Assessing the association between body mass index at diagnosis and the risk of progression in patients with monoclonal gammopathy of undetermined significance

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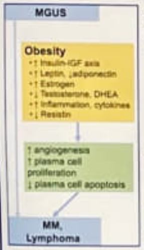
Introduction

Monoclonal Gammopathy of Undetermined Significance (MGUS) → ~1% per year → Multiple myeloma, AL amyloidosis, Lymphoma

What increases the risk of progression?

- M-protein isotype (IgM & IgA > IgG)[1,2]
- M-protein ≥15 g/L[2]
- Abnormal free light chain (FLC) ratio[2]
  (Surrogate measures of tumor burden)
- ?Genetic evolution of plasma cell clones[3]
- ?Immune microenvironment
- ?Environmental risk factors
  - **Obesity** (the only proposed modifiable risk factor)



Observational studies[4-7] have shown an association between obesity and increased risk of progression from MGUS to myeloma:

- Limited power to assess whether BMI is associated with progression independent of established biomarkers
- Studies done in patients screened for MGUS

Clinical and Public Health Relevance

- WHO estimates that in 2016 39% of adults were overweight and 13% were obese[8]

Understanding the role of obesity and disease progression may lead to studies of weight loss reduction for secondary prevention of multiple myeloma/lymphoma

Study Aim

In patients with **clinically-detected** MGUS, assess whether baseline BMI is associated with the risk of progression to myeloma, AL amyloidosis, or a lymphoproliferative disorder when accounting for baseline monoclonal protein risk factors.

Methods

Retrospective cohort study

Data collected from:
1. Prospectively maintained clinical database
2. EMR (BMI data)

Included

Patients evaluated by a hematologist at Mayo Clinic (Rochester, MN) between 2000-2020

Excluded

- BMI not documented within 30 days of MGUS diagnosis
- MGUS diagnosed >3 months from first evaluation
- Progression (multiple myeloma, AL amyloidosis, lymphoma, or monoclonal gammopathy of clinical significance requiring treatment) within 1 year of MGUS diagnosis

Statistical analysis

- Cox regression for competing risks was used to describe strength of association between BMI and progression accounting for **death as a competing risk**, using a subdistribution hazard ratio (sHR)
  - Time to progression was defined the time between date of MGUS diagnosis to date of last follow-up, progression, or death
  - Progression to MM, lymphoma, AL amyloidosis was the main event of interest
  - Given that the long lag period between onset and diagnosis of AL amyloidosis and indolent lymphomas can make the true time to progression difficult to discern, we conducted **sensitivity analyses assessing the risk of progressing to MM alone.**

Results

Study Cohort

MGUS diagnosis 2000-2020 (n=16744)
→ No BMI available +/- 30 days from MGUS diagnosis (n=3898)
→ Progression <1 year from MGUS diagnosis (n=33)
→ Underweight BMI (small subgroup, lacked power for statistical analyses) (n=249)
Study Cohort (n=12564)

Baseline characteristics of study cohort

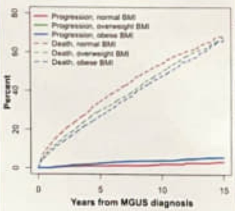
	Normal BMI* (n=3525)	Overweight* (n=4599)	Obese* (n=4440)	Total (n=12564)
Median height - cm (IQR)	169 (161-177)	173 (165-179)	172 (163-179)	171 (163-178)
Median weight - kg (IQR)	64 (57-72)	81 (73-89)	101 (91-113)	82 (70-96)
Median age at diagnosis - n (IQR)	71 (61-79)	71 (62-78)	68 (59-76)	70 (61-78)
Male sex - n(%)	1708 (49)	3063 (67)	2674 (60)	7445 (59)
Isotype - n(%)				
IgG	2173 (62)	2926 (64)	2944 (66)	8043 (64)
IgA	384 (11)	607 (13)	583 (13)	1574 (13)
IgM	903 (26)	981 (21)	834 (19)	2718 (22)
Other	27 (1)	40 (1)	43 (1)	110 (1)
Missing	*38 (1)*	*45 (1)*	*36 (1)*	*119 (1)*
MCP size at diagnosis - n(%)				
≥15 g/L	173 (5)	192 (4)	203 (5)	568 (5)
<15 g/L	3249 (92)	4243 (92)	4095 (92)	11587 (92)
Missing	*103 (3)*	*164 (4)*	*142 (3)*	*409 (3)*
FLCr at diagnosis - n(%)				
Abnormal	835 (24)	1103 (24)	1111 (25)	3052 (24)
Missing	*1816 (52)*	*2357 (51)*	*2185 (49)*	*6358 (51)*

Abbreviations: body mass index (BMI), monoclonal protein (MCP), free light chain ratio (FLCr)
*BMI is categorized as follows: **normal** (BMI 18.5-24.9 kg/m²), **overweight** (BMI 25-29.9 kg/m²), **obese** (BMI ≥30 kg/m²)

Baseline demographic and disease characteristics were evenly distributed between BMI categories

Cumulative incidence of progression

Cumulative incidence of progression to myeloma, lymphoma, or AL amyloidosis with death as a competing risk



"After accounting for death as a competing risk, an overweight or obese BMI was associated with an ***80%*** *increase in the risk of progression after a diagnosis of MGUS compared to a normal BMI"*

Age and sex are not effect modifiers of the association between BMI and progression:

Global p value for interaction terms:
- Age (continuous) * BMI category: **p=0.778**
- Sex * BMI category: **p=0.118**

Stratified and Adjusted Analyses

	Progression to MM, AL amyloidosis, or a lymphoproliferative disorder				Progression to MM only			
	#at risk/ # events	sHR	95% CI	p value	#at risk/ # events	sHR	95% CI	p value
BMI								
Normal *(18.5-24.9 kg/m²)*	3525/ 42	1.00	Ref.		3525/ 24	1.00	Ref. y	
Overweight *(25-29.9 kg/m²)*	4599/ 100	**1.79**	1.25-2.57	**0.001**	4599/ 70	**1.79**	1.25-2.57	**0.001**
Obese *(≥30 kg/m²)*	4440/ 94	**1.80**	1.25-2.58	**0.002**	4440/ 66	**1.80**	1.25-2.58	**0.002**
Recategorized BMI *(kg/m²)*								
Low normal *(18.5-22.9)*	1842/ 18	1.00	Ref.		1842/ 10	1.00	**Ref.**	
High normal *(23-24.9)*	1683/ 24	1.39	0.76-2.56	0.285	1683/ 14	1.46	0.65-3.28	0.358
Low overweight *(25-26.9)*	1949/ 42	**2.08**	1.2-3.61	**0.009**	1949/ 29	**2.58**	1.26-5.29	**0.009**
High overweight *(27-29.9)*	2650/ 58	**2.18**	1.29-3.69	**0.004**	2650/ 41	**2.77**	1.39-5.52	**0.004**
Low obese *(30-34.9)*	2645/ 60	**2.26**	1.33-3.81	**0.002**	2645/ 41	**2.77**	1.39-5.51	**0.004**
High obese *(≥35)*	1795/ 34	**1.97**	1.11-3.48	**0.020**	1795/ 25	**2.59**	1.25-5.39	**0.011**
Adjusted model #1								
Normal BMI	3491/ 42	1.00	Ref.		3491/ 24	1.00	Ref.	
Overweight	4554/ 100	**1.84**	1.27-2.67	**0.001**	4554/ 70	**2.18**	1.36-3.50	**0.001**
Obese	4375/ 94	**1.69**	1.16-2.47	**0.007**	4375/ 66	**1.96**	1.21-3.16	**0.006**
Adjusted model #2								
Normal BMI	3491/ 42	1.00	Ref.		3491/ 24	1.00	Ref.	
Overweight	4554/ 100	**1.84**	1.27-2.66	**0.001**	4554/ 70	**2.18**	1.36-3.50	**0.001**
Obese	4375/ 94	**1.71**	1.17-2.50	0.006	4375/ 66	**1.98**	1.22-3.19	**0.005**

Models were adjusted for:
1. Monoclonal protein size (≥15 or <15 g/L), isotype (IgG v. non-IgG), age (continuous), sex. **Available case analysis**
2. Monoclonal protein size (≥15 or <15 g/L), isotype (IgG v. non-IgG), age (continuous), sex, height at diagnosis. **Available case analysis**

Consistently, an increase in BMI (as a continuous or categorical variable) is associated with an increased risk of progression. Effect estimates are relatively similar even when progression is defined as MM only

Overweight/obese BMI is associated with increased risk of progression, independent of clinically established progression risk factors, and independent of baseline height

Discussion

Study Strengths

- Large study cohort
  - Largest study of BMI and progression risk in MGUS patients
  - Detailed clinical data
  - Sample size allowed sufficient statistical power to evaluate association between BMI and progression within multiple subgroups and conduct multiple sensitivity analyses

Study Limitations

- Missingness in abnormal FLCr data (it was routinely incorporated into practice in ~2010)
- Homogenous patient population (Majority Caucasian (>95%), single-center study)
- BMI as a marker of obesity
  - Doesn't account for fat distribution (visceral adiposity)
  - May overestimate obesity in people with higher muscle mass (blacks)
- Our study does not account for the effect of longitudinal changes in BMI on progression risk

Prior studies on BMI and MGUS progression

Study	n	Main results	Limitations
VA Cohort[4] (Retrospective)	7878	Risk of progression to MM (ref. = normal BMI): Overweight: HR 1.55; 95%CI 1.16-2.06 Obese: HR 1.98; 95%CI 1.47-2.68 Obese/overweight inc. risk of MM progression after adjusting for sociodemographic factors*	• Not adjusted for established clinical risk factors • Administrative health data
AGES-RA[5] (Prospective, screened MGUS)	575	High midlife BMI inc. risk of prog MM/Lymphoma (HR 2.66; 95%CI 1.17-6.05)	• Unadjusted analysis
PLCO[6] (Prospective, screened MGUS)	482	Trend towards inc. risk of progression to MM in obese patients (HR 1.24; 95%CI 0.59-2.60), **adjusted for demographic factors, m-protein isotype, size, FLCr, immunoparesis**	• Screened MGUS only • Small cohort
Olmstead County[7] (Prospective, screened MGUS)	594	BMI ≥25 kg/m2 inc. risk of prog. to MM/AL/lymphoma (HR 2.14; 95%CI 1.05-4.36), **adjusted for m-protein size, isotype, and FLCr**	• Screened MGUS only • Small cohort

*race, sex, marital status, income, Cr, diabetes mellitus, comorbidities
Abbreviations: multiple myeloma (MM), reference (ref.), increased (inc.), monoclonal protein (m-protein), free light chain ratio (FLCr)

Prior studies have shown a ~2X increased risk of progression in MGUS patients with higher BMI

This study reinforces that BMI (obesity) may be a risk factor for progression from MGUS to multiple myeloma, lymphoma, and AL amyloidosis, independent on clinically established risk factors

Conclusion

Increased BMI is associated with an ~80% increased risk of progression to multiple myeloma, lymphoma, and AL amyloidosis, independent of well characterized clinical risk factors (immunoglobulin isotype and size) when accounting for death as a competing risk.

Further work is needed to assess whether BMI reduction can mitigate the risk of progression and be used as a preventative strategy in MGUS patients

References

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