Diabetes mellitus and risk of plasma cell and lymphoproliferative disorders in 94,579 cases and 368,348 matched controls

The prevalence of co-occurring diabetes mellitus (DM) and cancer is increasing worldwide. Small studies have shown an association between overall plasma cell and lymphoproliferative disorders (LPD) and DM. We evaluated the association between DM and nine LPD as well as unspecified amyloidosis from a population-based matched case-control study in Sweden, including 94,579 cases and 368,348 controls. We found a significant increase of LPD diagnoses within 6 months of DM diagnosis, but >6 months after DM diagnosis, DM remained associated with increased risk of acute lymphoblastic leukemia (ALL; odds ratio [OR]: 1.47; 95% confidence interval [CI]: 1.04-2.06), chronic lymphocytic leukemia (CLL; OR: 1.18; 95% CI: 1.1-1.25), and amyloidosis (OR: 1.62; 95% CI: 1.44-1.83), as well as decreased risk of Waldenström macroglobulinemia (WM; OR: 0.77; 95% CI: 0.65-0.91). DM was not associated with increased risk of monoclonal gammopathy of undetermined significance (MGUS) after controlling for medical visits (OR: 0.99; 95% CI: 0.92-1.07) or with MGUS progression. Our findings show that DM association is time-dependent and suggest that some previously observed associations may be disease-specific or caused by detection bias. In contrast, our results suggest that there may be a biological mechanism for the association between DM and ALL.

Epidemiologic studies suggest patients with DM are at a higher risk for many cancers.[1-3] Smaller epidemiologic studies and a meta-analysis have shown an association between DM and LPD, including plasma cell disorders, suggesting increased risk for multiple myeloma (MM), leukemia, and non-Hodgkin lymphoma (NHL).[1,3-6] One study noted this risk only in CLL.[7] However, an association with DM has not yet been studied in related disorders such as MGUS, amyloidosis (unspecified including AL amyloidosis [AL] and related amyloid disorders), WM, Hodgkin lymphoma (HL), hairy cell leukemia (HCL), ALL, and T-cell malignancies, including T-cell lymphoma and mycosis fungoides (TCL). To our knowledge, this is the largest population-based study to evaluate this risk of specific LPD in relation to prior DM diagnosis.

In the main analysis, we conducted a population-based matched case-control study to evaluate the impact of preceding DM on the development of LPD in adults. We included cases of MM, WM, HL, NHL, TCL, HCL, ALL, and CLL in the Swedish Cancer Registry and cases of amyloidosis (International Classification of Diseases [ICD] codes E85.8, E85.9) and CLL in the Swedish National Patient Registry from 1987 to 2013. Individuals with MGUS were acquired from a network of Swedish hematology and oncology centers and the Swedish National Patient Registry as previsouly described.[8] For each case, up to four controls matched by age, sex, and county of residence were included from the general population. Cases with no matching controls were excluded. DM diagnosis was acquired from the Swedish National Patient Registry (ICD E10, E11, E12, E13, E14).

We first assessed the risk of LPD at any time after DM diagnosis. Second, because DM may be diagnosed or registered when patients seek care for the symptoms of LPD — which often have considerable diagnostic delay — we assessed the association of LPD diagnosis with DM diagnosis ≤6 months or >6 months before the LPD diagnosis. We also included a sensitivity analysis with a cut-off at 12 months. Conditional logistic regression, conditioned on the matching variables, was performed to estimate odds ratios. A sensitivity analysis was performed for individuals with MGUS. Because MGUS is asymptomatic, it is often diagnosed during medical visits for other disorders, and detection bias of MGUS and DM may result from DM or MGUS follow-up. We restricted the analysis to years with available outpatient visit data (≥2001); excluded participants with no clinical encounters (visit or admission) <1 year before the matched MGUS case diagnosis; and used logistic regression adjusting for number of visits in the year preceding inclusion, in addition to adjusting for sex, age, and year of inclusion.

In a secondary analysis, we assessed the risk of progression from MGUS to MM, WM, amyloidosis, or other LPD. Participants were followed from the date of MGUS diagnosis until diagnosis of LPD. In order to avoid immortal time bias we included DM as a time-dependent covariate in a Cox-model adjusting for age, sex, and year of MGUS diagnosis.

All analyses were performed in R (v3.6.3; R Core Team, 2020) using the survival and survminer packages. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Table 1. Prevalence of diabetes mellitus preceding the diagnosis of lymphoproliferative disorders compared to matched controls.

Diagnosis	LPD (n)		DM diagnosed before LPD				DM diagnosed ≤6 months before LPD				DM diagnosed >6 months before LPD			
	case	control	DM case	DM control	OR	95% CI	DM case	DM control	OR	95%CI	DM case	DM control	OR	95% CI
HCL	890	3,515	5.1%	5%	1.03	0.73-1.44	1.3%	0.4%	3.65	1.67-8.00**	3.7%	4.6%	0.8	0.54-1.18
HL	4,402	17,410	4.2%	3%	1.46	1.23-1.74***	0.9%	0.2%	5.81	3.59-9.4***	3.3%	2.8%	1.19	0.98-1.44
NHL	32,898	128,896	7.2%	5.9%	1.23	1.17-1.29***	1.4%	0.4%	4.08	3.58-4.64***	5.7%	5.6%	1.03	0.97-1.08
TCL	1,784	7,012	7%	5.3%	1.35	1.09-1.67**	1.3%	0.3%	3.72	2.07-6.66***	5.7%	4.9%	1.16	0.93-1.47
MM	15,275	59,695	8.1%	6.4%	1.30	1.22-1.39***	2.3%	0.4%	5.90	4.98-6.98***	5.9%	6%	0.97	0.9-1.05
ALL	1,198	4,738	6.5%	3%	2.35	1.75-3.15***	2.5%	0.1%	19.19	7.97-46.22***	4%	2.8%	1.47	1.04-2.06*
WM	3,380	13,260	7.6%	7.4%	1.03	0.89-1.19	2.2%	0.5%	4.04	2.91-5.6***	5.4%	6.8%	0.77	0.65-0.91*
MGUS#	19,172	75,032	10%	6.8%	1.55	1.46-1.64***	1.8%	0.4%	4.37	3.74-5.11***	8.2%	6.3%	1.33	1.25-1.41***
CLL	18,422	71,796	9.3%	6.7%	1.44	1.36-1.53***	2%	0.4%	4.82	4.14-5.61***	7.3%	6.2%	1.18	1.1-1.25***
Amyloidosis	5,373	21,200	9.6%	5.4%	1.93	1.72-2.15***	1.8%	0.4%	5.33	3.93-7.21***	7.8%	5%	1.62	1.44-1.83***

#Refer to text for MGUS adjustment per sensitivity analysis. *P<0.05; **P<0.01; ***P<0.001. DM: diabetes mellitus; LPD: ymphoproliferative disorders; HCL: hairy cell leukemia; HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma; TCL: T-cell lymphoma; MM: multiple myeloma; ALL: acute lymphoblastic leukemia; WM: Waldenström macroglobulinemia; MGUS: monoclonal gammopathy of undetermined significance; CLL: chronic lymphocytic leukemia; OR: odds ratio; CI: confidence interval.

Patients with MGUS, MM, amyloidosis, HL, NHL, TCL, ALL, and CLL were more likely to have a preceding DM diagnosis compared to matched controls, whereas patients with WM and HCL were not. These results remained significant for MGUS, amyloidosis, ALL, and CLL when DM was diagnosed >6 months prior to the LPD (Table 1). Large Israeli and Canadian studies showed an attenuated long-term risk for MM, NHL, and leukemia >1 year after DM diagnosis, although the association remained significant.[3,4] Our study had substantially more cases. Other studies that have not evaluated time-dependent risk showed an overall association of DM with MM, NHL, and CLL.[5-7] Prior data suggesting that maternal DM increases childhood ALL risk in offspring indicate biologic mechanisms behind this long-term increased risk of ALL associated with DM, thus warranting further study in adults.[9]

Diagnosis of DM >6 months prior was associated with decreased risk of development of WM (OR: 0.77; 95% CI: 0.65-0.91; P<0.05), which is unique compared to all other LPD and has not been reported before. This may be related to the protective effect of anti-diabetic drugs[10] although no data is available on their effect in patients with WM. However, further research is needed to expand on this finding of the study.

Risk of MGUS and CLL remained increased after excluding DM diagnoses <6 months prior. These disorders are often asymptomatic, particularly MGUS, and their diagnosis might be associated with medical follow-up. In a sensitivity analysis controlling for the number of clinic visits, we found that MGUS was not increased in DM (OR: 0.99; 95% CI: 0.92-1.07; P=0.89), indicating that detection bias during medical follow-up likely explains the association we had initially observed in MGUS. CLL can present both as an asymptomatic or symptomatic disease, meaning that a similar analysis for CLL would be difficult to interpret. However, a large proportion of CLL patients are asymptomatic, so a similar detection bias in part may be reasonably conjectured in CLL.

Long-term risk of amyloidosis was also increased in DM (OR: 1.62; 95% CI: 1.44-1.83; P<0.001). DM is a chronic inflammatory disorder associated with amyloid deposition in pancreatic islets[11] and kidneys.[12] However, these sites are not routinely biopsied, so these findings are likely to be incidental and underrepresented by international classification of diseases (ICD) codes. This suggests that the increased risk of AL may be related to DM. Light chain glycosylation is associated more frequently with AL than with other LPD[13] and DM is associated with higher incidence of protein glycosylation,[14] suggesting a possible mechanism for the role of DM in the development of AL.

Short-term risk of cancer diagnosis after DM diagnosis may result from detection bias, particularly because risk factors (aging, obesity, physical activity, diet, alcohol, and smoking) are common to both DM and cancer. In symptomatic conditions, patients may have DM diagnosed <6 months prior through clinical encounters for similar symptoms of fatigue and weight loss. In asymptomatic disorders such as MGUS and CLL, clinical encounters for DM may lead to increased rates of LPD diagnosis. Alternatively, a direct biological link via hyperinsulinemia (insulin like growth factor-1), chronic inflammation (cytokines), or hyperglycemia (epigenetic changes or protein glycation/glycosylation) may lead to development or acceleration of early-stage cancer, particularly as patients may have prediabetes or undiagnosed DM for many years.[15] Patients with DM for >6 months are likely to be on anti-diabetic medications including metformin, which protects against MGUS progression,[10] and insulin, which does not increase the risk for NHL and MM compared to untreated diabetics.[6] Sensitivity analysis using a 12 month cut-off for time between DM and LPD diagnosis showed essentially the same results (*data not shown*).

Table 2. Monoclonal gammopathy of undetermined significance progression to more advanced disease by diabetes mellitus state.

	Diabetes mellitus	No diabetes mellitus
n	2,224	12,563
Median age (years)	73	72
Age range (years)	26-95	18-99
male (%)	60	52
Diagnosed with DM after MGUS	739 (33%)	–
Progressed n (%)	220 (9.9%)	2,031 (16.2%)
MM	137 (6.2%)[#]	1,115 (8.9%)[#]
WM	35 (1.6%)	380 (3.0%)
Amyloidosis unspecified	14 (0.6%)[#]	153 (1.2%)[#]
Other LPD	35 (1.6%)	384 (3.1%)
Cox models (no DM as reference)		
Progressed (overall)	0.89 (95% CI: 0.78-1.03); P=0.11	
MM	1.06 (95% CI: 0.88-1.26); P=0.54	
WM	0.72 (95% CI: 0.51-1.02); P=0.06	
Amyloidosis unspecified	0.74 (95% CI: 0.43-1.29); P=0.29	
Other LPD	0.70 (95% CI: 0.50-1.00); P=0.047	

[#]These numbers include two individuals - one with diabetes mellitus (DM) with concomitant multiple myeloma (MM) and amyloidosis and one without DM with concomitant Waldenström macroglobulinemia (WM) and amyloidosis diagnosed on the same day. They have been counted once for each diagnosis. MGUS: monoclonal gammopathy of undetermined significance; LPD: lymphoproliferative disorder.

Patients with DM are not more likely to progress from MGUS to MM, WM, amyloidosis, or other LPD (Table 2). However, we could not control for the use of anti-diabetic drugs that may lower rates of MGUS progression.[10] Interestingly, we found decreased risk of progression from MGUS to WM of borderline significance (P=0.06) which is consistent with the findings of the main analysis showing an association of DM and decreased risk of WM.

The large sample size to detect differences in rare diseases is a major strength of this study. Limitations include lack of granular information related to DM (including DM subtypes), body mass index, LPD, and race/ethnicity, as well as a likely lack of racial/ethnic diversity in this population. Also, the diagnoses are based on ICD codes, relying on the correct registration by physicians.

This is the largest population-based study of preceding DM diagnosis on the time-dependent risk of individual LPD, showing there is an attenuated long-term risk with ALL, CLL, and amyloidosis. Furthermore, DM was not associated with MGUS progression.

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Data sharing statement: The data included in study is built on multiple population-based registries including the medical records of Swedish citizens. Although the data has been made unidentifiable before analysis, ethical board approval does not permit data sharing.

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