Metformin Use and the Transformation of Monoclonal Gammopathy of Undetermined Significance into Multiple Myeloma

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BACKGROUND

- Multiple myeloma (MM) is the second most common hematologic malignancy in the United States and is preceded by monoclonal gammopathy of undetermined significance (MGUS).
- Stimulation of the insulin-like growth factor receptor pathway is a hypothesized mechanism for the progression of MGUS to MM; therefore, alteration of this pathway with metformin could reduce the risk of progression.
- The goal of this study is to evaluate the influence of metformin use on the transformation of MGUS to MM.

METHODS

- Data from the Veterans Health Administration database were used.
- Patients with diagnosed MGUS (ICD-9 273.1) between October 1, 1999 and December 31, 2009 and at least one ICD-9 code of diabetes prior to their MGUS diagnosis were obtained.
- Two investigators (KKO and TST) reviewed patient-level clinical data to verify both MGUS and MM diagnoses and abstracted additional data, including size of baseline M protein, immunoglobulin (Ig) subtype, and serum-free light-chain ratio, when available.
- IgM or IgD MGUS patients were removed.
- Constant metformin users were defined as patients whose average duration between metformin prescriptions is less than 4 months over the 4-year period after their MGUS diagnosis.
- The time from MGUS diagnosis to MM diagnosis was the main outcome of interest.
- Chi-square tests and analysis of variance were conducted for categorical and continuous variables, respectively. Cox proportional hazards models were used. The time from MGUS diagnosis to MM diagnosis was the main outcome of interest.

RESULTS

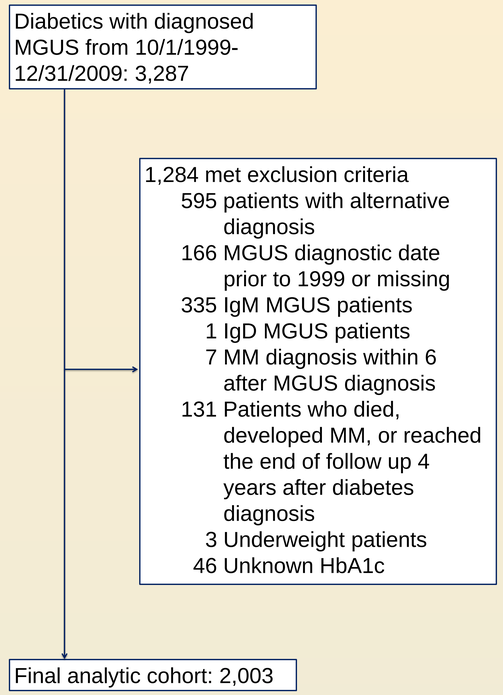
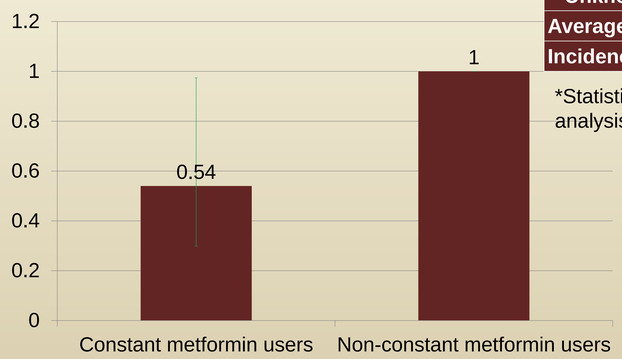


Figure 1. Data attrition diagram



Estimates from the Cox proportional hazard model controlling for age, sex, race, Hba1c, comorbidities, BMI categories, serum M-spikes*, Ig subtype, constant metformin use status*.
*Statistically significant at 5% level.

Figure 2. Hazard ratios for developing MM

Table 1. Demographic and clinical characteristics

Demographic and clinical characteristics	Overall	Constant Metformin use	
	N=2,003	Yes (n=452)	No (n=1,551)
Age (mean years)*	69.2	67.1	69.8
Male (%)	97.9	97.4	98.1
Race (%)*			
White	61.3	65.0	61.2
Black	32.3	25.4	34.2
Other	4.6	8.2	3.6
Unknown	1.9	1.3	2.1
Average BMI (%)			
18.5-24.9 kg/m^2	10.4	8.9	10.9
25-29.9 kg/m^2	34.6	32.3	35.3
≥30 kg/m^2	49.6	54.7	48.2
Unknown	5.3	4.2	5.7
Co-morbidities (mean Charlson score)*	5.2	3.6	5.6
Serum M Spike (%)			
<1.5 g/dL	53.9	49.3	55.3
≥1.5 g/dL	4.0	4.2	4.0
Unknown	42.0	46.5	40.8
Ig subtype (%)			
A	14.4	16.6	13.8
G	81.6	81.0	81.8
Light chain	1.3	0.4	1.6
Unknown	2.7	2.0	2.8
Average HbA1c (%)	7.1	7.2	7.1
Incidence of MM (%)	4.3	3.1	4.7

*Statistically significant at 5% level for Chi-square tests or analysis of variance.

RESULTS (cont'd)

Table 2. Hazard ratios for developing MM

Parameter	Hazard ratio	95% Confidence limits	
Constant metformin use*	0.54	0.30	0.97
Overweight	1.02	0.46	2.27
Obese	0.94	0.43	2.05
Black	1.12	0.71	1.76
Other race	0.90	0.28	2.90
Female	1.53	0.47	4.98
Age	1.00	0.97	1.02
Serum M spike ≥1.5g/dL*	5.72	3.08	10.64
IgA*	2.36	1.43	3.91
Light chain	2.61	0.61	11.05
Mean HbA1c	1.01	0.84	1.21
Comorbidity	0.97	0.90	1.05

*Statistically significant at 5% level.

CONCLUSIONS

- This is the first study to examine the association between metformin use and the development of MM in U.S. veterans with diabetes diagnosed with MGUS from 1999 to 2009.
- After verification from patients' clinical data and exclusion of patients inappropriate for analysis, 2,003 MGUS patients with diabetes were identified. Among them, 23% were constant metformin users and 87 patients developed MM.
- We found that constant metformin users were associated with a reduced risk of transformation from MGUS to MM. In addition, patients with M protein concentration ≥1.5 g/dL and IgA monoclonal protein were associated with an elevated risk of progression.

ACKNOWLEDGEMENTS

Funding from the Barnes-Jewish Hospital Foundation and the National Institutes for Health Grant U54 CA155496 supported this research. S.-H. Chang is supported by the Agency for Healthcare Research and Quality Grant K01 HS022330. G.A. Colditz is supported by the American Cancer Society Clinical Research Professorship. K.R. Carson is supported by the American Cancer Society Grant MSRG-13-077-01-CPHPS.