writing the manuscript.

HO: Editing and writing the manuscript.

YM: Collecting data, writing and editing the manuscript, productive discussions.

IR: Productive discussions, reviewing the literature, editing the manuscript.

MM: Established collaboration, study conception, manuscript writing and editing.

EM: Established collaboration, study conception, data access, manuscript writing and editing.

Disclosure of Conflicts of Interest:

All authors declared no competing interests.

Data Availability Statement:

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

Correspondence address: Moshe Mittelman MD

Department of Hematology

Tel-Aviv Sourasky Medical Center

6 Weizmann St, Tel-Aviv, 6423906, ISRAEL

E-mail address: moshemt@gmail.com

We[1,2] and others[3] have suggested an association between myelodysplastic syndromes (MDS) and diabetes mellitus (DM). However, the nature of this co-occurrence is unclear. Another question is whether DM in MDS patients differs in features and complications from DM in non-MDS individuals. Here, we show that DM is common in MDS more than in the general population. Diabetic complications are common in diabetic MDS patients more than in non-MDS diabetics. We hypothesize that the hematologic disease results in a low/normal HbA1C, which is responsible for a delayed DM diagnosis. Thus, DM in MDS patients is diagnosed late, advanced and with complications.

MDS is a heterogenous group of aging clonal bone marrow stem cell neoplasms, characterized by ineffective hematopoiesis and a propensity to leukemia[4,5]. DM is a global epidemic affecting over $530x10^6$ people, with prevalence increasing with age[6]. Early diagnosis and treatment are critical. Glycemic control is monitored using glycated hemoglobin (HbA1C)[7,8]. HbA1C is superior to fasting plasma glucose and glucose tolerance test, convenient, stable, with fewer perturbations during stress, nutritional change or illness[7].

We conducted a retrospective case-control study based on the electronic health records (EHR) of the Leumit Health Services (LHS). LHS is one of Israel's public healthcare organizations, providing comprehensive community medical care across the entire country to all parts of the population. It offers a wide range of services, including primary care, specialist consultations, and preventive medicine programs, covering 725,000 residents. We identified 901 MDS patients who met the inclusion criteria (18-90yr, MDS diagnosis in 2000- through 2023). LHS members with no MDS were 20:1 matched (by age, sex and geographic region) and served as controls.

Data regarding demographics, comorbidities, medications and laboratory values (for MDS patients- within 15 days of diagnosis; for controls- at the same time and facility) as well as DM-related neuropathy, retinopathy and nephropathy, were compared between diabetic MDS patients and controls. Cardiovascular and cerebrovascular diseases (CVD) and peripheral vascular disease (PVD) were excluded from the analysis since the EHR did not specify the etiology- DM or another disease. The study was approved by the LHS Institutional Review Board.

Initially, diabetic MDS patients were compared with non-MDS controls. The two-sample t-test was employed to assess statistical significance of observed differences regarding continuous variables. Categorical variables were analyzed using Fisher's Exact Test, to determine odds ratios (OR), 95% confidence intervals and P-values.

Table 1 presents the patients' and controls' characteristics. The mean age was 72.4 years and 48.6% were females. The mean body mass index (BMI) was similar between the groups, but more MDS patients than controls had BMI<25 kg/m^2. Fewer MDS patients than controls were active smokers (8.6 vs 10.8%). The prevalence of hypertension was similar (65-66%) between both groups but fewer MDS patients had dyslipidemia (54.6 vs 59.5%).

DM was significantly more common in MDS patients compared with controls: 35.3% vs 28.0% [p<0.0001; OR 1.4, **Table 2a**]. MDS patients also tended to suffer more from hypoglycemic events (3.3 vs 1.6%, p=0.0004, OR 2.2). Also, DM-related neuropathy (8.4 vs 5.7%), retinopathy (6.4 vs 3.8%), and nephropathy (26.3% vs 15.9%) were significantly more common in MDS patients than in controls. The MDS cohort consumed anti-diabetic agents more than controls (data not presented).

Figure 1A displays a forest plot based on conditional logistic regression models for each outcome.

Given the higher prevalence of DM in MDS, an increase in DM-related complications was anticipated. However, the magnitude of the excess risk differed: while the OR for DM itself was modest (1.40), the ORs for major DM-related complications were higher (neuropathy 1.51; retinopathy 1.74; nephropathy 1.90). This pattern suggests that the burden of DM complications among MDS patients exceeds what would be expected based solely on increased DM prevalence. In other words, diabetes in MDS appears to be more advanced or less well-controlled at the time it is clinically recognized.

Figure 1B presents a multivariable conditional logistic regression analysis adjusting for age, sex, systolic blood pressure, socioeconomic status category, BMI category (5-kg/m^2 intervals), and diagnoses of diabetes mellitus, hypertension, and dyslipidemia. Even after controlling for these factors, including the presence of DM itself, diabetic complications remained significantly more prevalent among MDS patients than among matched controls. This reinforces the possibility that diabetes in MDS is underdiagnosed or undertreated prior to the development of complications, rather than merely more common.

The mean fasting serum glucose at MDS diagnosis was higher in MDS patients than in controls (112±33 vs 109±31 mg/dL, p=0.02). Interestingly, more MDS patients than controls had serum glucose levels in the DM defining range 126-199 mg/dL: 19.3% vs 15.3% (p=0.002) (**Table 2b**). Surprisingly, mean HbA1C levels were lower in MDS patients than in the controls (**Table 2b**): 5.9±1.1 vs 6.2±1.05% (p<0.0001). Subgroup

analysis of HbA1C levels revealed that a value <5% was more common in MDS than in controls (16.1% vs 4.9%, p<0.0001).

Previous reports suggested an increased prevalence of DM in MDS. The EUMDS group reported 23% DM incidence[1]. We reported 26% DM incidence in 700 MDS patients[2]. These patients had more comorbidities than other MDS patients, however no overall survival difference was noted. Little information has been reported, often without comparison to control non-MDS populations. Goldberg et al. analyzed data of US Medicare and found that DM was more prevalent in MDS than non-MDS individuals aged ≥65y (40 vs. 33.1%)[3]. Others reported lower prevalences of DM among MDS patients (17–21%), often associated with worse OS and more complications[9].

We confirmed that DM was more common in MDS patients compared with non-MDS controls (35.3% vs. 28.0%). Diabetic MDS patients had more hypoglycemic events, used more anti-diabetic medications and had higher glucose levels. Moreover, our analysis shows that not only DM is more common in MDS patients compared to controls, but also DM-related complications in diabetic MDS patients are more common than in non-diabetic MDS patients, suggesting more advanced or poorly managed DM.

A possible explanation lies in HbA1C. While HbA1C is a standard tool for diagnosing and monitoring DM[10], it may be unreliable in MDS patients. HbA1C is an irreversible product of a protein glycosylation process that reflects glucose exposure over the lifespan of red blood cells (RBC), occurring throughout the entire lifetime of RBC, typically 120 days[11]. Nevertheless, about half of the RBC glycosylation takes place during days 90-120[12]. Thus, a shortened RBC lifespan results in a falsely low HbA1C

that does not represent the real levels of glucose balance over time. In MDS, RBC are structurally abnormal and often have shortened lifespan due to hemolysis, ineffective erythropoiesis or transfusions. Prior studies show increased apoptosis, oxidative stress and hemolysis in MDS RBC and structural hemoglobin changes may further impair glycosylation[13,14]. These factors may lead to falsely low HbA1C levels, masking the true prevalence and/or severity of DM. As a result, since HbA1C is falsely low or normal in MDS patients (possible in other hematological diseases as well), DM may be undetected or diagnosed late, only when complications develop.

In summary, we found: 1) Higher prevalence of DM in MDS patients compared with the general populations. 2) Increased prevalence of DM-related complications among diabetic MDS patients, which is not only due to the higher prevalence of DM but may also be related to more advanced DM when diagnosed. 3) The relatively low/normal than expected HbA1C in MDS patients appears to be responsible for the late DM diagnosis and the more advanced disease and complications upon diagnosis of DM in MDS patients. 4) Our findings and conclusions draw the attention of the clinical community to be aware of this phenomenon and not to trust HbA1C as a reliable marker for DM diagnosis and glucose control in MDS patients (and probably other hematological diseases).

References

1. Symeonidis A, Yu G, Smith A, et al. The Impact of Diabetes Mellitus As Comorbid Condition, in Patients with Lower-Risk Myelodysplastic Syndromes (MDS)- a Study of the European LeukemiaNet-Based MDS (EUMDS) Registry. Blood. 2017;130(Supplement 1):4264.
2. Moshe Y, Joffe E, Uri G, et al. Characteristics and Survival of Diabetic and Non-diabetic Patients With Myelodysplastic Syndromes. Hemasphere. 2018;2(S1):941.
3. Goldberg SL, Chen E, Corral M, et al. Incidence and Clinical Complications of Myelodysplastic Syndromes Among United States Medicare Beneficiaries. J Clin Oncol. 2010;28(17):2847-2852.
4. Malcovati L, Hellström-Lindberg E, Bowen D, et al. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. Blood. 2013;122(17):2943-2964.
5. Sekeres MA, Taylor J. Diagnosis and Treatment of Myelodysplastic Syndromes: A Review. JAMA. 2022;328(9):872-880.
6. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119.
7. 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.
8. American Diabetes Association Professional Practice Committee. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022;45(Suppl 1):S125-S143.
9. Rozema J, Hoogendoorn M, Kibbelaar R, van den Berg E, Veeger N, van Roon E. Comorbidities and malignancies negatively affect survival in myelodysplastic syndromes: a population-based study. Blood Adv. 2021;5(5):1344-1351.
10. American Diabetes Association Professional Practice Committee. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022; 45(Suppl 1):S17-S38.

11. Lin H, Yi J. Current Status of HbA1c Biosensors. Sensors (Basel). 2017;17(8):1798.
12. Reynolds TM, Smellie WS, Twomey PJ. Glycated haemoglobin (HbA1c) monitoring. BMJ. 2006;333(7568):586-588.
13. Vryttia P, Theocharaki K, Kazolia, et al. Myelodysplastic Syndrome Red Blood Cell Physiology Abnormalities and Their Correlation with Disease Risk and Therapeutic Interventions. Blood. 2023;142(Supplement 1):6451.
14. Steensma DP, Viprakasit V, Hendrick A, et al. Deletion of the alpha-globin gene cluster as a cause of acquired alpha-thalassemia in myelodysplastic syndrome. Blood. 2004;103(4):1518-1520.

Table 1. MDS patient characteristics vs non-MDS control group.

		MDS Patients (n=901)		**Non-MDS controls (n= 18,020)**		**P value**	**OR** [CI]
		Mean ± SD	**n (%)**	**Mean** ± SD	**n (%)**		
Age (years)		**72.4** ± 13.2		**72.4** ± 13.2		0.956	
Sex	Females		438 **(48.6%)**		8,760 **(48.6%)**	1	1.00 [0.87 - 1.15]
BMI (Kg/m^2)		**27.8** ± 5.3		**28.1** ± 5.1		0.111	
BMI categories*	Underweight		20 **(2.3%)**		231 (**1.4%)**	**0.025**	**1.75** [1.04 - 2.78]
	Normal		255 **(29.5%)**		4,472 **(26.1%)**	**0.033**	**1.20** [1.03 - 1.39]
	Overweight		311 **(35.9%)**		7,021 **(41.0%)**	**0.003**	**0.83** [0.72 - 0.95]
Smoking	Active		77 **(8.6%)**		1,946 **(10.8%)**	**0.031**	**0.77** [0.60 - 0.98]
Comorbidities	Hypertension		601 (66.7%)		11,658 (64.7%)	0.224	1.09 [0.95 - 1.26]
	Dyslipidemia		492 **(54.6%)**		10,717 **(59.5%)**	**0.004**	**0.82** [0.72 - 0.94]
Hb (gr/dL)		**10.6** ± 2.0		**13.5** ±1.5		**< 0.0001**	**11.8**

MDS- myelodysplastic syndrome; SD- standard deviation; OR- odds ratio; CI- 95% confidence interval; BMI- body mass index; Kg- kilogram; m- meter; gr- gram; dL- deciliter.

* Underweight: BMI<18.5 kg/m^2; Normal 18.5≤BMI<25 kg/m^2; Overweight BMI ≥ 25 kg/m^2

Table 2. Diabetes Mellitus and related clinical outcomes of MDS patients vs non-MDS controls.

Table 2A. DM and complications.

	MDS Patients (n=901)		**Non-MDS controls (n=18,020)**		**Statistics**	
	n	**%**	**n**	**%**	**P value**	**OR** [CI]
Diabetes Mellitus	318	**35.3%**	5049	**28.0%**	**<0.0001**	**1.40** [1.22 - 1.61]
Hypoglycemia	30	**3.3**	286	**1.6**	**0.0004**	**2.20** [1.41 - 3.14]
Neuropathy	75	**8.4%**	1023	**5.7%**	**0.001**	**1.51** [1.18 to 1.93]
Retinopathy	58	**6.4%**	684	**3.8%**	**<0.0001**	**1.74** [1.32 to 2.30]
Nephropathy	237	**26.3%**	2859	**15.9%**	**<0.0001**	**1.89** [1.62 to 2.21]

Table 2B. Glucose and HbA1C levels.

		MDS Patients (n = 901)		**Non-MDS controls (n = 18,020)**		**P value**	**OR** [CI]
		Mean ± SD	**n (%)**	**Mean** ± SD	**n (%)**		
Glucose (mg/dL)		**112** ± 33		**109** ± 31		**0.02**	
	0 – 99		394 (45.3%)		8,086 (47.7%)	0.19	0.95 [0.83 - 1.09]
	100 – 125		289 (33.3%)		5,930 (34.95%)	0.32	0.96 [0.83 - 1.11]
	126 – 199		168 **(19.3%)**		2,592 **(15.3%)**	**0.002**	**1.36** [1.14 - 1.62]
	200+		18 (2.1%)		358 (2.1%)	1	1.01 [0.59 – 1.02]
HbA1C (%)		**5.9** ± 1.1		**6.2** ± 1.05		**<0.0001**	
	HbA1C**<5**		145 **(16.1%)**		891 **(4.9%)**	**<0.0001**	**3.69** [3.03 - 4.47]
	HbA1C**<6.5**		592 **(77.5%)**		10,493 **(74.7%)**	0.09	1.16 [0.98 - 1.39]

DM- diabetes mellitus; MDS- myelodysplastic syndrome; HbA1C- hemoglobin A1C; SD- standard deviation; OR- odds ratio; CI- 95% confidence interval; mg- milligram; dL- deciliter.

Figure 1. Association of MDS with diabetes mellitus and diabetes-related complications: univariable and multivariable conditional logistic regression analyses
Forest plots presenting the associations between myelodysplastic syndromes (MDS) and diabetes-related outcomes based on conditional logistic regression analyses accounting for the matched study design.
A. Univariable models with MDS as the explanatory variable.
B. Multivariable models Multivariable models adjusted for age, sex, systolic blood pressure, socioeconomic status category, BMI category (5-kg/m^2 intervals), and diagnoses of hypertension and dyslipidemia. For models where diabetic neuropathy, retinopathy, or nephropathy were the outcomes, diagnosed diabetes mellitus (DM) was also included as a covariate. Odds ratios (OR) / adjusted OR (aOR) >1 indicate increased prevalence in MDS compared with matched controls. Horizontal bars indicate 95% confidence intervals.