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

We[1,2] and others[3] have previously 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 more common in MDS 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, at advanced stage, and with complications.

Myelodysplastic syndromes 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, is convenient, stable, and with fewer perturbations during stress, changes in diet or illness.[7]

We conducted a retrospective case-control study based on the electronic health records (EHR) of the Leumit Health Services (LHS). The 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 (age 18-90 years, 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 other 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 used 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.

Table 1. Myelodysplastic syndrome patient characteristics *versus* non-MDS control group.

	MDS patients N=901		Non-MDS controls N=18,020		*P*	OR (95% CI)
	Mean ±SD	N (%)	Mean ±SD	N (%)		
Age, years	72.4±13.2	-	72.4± 13.2	-	0.956	-
Female sex	-	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)
Active smokers	-	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, g/dL	10.6±2.0	-	13.5±1.5	-	<0.0001	11.8

BMI: body mass index; CI: confidence interval; Hb: hemoglobin; MDS: myelodysplastic syndrome; OR: odds ratio; SD: standard deviation. *Underweight: BMI<18.5 kg/m^2; Normal: BMI ≤18.5 to <25 kg/m^2; Overweight: BMI ≥25 kg/m^2.

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%).

Diabetes mellitus was significantly more common in MDS patients compared with controls: 35.3% *vs*. 28.0% (OR 1.4, *P*<0.0001) (Table 2A). MDS patients also tended to suffer more from hypoglycemic events (3.3% *vs*. 1.6%, OR 2.2, *P*=0.0004). 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 shows 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 OR 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 had suggested an increased prevalence of DM in MDS. The European MDS (EUMDS) group reported DM incidence of 23%.[1] We reported 26% DM incidence in 700 MDS patients.[2] These patients had more comorbidities than other MDS patients; however, no difference in overall survival (OS) was noted. Little information has been reported, often without comparison to non-MDS control populations. Goldberg *et al*. analyzed US Medicare data and found that DM was more prevalent in MDS than non-MDS individuals aged ≥65 years (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 confirm that DM was more common in MDS patients

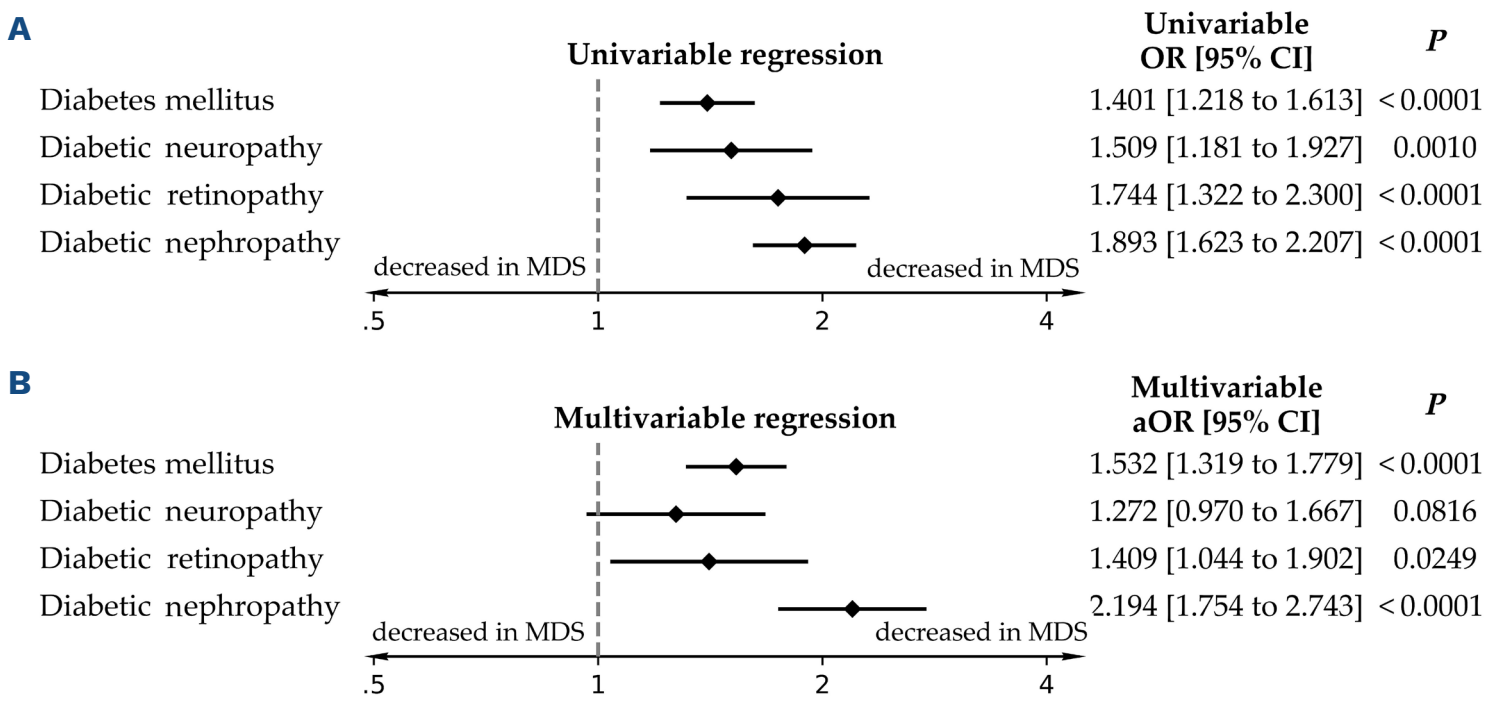

Figure 1. Association of myelodysplastic syndrome with diabetes mellitus and diabetes-related complications: univariable and multivariable conditional logistic regression analyses. Forest plots presenting the associations between myelodysplastic syndromes (MDS) and diabetes-related outcomes based on conditional logistic regression analyses accounting for the matched study design. (A) Univariable models with MDS as the explanatory variable. (B) Multivariable models adjusted for age, sex, systolic blood pressure, socioeconomic status category, Body Mass Index (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 co-variate. Odds ratios (OR) / adjusted OR (aOR) >1 indicate increased prevalence in MDS compared with matched controls. Horizontal bars indicate 95% confidence intervals.

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 is DM 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 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 a shortened lifespan due to hemolysis, ineffective erythropoiesis or transfusions. Prior studies have showed 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 (and possibly also in other hematologic diseases), DM may be undetected or diagnosed late, and only when complications develop.

In summary, we found: 1) higher prevalence of DM in MDS patients compared with the general population; 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 lower / more 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. Our findings and conclusions aim to promote awareness of this phenomenon in the clinical community and to suggest that HbA1C is not a reliable marker for DM diagnosis and glucose control in MDS patients. This could also be the case in other hematologic diseases.

Table 2. Diabetes mellitus and related clinical outcomes of myelodysplastic syndrome patients *versus* non-myelodysplastic syndrome controls.

A. Diabetes mellitus and complications.

	MDS patients N=901		Non-MDS controls N=18,020		Statistics	
	N	%	N	%	*P*	OR (95% CI)
Diabetes mellitus	318	35.3	5,049	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	1,023	5.7	0.001	1.51 (1.18-1.93)
Retinopathy	58	6.4	684	3.8	<0.0001	1.74 (1.32-2.30)
Nephropathy	237	26.3	2,859	15.9	<0.0001	1.89 (1.62-2.21)

B. Glucose and HbA1C levels.

	MDS patients N=901		Non-MDS controls N=18,020		*P*	OR (95% 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	
<5		145 (16.1)		891 (4.9)	<0.0001	3.69 (3.03-4.47)
<6.5		592 (77.5)		10,493 (74.7)	0.09	1.16 (0.98-1.39)

CI: confidence interval; DM: diabetes mellitus; HbA1C: hemoglobin A1C; MDS: myelodysplastic syndrome; OR: odds ratio; SD: standard deviation.

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No conflicts of interest to disclose.

Contributions

AI is responsible for study conception, data access, cleaning and analysis, and writing the manuscript; RG is responsible for data analysis, literature review, and writing the manuscript; HO is responsible for writing and editing the manuscript; YM is responsible for collecting data, writing and editing the manuscript, and productive discussions; IR is responsible for productive discussions, reviewing the literature, and editing the manuscript; MM is responsible for establishing the collaboration, study conception, and writing and editing the manuscript; EM is responsible for establishing the collaboration, study conception, data access, and writing and editing the manuscript.

Data-sharing statement

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

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