

ORIGINAL ARTICLE

Prevalence of Monoclonal Gammopathy of Undetermined Significance

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ABSTRACT

BACKGROUND

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The prevalence of monoclonal gammopathy of undetermined significance (MGUS), a premalignant plasma-cell disorder, among persons 50 years of age or older has not been accurately determined. We used sensitive laboratory techniques to ascertain the prevalence of MGUS in a large population in a well-defined geographic area.

METHODS

We identified all living residents of Olmsted County, Minnesota, as of January 1, 1995. We obtained serum that remained after the performance of routine clinical tests at Mayo Clinic or asked subjects for whom such serum was unavailable to provide a sample. Agarose-gel electrophoresis was performed on all serum samples, and any serum sample with a discrete band of monoclonal protein or thought to have a localized band was subjected to immunofixation.

RESULTS

Serum samples were obtained from 21,463 of the 28,038 enumerated residents 50 years of age or older (76.6 percent). MGUS was identified in 694 (3.2 percent) of these persons. Age-adjusted rates were higher in men than in women (4.0 percent vs. 2.7 percent, $P < 0.001$). The prevalence of MGUS was 5.3 percent among persons 70 years of age or older and 7.5 percent among those 85 years of age or older. The concentration of monoclonal immunoglobulin was less than 1.0 g per deciliter in 63.5 percent and at least 2.0 g per deciliter in only 4.5 percent of 694 persons. The concentration of uninvolved immunoglobulins was reduced in 27.7 percent of 447 persons tested, and 21.5 percent of 79 tested had a monoclonal urinary light chain.

CONCLUSIONS

Among residents of Olmsted County, Minnesota, MGUS was found in 3.2 percent of persons 50 years of age or older and 5.3 percent of persons 70 years of age or older.

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ALTHOUGH MULTIPLE MYELOMA IS THE prototypical monoclonal gammopathy, the most common plasma-cell disorder is the premalignant precursor of myeloma, monoclonal gammopathy of undetermined significance (MGUS). MGUS is defined by a monoclonal immunoglobulin concentration in serum of 3 g per deciliter or less; the absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the proliferation of monoclonal plasma cells; and a proportion of plasma cells in the bone marrow of 10 percent or less.¹⁻³ In large referral centers, half the patients with a monoclonal gammopathy have MGUS, whereas only 15 to 20 percent have multiple myeloma.

MGUS is associated with a rate of progression to multiple myeloma or a related malignant condition of 1 percent per year.^{1,2} Since this rate does not decrease with time, a patient with MGUS requires follow-up indefinitely. A serum monoclonal protein concentration of at least 1.5 g per deciliter, a monoclonal immunoglobulin other than IgG, and an abnormal serum free light-chain ratio (kappa:lambda light chains) are the main risk factors for progression to a malignant condition.⁴ Twenty years after the diagnosis of MGUS, the risk of a malignant condition is 58 percent in patients with all three risk factors, 37 percent in patients

with any two of the risk factors, 21 percent in patients with one risk factor, and 5 percent in patients with no risk factors. This classification identifies patients who are at highest risk for progression to multiple myeloma or a related malignant condition and who might benefit from an intervention that could prevent multiple myeloma.⁵

Opportunities to test preventive strategies are hampered by the underdiagnosis of MGUS in routine clinical practice. The coincidental finding of MGUS is not rare and is virtually never related to the patient's primary medical problem. Indeed, the frequency of monoclonal immunoglobulins in serum from a normal population has been reported to be 0.5 to 3.6 percent among patients seen in community practice⁶⁻⁸ or in hospitals⁹⁻¹¹ (Table 1). The true prevalence of MGUS has not been estimated accurately, however, because previous studies lacked a geographically defined population in which testing could be performed during a specified period. Furthermore, the screening methods used in many previous studies are less sensitive than current techniques. To overcome these limitations, we used sensitive laboratory procedures to determine the prevalence of MGUS in a large population in a well-defined geographic area.

Table 1. Prevalence of MGUS in Reported Studies.

Location	Age (yr)	No. of Persons Studied	Prevalence of MGUS (%)	Test Used to Identify Monoclonal Protein	Population Based	Reference
Swedish nursing home	≥70	294	3.1	Paper electrophoresis Immunoelectrophoresis	No	Hallen ⁶
Southern Sweden	≥25	6,995	0.9	Paper electrophoresis Immunoelectrophoresis	No	Axelsson et al. ⁷
Finistère, France	≥50	17,968	1.7	Cellulose acetate Immunoelectrophoresis	No	Saleun et al. ⁸
Ragiora, New Zealand	>21	2,192	0.5	Cellulose acetate	No	Carrell et al. ¹²
Northern Minnesota	≥50	1,200	1.2	Cellulose acetate Immunoelectrophoresis	No	Kyle et al. ¹³
North Carolina (1 urban and 4 rural counties)	≥70	816	3.6	Agarose gel Immunofixation	No	Cohen et al. ¹⁴
Large city hospital, United States	Not given	73,630	1.2	Agarose gel Immunoelectrophoresis	No (inpatient)	Vladutiu ⁹
General hospital, Italy	Not given	102,000	0.7	Cellulose acetate Immunoelectrophoresis	No (inpatient)	Malacrida et al. ¹⁰
Provincial hospital, Italy	11 to >75	35,005	2.9	Cellulose acetate Immunofixation	No (inpatient and outpatient)	Aguzzi et al. ¹¹
Olmsted County, Minnesota	≥50	21,463	3.2	Agarose gel Immunofixation	Yes	Current study

METHODS

After the study was approved by the institutional review boards of the Mayo Foundation and the Olmsted Medical Center, we obtained a list of residents of Olmsted County, Minnesota, as of January 1, 1995, from the Rochester Epidemiology Project.¹⁵ For some residents who were included in this study, MGUS had been discovered during their routine clinical care. For the others, we obtained serum that remained unused after routine clinical tests in the Mayo Clinic central-processing laboratory, which receives all blood samples from Mayo Clinic outpatients and inpatients at its affiliated Saint Marys and Rochester Methodist hospitals in Rochester, Minnesota. In patients for whom three or more chemistry studies are ordered, an additional amount of blood is removed at initial phlebotomy; this practice permits physicians to order additional tests without performing another phlebotomy. These serum samples are held in the central-processing laboratory for six days and then discarded.

We developed a computerized system to track samples assayed by the central-processing laboratory, matched this information with demographic data in Mayo Clinic registration databases, and printed a daily listing of each sample from any resident of Olmsted County who was 50 years of age or older who had not already been incorporated into the study. These samples were retrieved on the sixth day after phlebotomy and frozen at -70°C . A letter, also approved by the institutional review boards, was then sent to each patient asking for permission to study the blood sample. The consent form enclosed in the letter was signed by the patient, witnessed, and returned to us. If the patient did not respond within 30 days, a second letter was sent, and if there was still no response, a third letter was sent 30 days later.

Any patient who had not responded to the three letters after six months and who returned to provide another blood sample was contacted again, as had been done initially, for permission to use the sample. If a patient had died, a letter was sent to the next of kin to obtain permission. Finally, all Olmsted County residents eligible for the study who had not been seen at Mayo Clinic during the collection period, with the exception of those who had died or had moved away, were sent a letter asking them to provide a serum

specimen. Residents who obtained their medical care from Olmsted Medical Center were also contacted by letter and asked to provide a serum sample.

LABORATORY TESTS

Approximately four months after the collection of serum, when most of the subjects had replied to our letter, the samples from those who consented were thawed. Electrophoresis was performed on agarose gel (REP, Helena Laboratories). The agarose strip was inspected by a technician and by Dr. Kyle. Any serum with a discrete band or thought to have a localized band was subjected to immunofixation (Hydrasys and Hydragel, Sebia).¹⁶ If the patient did not give consent for use of the specimen, all patient-specific information, with the exception of sex and age group, was deleted to ensure anonymity, and the specimen was unmarked. These samples were tested in large batches, as prescribed by the institutional review board. MGUS was defined in accordance with previous definitions.¹⁻³

STATISTICAL ANALYSIS

Although serum samples were collected over a period of several years, each subject was assessed only once. Because MGUS is a chronic condition, the first value obtained was presumed to represent the status of that subject as of January 1, 1995. Prevalence rates were calculated by dividing the number of persons with MGUS in each age and sex stratum by the number of subjects in that stratum for whom an assayed serum sample was available. Age-adjusted and overall age- and sex-adjusted prevalence rates were obtained by direct standardization to the total population of the United States that was 50 years of age or older in 2000.

The age- and sex-specific prevalence pattern was examined with a smoothed function of age, separately by sex, with the use of generalized-additive-model procedures for Poisson regression.¹⁷ The number of persons with MGUS was entered as the dependent variable, age as the independent variable, and the number of samples as an offset. This method has been illustrated previously with regard to trends in the prevalence of hip fractures.¹⁸ The study was designed, the data were gathered and analyzed, and the manuscript was written by all the authors.

RESULTS

A total of 28,038 enumerated residents of Olmsted County were 50 years of age or older as of January 1, 1995. From January 1, 1995, to December 31, 2001, serum samples were obtained from 20,581 of these residents in the course of their routine clinical care. Permission to study the blood sample was obtained from 16,485 (79.1 percent) (Table 2). Of the families of deceased patients, 60.9 percent gave permission to use the sample.

In addition, 229 patients who were known to have MGUS at the time of study entry and who would have been identified as part of the central-processing method intentionally were not retested. Among 220 participants, MGUS had been

identified in 174 before the start of the study on January 1, 1995, and was identified in 46 by their physicians during the collection period. The nine remaining patients had monoclonal kappa or lambda light chains in the serum or urine.

By the end of the accrual period, 7228 residents still had not provided a sample. Letters requesting a sample were sent to 5117 residents, of whom 653 provided a sample. Letters were not sent to 2111 residents for the following reasons: 1609 had died, 262 had not given permission for their medical records to be reviewed,¹⁹ 116 could not be contacted, 93 had moved outside Olmsted County, and 31 had a known MGUS but were not seen at Mayo Clinic during the sampling period (Table 2). Even though these 31

Table 2. Results of Requests of Investigators to Study Serum Samples.*

Type of Contact	Permission Granted	Permission Refused† <i>number</i>	Other‡	Permission Granted %	Total No.
Face-to-face	244	NA	NA	100	244
Status already known	NA	NA	473	NA	473
Letter to patient					
1st	12,989	625	58	95.0	13,672
2nd	2,177	271	74	86.3	2,522
3rd	885	541	1932	26.3	3,358
Letter to family	190	18	104	60.1	312
Total	16,485	1455	2641	80.1	20,581
Percent	80.1	7.1	12.8	100	
Results		No. of Patients		No. of Patients with MGUS	
Patients with samples analyzed					
Identified in central-processing laboratory		20,581§		460	
Previously known		229¶		220	
Patients responded to letter at end of accrual		653		14	
Total		21,463		694	
Patients with no samples analyzed					
Patient or family did not respond to letter		4,464		NA	
Patient could not be contacted		2,111		NA	
Total		6,575		NA	
Total population		28,038		NA	

* NA denotes not applicable.

† Patient-specific information was removed before electrophoresis.

‡ "Other" includes patients classified as "missing," "do not contact," and "refused research," as well as those who did not respond.

§ Of these 20,581 patients, 4069 had blinded samples.

¶ Nine patients had Bence Jones proteinuria.

|| Patients were not contacted for the following reasons: 1609 had died, 262 had declined to provide authorization for research, 116 could not be contacted, 93 had moved out of Olmsted County, and 31 had known MGUS but were not seen at Mayo Clinic.

persons were known to have MGUS, they were excluded to avoid a biased estimate of prevalence.

Overall, 1455 patients declined to grant permission to use their samples and 2641 did not respond to our requests for permission. After all identification data except sex and age group were removed, electrophoresis was performed on the samples from these 4096 patients.

PREVALENCE

A monoclonal immunoglobulin was found in the serum of 371 of the 16,485 participants who had given permission (2.3 percent), 89 of the 4096 with blinded samples (2.2 percent), and 14 of the 653 who responded to our letters at the end of the accrual period (2.1 percent). In addition, samples from 229 participants who were known to have MGUS at study entry would have been analyzed. Thus, 694 of the 21,463 Olmsted County residents (3.2 percent) had MGUS.

MGUS was found in 350 of 9469 men, as compared with 344 of 11,994 women (3.7 percent vs. 2.9 percent, $P<0.001$) (Table 3). Of the 20,072 Olmsted County residents whose race or ethnic group was known, 97.3 percent were white and 1.4 percent were Asian. Of the 605 patients with MGUS whose race or ethnic group was known, 99.3 percent were white.

The overall prevalence of MGUS was 3.2 per 100 persons who were 50 years of age or older (95 percent confidence interval, 3.0 to 3.5) (Table 3). Age-adjusted rates were higher in men (4.0 per 100; 95 percent confidence interval, 3.5

to 4.4) than in women (2.7 per 100; 95 percent confidence interval, 2.4 to 3.0) ($P<0.001$). The rate among men was similar to that among women a decade older (Table 3). In both sexes, the prevalence increased with advancing age and was almost four times as high among persons 80 years of age or older as among those 50 to 59 years of age (Table 3). The prevalence leveled off after 85 years of age in men (Fig. 1) and after 90 years of age in women. In persons older than 85 years of age, the prevalence of MGUS was 8.9 percent in men and 7.0 percent in women (total, 7.5 percent). There was no significant difference in the concentration of the monoclonal protein among the age groups.

The prevalence of MGUS decreased slightly throughout the data-collection period, from 4.4 percent in the first year to 3.2 percent through the last year of sample collection ($P=0.41$). Thus, patients who sought medical care frequently and, therefore, had blood samples analyzed earlier were at no greater risk for MGUS than the apparently healthier population who did not seek medical care regularly (and had blood samples analyzed later).

LABORATORY CHARACTERISTICS

The isotype of the monoclonal immunoglobulin was IgG in 68.9 percent of the 694 patients with MGUS, IgM in 17.2 percent, IgA in 10.8 percent, and biclonal in 3.0 percent. The serum light-chain type was kappa in 62.0 percent and lambda in 37.9 percent of these 694 patients. The monoclonal immunoglobulin concentration was less than 1.00 g per deciliter in 63.5 percent of patients, 1.00 to 1.49 g per deciliter in 16.6 percent, 1.50 to 1.99 g per deciliter in 15.4 percent, and at least 2.00 g per deciliter in 4.5 percent; it was too low to measure in 91 patients (13.1 percent). Individual values ranged from unmeasurable to 2.94 g per deciliter; the median was 0.5 g per deciliter, or 0.7 g per deciliter if the unmeasurable proteins were excluded. The concentration of uninvolved (normal, polyclonal, or background) immunoglobulins was reduced in 124 of the 447 patients whose immunoglobulin concentration was measured (27.7 percent). One of the two measured isotypes of polyclonal immunoglobulins was reduced in 21.9 percent of patients, and both were decreased in 5.8 percent. Urine from 79 subjects with MGUS was tested by means of immunofixa-

Table 3. Prevalence of MGUS According to Age Group and Sex among Residents of Olmsted County, Minnesota.

Age	Men	Women	Total
	<i>number/total number (percent)*</i>		
50–59 yr	82/4038 (2.0)	59/4335 (1.4)	141/8373 (1.7)
60–69 yr	105/2864 (3.7)	73/3155 (2.3)	178/6019 (3.0)
70–79 yr	104/1858 (5.6)	101/2650 (3.8)	205/4508 (4.6)
≥80 yr	59/709 (8.3)	111/1854 (6.0)	170/2563 (6.6)
Total	350/9469 (3.7)†	344/11,994 (2.9)†	694/21,463 (3.2)†‡

* The percentage was calculated as the number of patients with MGUS divided by the number who were tested.

† Prevalence was age-adjusted to the 2000 U.S. total population as follows: men, 4.0 percent (95 percent confidence interval, 3.5 to 4.4); women, 2.7 percent (95 percent confidence interval, 2.4 to 3.0); and total, 3.2 percent (95 percent confidence interval, 3.0 to 3.5).

‡ Prevalence was age- and sex-adjusted to the 2000 U.S. total population.

tion. A monoclonal kappa light chain (16.5 percent) or lambda light chain (5.0 percent) was found in 17 patients tested. Table 4 lists the laboratory features of patients in the nonblinded, blinded, and clinically recognized samples.

PREVALENCE OF MGUS IN NEW RESIDENTS

During the seven-year accrual period, 2818 persons 50 years of age or older moved to Olmsted County and provided a blood sample during our collection process. Of these, 1778 (63.1 percent) gave permission to study their serum sample. They were not included in the prevalence estimate. The median age of this group was 65.9 years, and 47.4 percent were men. Sixty-five (3.7 percent) had MGUS. The median monoclonal immunoglobulin value was 0.6 g per deciliter, and the isotype was IgG in 69.2 percent. These values are similar to those for the long-time residents of Olmsted County.

DISCUSSION

Although the term "monoclonal gammopathy of undetermined significance," or "MGUS" was introduced more than 25 years ago¹ and long-term studies of the prognosis have been reported,^{1,2,20} we are unaware of any previous studies that have established the prevalence of MGUS in a geographically defined population with the use of sensitive laboratory techniques. With the use of our computerized system, we obtained results from 76.6 percent of the enumerated population of Olmsted County that was 50 years of age or older, and MGUS was found in 3.2 percent. The prevalence of MGUS in this study of Olmsted County residents is approximately twice that reported in some other studies^{7,8} (Table 1). In particular, the 5.3 percent prevalence of MGUS among the Olmsted County residents 70 years or older was almost double that reported previously.^{7,8}

Our results are almost fully representative of the entire population and are unlikely to be different had the total population been analyzed. Within the study cohort, the frequency of MGUS among subjects who gave permission to perform the serum studies was the same as that among subjects who did not give permission. The relatively high prevalence of MGUS in the general population in this study has implications for any screening programs or preventive strategies that are developed to reduce mortality from myeloma.

We found that the prevalence of MGUS increases with advancing age. In addition, we found that men have a higher frequency of MGUS than women; this finding corresponds to that in multiple myeloma, in which men account for almost 60 percent of patients.²¹ The association with age and sex was particularly notable in men 80 years of age or older, 8.3 percent of whom had MGUS. Knowledge of the age- and sex-specific prevalence rates of MGUS can influence patient care. Awareness of the frequency of MGUS in the elderly may limit the number of diagnostic tests to investigate the abnormality, because in most cases, the presence of a small monoclonal protein will be unrelated to the patient's medical problem. In fact, the presence of such a monoclonal immunoglobulin can be coincidental even among patients in whom a plasma-cell disorder is suspected. For example, elderly patients in whom systemic amyloidosis is diagnosed may have senile systemic amyloidosis and an unrelated MGUS, rather than a monoclonal protein associated with primary systemic amyloidosis. Nevertheless, all patients with MGUS must be monitored indefinitely for progression to a malignant condition.

The prevalence of MGUS increases with advancing age, but after adjustment for the concentration of the monoclonal protein, the annual risk of progression to myeloma or a related cancer is not affected by age or the duration of MGUS.² Younger patients are more likely to have progression to cancer during their lifetimes simply

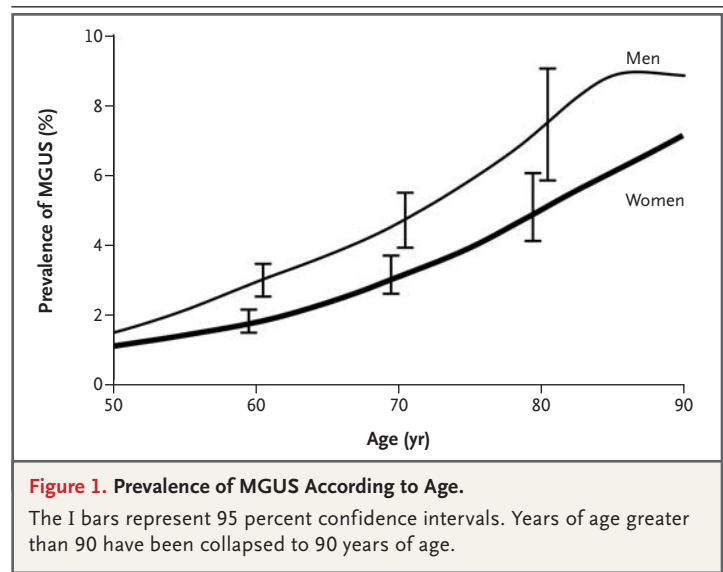


Table 4. Characteristics of Patients with MGUS among Residents of Olmsted County, Minnesota.

Characteristic	Nonblinded Sample (N=385)*	Blinded Sample (N=89)†	Clinical Sample (N=220)‡	Total (N=694)
Male sex (%)	54	46	45	50
Age				
Median (yr)	68	NA	75	70
50–59 yr (%)	24.7	23.6	11.4	20.3
60–69 yr (%)	29.6	13.5	23.6	25.7
70–79 yr (%)	28.1	34.0	30.0	29.5
≥80 yr (%)	17.7	28.1	35.0	24.5
Immunoglobulin isotype (%)				
IgG	68.1	68.2	70.9	68.9
IgA	11.4	9.1	10.5	10.8
IgM	16.9	18.2	17.3	17.2
Biclonal	3.6	4.6	1.4	3.0
Monoclonal protein (g/dl)				
Median	0.5	0.5	1.0	0.5
Range	Unmeasurable–2.94	Unmeasurable–2.14	Unmeasurable–2.76	Unmeasurable–2.94
Reduced concentration of uninvolved immunoglobulins (%)				
0	75.3	NA	62.8	72.3
1	19.8	NA	28.3	21.9
2	4.9	NA	8.9	5.8

* Patients in the nonblinded sample gave permission to have their serum sample studied. A monoclonal immunoglobulin was found in the serum of 371 of the 16,485 participants who had given permission (2.3 percent), as well as in 14 of the 653 who responded to our letters at the end of the accrual period (2.1 percent). NA denotes not applicable.

† Serum samples from patients who did not give permission to have their sample studied were blinded. A monoclonal immunoglobulin was found in the serum of 89 of the 4096 with blinded samples (2.2 percent). NA denotes not applicable.

‡ Patients in the clinical sample were known to have MGUS at entry into the study. Of 229 patients who were thought to have MGUS at study entry, 220 (96.1 percent) had the disorder and 9 (3.9 percent) had Bence Jones proteinuria.

because they are at risk for a longer time than are elderly patients.

The most common immunoglobulin type in MGUS identified in this study was IgG (more than two thirds of cases). This finding is similar to that in a French study,⁸ in which 68 percent of cases were of the IgG type. IgM MGUS was, however, found in 17 percent of our patients, 24 percent of patients in the French study, and only 8 percent in a Swedish study⁷; there is no apparent explanation for this discrepancy. The concentration of monoclonal protein in our study was small (median, 0.5 g per deciliter); 13.1 percent of patients had unmeasurable protein concentrations, and only 4.5 percent had a concentration of 2 g per deciliter or more.

In summary, this population-based study, which used sensitive laboratory techniques to detect monoclonal gammopathies, provides age- and sex-specific estimates of MGUS in a geographically defined population that is generally representative of the white population of the United States.¹⁵ Our results can form the basis of future screening programs and preventive strategies.

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No potential conflict of interest relevant to this article was reported.

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