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Impact of metformin on the progression of MGUS to multiple myeloma

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Multiple myeloma (MM) arises from asymptomatic precursor states, monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma (SMM) [1,2]. These precursor states are present in about 4% of those over the age of 50 and are easily identified with simple, widely available tests on peripheral blood [3]. Although the survival of MM has improved dramatically due to several major therapeutic advances in recent years, MM remains incurable and is associated with significant morbidity [4]. The average risk of progression from MGUS to MM is about 1% per year [5]. Given the low risk of progression and the lack of available agents with acceptable efficacy to toxicity ratios, chemoprevention interventions to reduce the development of MM in MGUS has not been studied [6].

Metformin is a widely used drug for diabetes that has been shown to reduce the risk of developing multiple solid cancers among diabetics [7]. There are several potential mechanisms by which metformin may exert its anti-cancer properties [8]. Metformin reduces insulin like growth factor-1 and insulin levels, both of which are known to be growth factors for cancer, including MM [9]. Metformin is associated with weight loss, which could also modify the risk of MGUS to MM progression as obesity is a known risk factor for MM [10]. Metformin has also been shown to change adipokine levels, activate AMPK signaling and inhibit mTOR, all of which have a net anti-cancer effect. Recently, Chang has shown that metformin use among diabetics with MGUS was associated with a reduced risk of developing active MM in a large study of overwhelming male US military veterans [11]. We

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sought to evaluate the impact of metformin use on the development of MM among patients with MGUS, using a large population-representative dataset from the United Kingdom (UK).

We conducted a matched case-control study nested within The Health Improvement Network, THIN, a population-representative database of approximately 11,000,000 individuals treated by general practitioners in the UK between 1995-2013 (<http://www.thin-uk.com/>). We identified 124 MGUS cases transformed to MM and 760 MGUS controls without documented transformation during follow-up. Diagnoses of MGUS and MM were determined using READ codes, the standard primary care classification system in the UK.

Selection of controls was based on incidence density sampling [12]. For each individual with MGUS and subsequent MM, up to ten controls were randomly selected after matching on age, sex, practice site, and duration of follow-up from MGUS diagnosis. Each control subject could not have been diagnosed with MM as of the date of MM diagnosis of the matched case subject. The date that the case subject was first diagnosed with MM served as the index date for both the case subject and for the matched control.

Exposure to metformin was defined as receipt of at least two prescriptions for metformin at the time of MGUS diagnosis. Conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CI) for MM in MGUS patients with diabetes treated with metformin, other anti-diabetic medications, or no treatment, compared to patients without diabetes. In addition to matching, analyses were adjusted for obesity (BMI>30mg/m²) and smoking (ever). In a sensitivity analysis to reduce confounding by indication, we repeated the primary analysis using an alternative exposure definition of metformin use of > 2 years and < 2 years and adjusted for glucose levels prior to MGUS diagnosis. We also repeated this analysis in the subgroup of patients with diabetes using diabetic individuals without metformin exposure as the reference group.

There was no statistically significant difference between cases and controls in age (72.2±10.4 vs. 73.4±9.3, respectively), sex (61.3% males vs. 59.6%, respectively) or duration of follow-up (2.3±2.7 years vs. 1.7±2.2 years, respectively). We first looked at the impact of metformin and other anti-diabetic therapy on incident MM in patients with MGUS (Table 1A) relative to patients without diabetes. In diabetics who were not on therapy there was no increased risk of developing MM (OR 0.96 (0.38-2.38)). In contrast, among diabetics who have been exposed to metformin, there was a reduced but non-significant risk of incident MM (OR 0.39 (0.14-1.13)). For diabetics receiving other therapies (sulfonylureas, thiazolidiones and insulin) without metformin exposure, there was a similar impact on MM risk (OR 0.17 (0.02-1.28)).

Because of the trend towards reduced risk of MM in metformin-exposed patients, we explored duration of metformin exposure in relation to incident MM. When metformin exposure was defined as cumulative duration > 2 years and analyses were adjusted for serum glucose level, we observed a statistically significant reduction in myeloma risk (OR 0.19, 0.04-0.99). In analyses limited to diabetic patients, metformin treatment > 2 years was associated with an OR of 0.40 (95 CI%, 0.08-2.04) and metformin treatment < 2 years was

associated with no change in risk (OR 1.01 (0.18-5.65), relative to diabetes patients not treated with metformin (Table 1B).

In the current matched case-control study, we have shown that anti-diabetic medications may be associated with a reduced risk of developing active MM among MGUS patients with diabetes. For metformin, the impact was shown mainly for patients who have been treated for at least two years, but not for patients who have been on therapy for a shorter period of time.

Our study has distinct differences from the previous work by Chang [11]. While Chang examined the effect of metformin, but not other anti-diabetic therapies, on MM risk the current study evaluated different anti-diabetic medications and was able to demonstrate a protective effect that was not unique to metformin alone. These results suggest that glycemic control may reduce the risk of developing MM among diabetic patients with MGUS. Additionally, our study matched on duration of time from MGUS diagnosis to MM diagnosis and assessed medication exposure at the time of MGUS diagnosis to reduce time-window bias [13]. Finally, the current study was based on a large population-representative dataset of MGUS patients. The incidence of cancer in THIN was previously shown to be valid compared to cancer registry data in the UK [14,15]. Limitations of the study included reduced sample size, particularly in the diabetes subgroup analysis, inability to assess pathological characteristics of MGUS, (including M-protein isotype, M-protein concentration and ratio of free serum light chains), inability to assess race, and relatively short follow-up time from MGUS diagnosis.

In conclusion, we have shown that anti-diabetic medications may have a protective effect on the development of MM in diabetic patients with MGUS. These results add to previous data by Chang et al and other studies showing a protective effect of metformin on the development of cancer [11]. Preclinical studies have also shown anti-myeloma effects of metformin [16,17]. Future studies should address the effect of tight glycemic control, in addition to other metformin-specific mechanisms, on MGUS progression to MM in diabetic patients. MM will be an increasing burden on our population due to aging and increasing rates of obesity. Therefore, exploring opportunities to prevent the development of MM is critical.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
The impact of metformin on the development of myeloma in MGUS

<i>A) Association of metformin and other diabetes therapy with incident myeloma in patients with MGUS.</i>				
	Cases N=124	Controls N=760	Unadjusted OR	Adjusted § OR
No diabetes	113	633	Ref	Ref
Diabetes, no therapy	6	38	0.95 (0.38-2.35)	0.96 (0.38-2.38)
Diabetes, metformin exposed	4	65	0.39 (0.14-1.10)	0.39 (0.14-1.13)
Diabetes, other therapy without metformin exposure **	1	24	0.17 (0.02-1.29)	0.17 (0.02-1.28)
<i>B) Association of metformin duration with incident MM in patients with MGUS and diabetes*.</i>				
	Cases (n=11)	Controls (n=127)	Unadjusted OR	Adjusted ** OR
Diabetes, never exposed to metformin	7	62	Ref	Ref
Diabetes, metformin exposure < 24 mos	2	17	1.04 (0.20- 5.48)	1.01 (0.18-5.65)
Diabetes, metformin exposure > 24 mos	2	48	0.37 (0.07-1.87)	0.40 (0.08-2.04)

§ Adjusted for obesity (BMI>30mg/m2) and smoking (ever).

* This analysis was unmatched.

** Unconditional logistic regression was used adjusted for age, sex, obesity and smoking.