

Prevalence and risk of progression of light-chain monoclonal gammopathy of undetermined significance: a retrospective population-based cohort study



Angela Dispenzieri, Jerry A Katzmann, Robert A Kyle, Dirk R Larson, L Joseph Melton III, Colin L Colby, Terry M Therneau, Raynell Clark, Shaji K Kumar, Arthur Bradwell, Rafael Fonseca, D F Jelinek, S Vincent Rajkumar

Summary

Background Monoclonal gammopathy of undetermined significance (MGUS) is defined by expression of heavy-chain immunoglobulin (IgH) and is the precursor lesion for 80% of cases of multiple myeloma. The remaining 20% are characterised by absence of IgH expression; we aimed to assess prevalence of a corresponding precursor entity, light-chain MGUS.

Methods We used a population-based cohort, previously assembled to estimate MGUS prevalence, of 21 463 residents of Olmsted County, MN, USA, aged 50 years and older. We did a serum free light-chain assay on all samples with sufficient serum remaining, and immunofixation electrophoresis was done for all samples with an abnormal free light-chain ratio or abnormal protein electrophoresis results from the original study. Light-chain MGUS was defined as an abnormal free light-chain ratio with no IgH expression, plus increased concentration of the involved light chain. We calculated age-specific and sex-specific prevalence and rates of progression to lymphoproliferative disorders for light-chain and conventional MGUS and assessed incidence of renal disorders in patients with light-chain MGUS.

Findings 610 (3·3%) of 18 357 people tested had an abnormal free light-chain ratio, of whom 213 had IgH expression that was diagnostic of conventional MGUS. 146 of the remaining 397 individuals had an increase of at least one free light chain and met criteria for light-chain MGUS. Prevalence of light-chain MGUS was 0·8% (95% CI 0·7–0·9), contributing to an overall MGUS prevalence of 4·2% (3·9–4·5). Risk of progression to multiple myeloma in patients with light-chain MGUS was 0·3% (0·1–0·8) per 100 person-years. 30 (23%) of 129 patients with light-chain MGUS were diagnosed with renal disease.

Interpretation We define a clinical entity representing the light-chain equivalent of conventional MGUS and posing a risk of progression to light-chain multiple myeloma and related disorders.

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Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is a precursor lesion for multiple myeloma, which is an incurable malignant disease affecting bone marrow that has a yearly incidence of roughly 4·6 per 100 000 population.¹ Historically, MGUS has been characterised by evidence of immunoglobulin heavy-chain (IgH) expression, but could therefore account for only 80% of cases of multiple myeloma, since in the remaining 20% no IgH (eg, IgG, IgA, IgD, or IgE) is secreted.² The prevalence and risk of progression of the premalignant precursor entity for light-chain multiple myeloma is unknown.

We postulated that an equivalent of MGUS in which IgH is not expressed—ie, light-chain MGUS—is the premalignant precursor of light-chain multiple myeloma. We previously used a serum agarose gel electrophoretic screening method to show that the prevalence of standard heavy-chain-associated MGUS was 3·2% in the population aged 50 years or older in Olmsted County, MN, USA (a predominantly white population), but identified only two patients in

21 463 people tested who had free light-chain expression in serum without heavy-chain expression.² We postulated that the serum immunoglobulin free light-chain assay,³ which can detect imbalances of unbound κ and λ light chains when circulating concentrations are as low as 10–30 mg/L,^{4–7} might provide us with better sensitivity than would protein electrophoresis to detect this putative entity of light-chain MGUS. Clonality is defined as a ratio of κ to λ that is outside the reference range. This definition depends on the ratio, rather than the absolute concentration of either chain independently, because both renal disease and polyclonal activation of B cells can cause a diffuse increase of both κ and λ plasma cells, yielding raised absolute concentrations of free κ and λ chains, but maintaining a normal ratio. We aimed to use the free light-chain assay to estimate prevalence of light-chain MGUS in the large, well defined, Olmsted County cohort that was originally assembled to estimate prevalence and progression of plasma-cell disorders.² We also described progression of this novel disorder to myeloma or related malignant disease.

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Hematology

(Prof A Dispenzieri MD, Prof R A Kyle MD, S K Kumar MD, Prof S V Rajkumar MD),

Laboratory Medicine

(Prof A Dispenzieri, J A Katzmann PhD, Prof R A Kyle, R Clark, S K Kumar, Prof S V Rajkumar), Biostatistics (D R Larson MS, C L Colby, Prof T M Therneau PhD),

Epidemiology

(Prof L J Melton III MD), and

Immunology

(Prof D F Jelinek PhD), Mayo Clinic, Rochester, MN, USA; University of Birmingham, Birmingham, UK (Prof A Bradwell MB ChB); and Hematology/Oncology Mayo Clinic, Scottsdale, AZ, USA (Prof R Fonseca MD)

Correspondence to:

Prof A Dispenzieri, Hematology, Mayo Clinic, Rochester, MN 55905, USA
dispenzieri.angela@mayo.edu

	Normal FLCR	Abnormal FLCR		All
		No increase in FLC concentration	Concentration of at least one FLC raised	
No IgH	17 337*	251	146	17 734
Previously found IgH ²	410	28	128	566
Newly discovered IgH	ND*	12	45	57
Total	17 747	291	319	18 357

Data are number of participants. FLCR=free light-chain ratio. FLC=free light chain. IgH=monoclonal immunoglobulin heavy chain. ND=immunofixation electrophoresis not done. *IgH not tested for in these patients since serum protein electrophoresis results and FLCRs were normal.

Table 1: Abnormalities in free light-chain ratios by presence of intact heavy-chain immunoglobulin

Methods

Patients

We used a population-based cohort that we had previously assembled to estimate prevalence of MGUS.² The original cohort consisted of 21 463 of the 28 038 enumerated Olmsted County residents aged 50 years or older on Jan 1, 1995 who had serum samples available. Written informed consent for the previous study included permission for further tests and studies on the samples, and for this study we did a serum immunoglobulin free-light-chain assay on all samples with sufficient remaining serum.

Procedures

After approval by the Mayo Clinic institutional review board, we applied the free light-chain assay (FREELITE, The Binding Site Ltd, Birmingham, UK) to stored serum samples using a Dade Behring BNII automated nephelometer (Siemens, Newark, DE, USA). The assay reports free κ and λ light-chain concentrations and the κ to λ ratio.⁸ We defined an abnormal result as a ratio outside the normal diagnostic range (0.26–1.65). The serum protein electrophoresis assay and serum immunofixation electrophoresis were done as previously reported.⁹ The limit of detection for these assays in our laboratory was 10 mg/L. Light-chain MGUS was defined as an abnormal free light-chain ratio with no IgH expression, plus an increase in concentration of the involved light chain.

Statistical analysis

Although serum samples were obtained during several years,² each participant was assessed only once. We calculated age-specific and sex-specific prevalence rates using number of patients with light-chain MGUS in each age and sex stratum as the numerator and number of people tested in the corresponding age and sex stratum as the denominator. Age-adjusted and overall age-adjusted and sex-adjusted prevalence rates were obtained by direct standardisation to the US population aged 50 years and older in 2000. 95% CIs for prevalence rates were calculated with the assumption of a Poisson distribution. We checked Poisson models for overdispersion (a form of goodness of fit). The age-specific prevalence pattern was examined as a smoothed function of age, separately by sex, with the use

of generalised additive model procedures for Poisson regression.¹⁰ The number of people with an abnormal free light-chain ratio, MGUS, or light-chain MGUS was entered as the dependent variable, age as the independent variable, and the number of people with samples tested as an offset. This method has been used previously to study prevalence of hip fractures.¹¹ Samples for which identifying data had been masked were necessarily omitted from calculation of progression.

We calculated progression rates using a person-years approach, in which number of recorded progressions was divided by total person-years of exposure. Rates were expressed as number of progression events per 100 person-years. Risk of progression was also analysed in the context of our previous MGUS risk model, in which we showed that patients with intact immunoglobulin MGUS and an abnormal free light-chain ratio had a higher risk of progression than did patients with a normal ratio (hazard ratio 3.5, 95% CI 2.3–5.5; $p < 0.0001$).¹² We depicted progression rates graphically using Kaplan-Meier curves. We checked Cox models for goodness of fit with respect to outliers and proportional hazards using the methods of Therneau and Gronbach.¹³ We also assessed incidence of renal disorders in patients with light-chain MGUS by crossreferencing free-light-chain MGUS data with patients in our disease-association study, which used the Hospital Adaptation of the International Classification of Diseases (8th edn) to assign diagnoses.¹⁴ All analyses were done with SAS (version 8.2) and Splus (version 8.0).

Role of the funding source

The Binding Site, UK, which provided reagents for this study, had no role in study design, collection, analysis, and interpretation of data, writing of the report, or the decision to submit for publication. AB, director of The Binding Site, participated in critical review of the report. AD and her Mayo Clinic colleagues had full access to all data in the study and had final responsibility for the decision to submit for publication. Neither The Binding Site nor AB participated in this decision.

Results

Sufficient serum for further analysis remained for 18 372 (86%) of the original 21 463 Olmsted County residents. Samples from 15 patients with malignant plasma-cell disorders were excluded.² An abnormal free light-chain ratio was reported for 610 of the remaining 18 357 participants (table 1). Serum immunofixation showed IgH expression in 213 of these 610 people, showing presence of conventional MGUS. These 213 patients included 57 for whom IgH expression was previously undetected with serum protein electrophoresis as the screening test. As a result, the overall age-adjusted and sex-adjusted prevalence of conventional MGUS in people aged 50 years and older in Olmsted County was 3.4% (95% CI 3.2–3.7)—an increase from our previous estimate, which was 3.2%.²

	Light-chain MGUS*†			Any MGUS*		
	Men (%)	Women (%)	Total (%)	Men (%)	Women (%)	Total (%)
50–59 years	22/3450 (0.6%)	14/3717 (0.4%)	36/7167 (0.5%)	95/3450 (2.8%)	64/3717 (1.7%)	159/7167 (2.2%)
60–69 years	25/2554 (1.0%)	15/2776 (0.5%)	40/5330 (0.8%)	122/2554 (4.8%)	85/2776 (3.1%)	207/5330 (3.9%)
70–79 years	28/1608 (1.7%)	15/2242 (0.7%)	43/3850 (1.1%)	116/1608 (7.2%)	112/2242 (5.0%)	228/3850 (5.9%)
80–89 years	6/577 (1.0%)	21/1433 (1.5%)	27/2010 (1.3%)	57/577 (9.9%)	118/1433 (8.2%)	175/2010 (8.7%)
Total	81/8189 (1.0%)	65/10 168 (0.6%)	146/18 357 (0.8%)	390/8189 (4.8%)	379/10 168 (3.7%)	769/18 357 (4.2%)
Age-standardised prevalence‡	1.0% (0.8–1.2) ‡	0.6% (0.5–0.8)‡	..	5.1% (4.6–5.6)‡	3.5% (3.2–3.9)‡	..
Prevalence standardised for age and sex§	..	..	0.8% (0.7–0.9)§	..	..	4.2% (3.9–4.5)§

Data are number/total number of men or women in age group (%), or % (95% CI). MGUS=monoclonal gammopathy of undetermined significance. *Abnormal free light-chain ratio with concentration of at least one free light chain higher than the normal range. †Excludes patients with intact heavy-chain MGUS. ‡Age-adjusted to the total US population aged 50 years and older in 2000. §Adjusted for age and sex to the total US population aged 50 years and older in 2000.

Table 2: Age-specific and sex-specific prevalence of light-chain MGUS and any MGUS

κ and λ concentrations relative to the normal range are delineated in the webappendix p 1 for the 397 people with abnormal free light-chain ratios and no IgH expression. 146 (37%) of these individuals had an increase in concentration of the light chain that was the cause of the abnormal ratio and met criteria for light-chain MGUS. The overall prevalence of light-chain MGUS was 0.8% (95% CI 0.7–0.9; table 2). Figure 1 shows the prevalence of an abnormal free light-chain ratio without increased absolute concentrations of either κ or λ .

Demographic characteristics of participants are shown in the webappendix p 2. The median age of patients with light-chain MGUS was 68 (range 50.0–96.0) years, compared with 70 (50.0–96.0) years for those with conventional MGUS. 108 people with light-chain MGUS had κ and 38 had λ predominance (2.8:1). The monoclonal free light chain could be detected with serum immunofixation electrophoresis for only 26 (18%) of the 146 individuals with light-chain MGUS (nine κ and 17 λ). Two of these patients had been identified by protein electrophoresis in the original survey,² but were not included in the intact immunoglobulin MGUS group. For two additional patients with light-chain MGUS, a discrepancy between immunofixation electrophoresis and free light-chain ratio results was noted, representing either assay error or biconality. The median concentration of involved free light chain in patients with light-chain MGUS who had positive immunofixation electrophoresis results was significantly higher than in patients with light-chain MGUS who had normal immunofixation electrophoresis results (176 mg/L vs 48 mg/L, $p < 0.0001$).

59 samples for which identifying data had been masked were necessarily omitted from calculation of progression, leaving 133 patients with light-chain MGUS and 577 with conventional MGUS. At 155 540 patient-years of follow-up for the entire cohort, progression to multiple myeloma or other disease had occurred in 62 patients (figure 2, table 3). Only three of the 133 unmasked cases

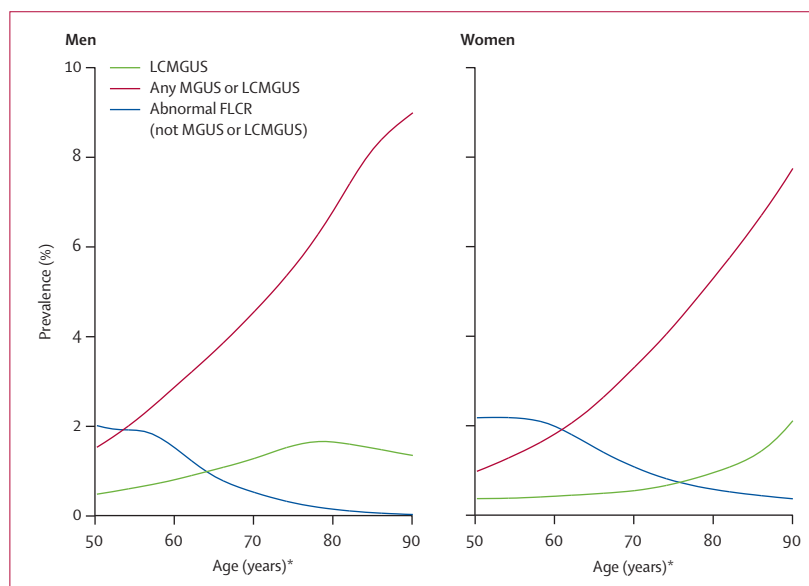


Figure 1: Prevalence of MGUS, light-chain MGUS, and abnormal FLCR without raised free light-chain concentration

MGUS=monoclonal gammopathy of undetermined significance. LCMGUS=light-chain monoclonal gammopathy of undetermined significance. FLCR=free light-chain ratio. *Ages greater than 90 years have been collapsed to 90 years.

of light-chain MGUS have progressed to multiple myeloma during 1100 patient-years of follow-up (table 4). These three progressions, which occurred at 19, 23, and 98 months, were all to light-chain multiple myeloma. The rate of progression from light-chain MGUS to any lymphoproliferative disorder was higher than the rate of progression in patients with normal free light-chain ratios ($p < 0.0001$), suggesting that light-chain MGUS is a premalignant plasma-cell disorder that is analogous to MGUS (table 3).

We next compared risk of progression for light-chain MGUS with that of conventional MGUS, which has an overall progression rate of 1.0% (0.73–1.33) per 100 person-years.² A coexisting abnormal free light-chain ratio increased risk of progression within the conventional MGUS cohort, but risk of progression did

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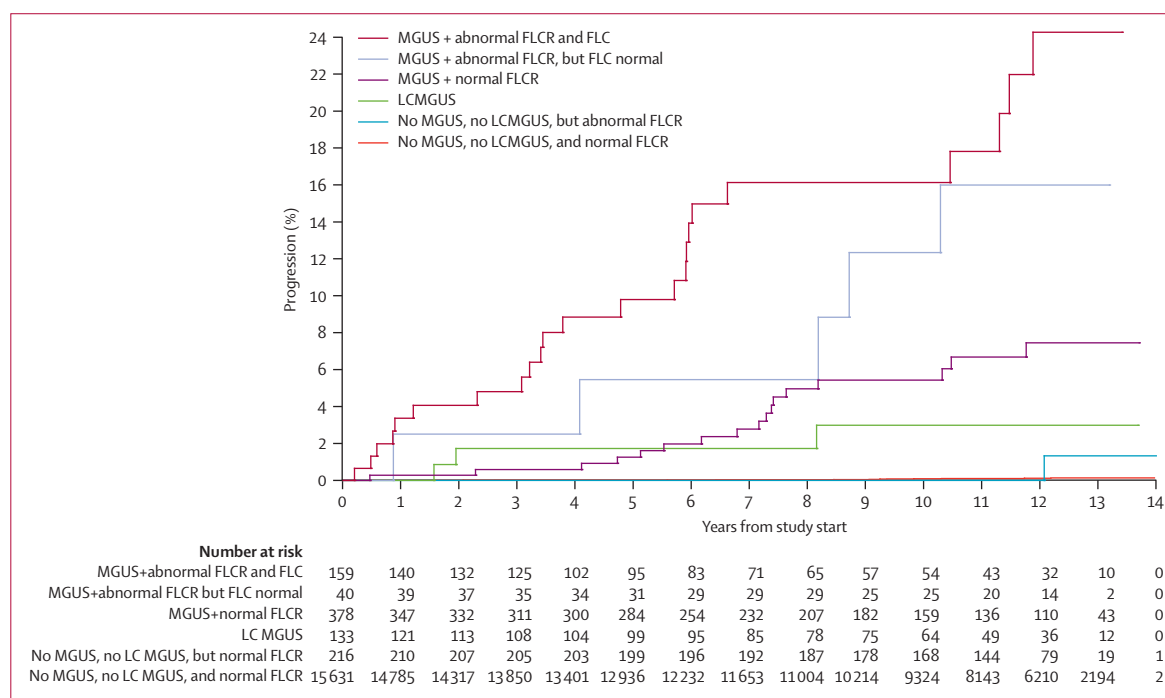


Figure 2: Rates of progression to multiple myeloma and related disorders

MGUS=monoclonal gammopathy of undetermined significance. FLCR=free light-chain ratio. FLC=free light chain. LCMGUS=light-chain monoclonal gammopathy of undetermined significance.

not differ between patients with low-risk conventional MGUS (ie, no coexisting abnormal ratio) and those with light-chain MGUS ($p=0.1822$). Thus, either the rates were similar or the power to detect a difference was restricted by the small sample size. Finally, we assessed overall survival of all groups to correct for missed progression events (eg, undiagnosed amyloidosis) that could have contributed to early mortality. Overall survival mirrored progression events (data not shown).

Renal disease raises serum concentrations of both κ and λ free light chains and in view of changes in catabolism of light chains during renal failure a so-called renal reference range has been proposed for use in interpretation of free light-chain ratios in patients with renal insufficiency.¹⁶ When the renal reference

range rather than the normal range was applied to the entire cohort, 69 individuals with apparent κ restriction were no longer deemed to have light-chain MGUS, but 57 people with apparent λ restriction were added (figure 3; webappendix p 3), including one patient who developed IgG λ multiple myeloma 90 months after acquisition of her research specimen. Because full medical information was not available for all patients, we did not use the renal reference range to calculate prevalence data. However, we noted an association between light-chain MGUS and renal diagnoses. By merging the present dataset with that from our report on MGUS disease association,¹⁴ we showed that in the 16 255 patients in both datasets, risk of a renal diagnosis was increased in patients with MGUS or light-chain MGUS (table 5). 30 (23%) of 129 patients with light-

	Abnormal FLCR with raised light-chain concentration		Abnormal FLCR without high component		Normal FLCR		Total	
	Number of progressors/PY	Progression rate per 100 PY (%)	Number of progressors/PY	Progression rate per 100 PY (%)	Number of progressors/PY	Progression rate per 100 PY (%)	Number of progressors/PY	Progression rate per 100 PY (%)
No conventional MGUS	3/1110	0.27% (0.06–0.79)*	1/2293	0.04% (0.00–0.24)	13/147 618	0.01% (0.01–0.02)	17/151 021	0.01% (0.01–0.02)
MGUS (detected in original study) [‡]	20/847†	2.36% (1.44–3.65)†	4/251†	1.59 (0.43–4.07)†	17/3072‡	0.55% (0.32–0.89)‡	41/4170	0.98 (0.71–1.33)
MGUS (newly detected)	3/237†	1.27% (0.26–3.70)†	1/115†	0.87% (0.02–4.84)†	NA‡	NA‡	4/352	1.14% (0.31–2.91)
Total	26/2194	1.19% (0.77–1.74)	6/2659	0.23% (0.08–0.49)	30/150 690	0.02% (0.01–0.03)	62/155 543	0.04% (0.03–0.05)

Data are n/PY or % (95% CI). MGUS=monoclonal gammopathy of undetermined significance. FLCR=free light-chain ratio. PY=person-years. NA=not applicable. *Light-chain MGUS population. †Conventional MGUS, increased risk as defined as abnormal FLCR. ‡Conventional MGUS, low risk as defined as normal FLCR.

Table 3: Risk of progression to multiple myeloma and related disorders

Research sample					At clinical progression, before initiation of chemotherapy												
Date	FLC (mg/L)			SIFE	Date	Symptoms	Hb (g/L)	Ca (mmol/L)	Cr (μmol/L)	FLC (mg/L)*			SIFE	UIFE/ UPEP (mg per day)	ISS	BMBX (%)	Bone disease
	κ	λ	Ratio							κ	λ	Ratio					
1 May 30, 1996	68.8	15.6	4.4	Neg	March, 1998	84-year-old woman with history of osteoporosis, hypertension, sick sinus syndrome, primary hyperparathyroidism, and goitre, presented with 3 months of left-hip pain and new-onset anaemia	92	2.7	97	85.7	1.58	54.2	Neg	κ/713	II	40%	Yes
2 Jan 17, 1997	60.2	16.7	36.0	Neg	August, 1998	65-year-old man with no medical history presented with 3 months of back pain	119	3.6	141	7.83	1.24	6.29	Neg	κ/NM	II	25%	Yes
3 May 17, 1996	66.2	10.7	6.19	Neg	July, 2004	79-year-old man with history of pseudogout, PVCs, BPH, hyperlipidaemia, and IBS, presented with 2–3 months of fatigue and renal insufficiency; renal biopsy showed cast nephropathy	109	2.7	203	1360	0.54	2500	κ/NM	κ/1980	III	60%	Yes

MGUS=monoclonal gammopathy of undetermined significance. FLC=free light chain. SIFE=serum immunofixation electrophoresis. Hb=haemoglobin. Ca=serum calcium. Cr=serum creatinine. UIFE=urine immunofixation electrophoresis. UPEP=urine protein electrophoresis. ISS=International Staging System.¹⁵ BMBX=bone marrow biopsy percent myelomatous involvement. NM=not measurable. PVCs=premature ventricular complexes. BPH=benign prostatic hypertrophy. IBS=irritable bowel syndrome. *Test done retrospectively on stored serum sample.

Table 4: Characteristics of three patients with light-chain MGUS who progressed to multiple myeloma

chain MGUS had some form of renal diagnosis that was not recognised as being related to a plasma-cell dyscrasia either at the time of acquisition of the test sample or subsequently. 18 (60%) of 2707 patients who had renal disease had λ-restricted light-chain MGUS.

Discussion

The term MGUS was coined more than 30 years ago at the Mayo Clinic in reference to asymptomatic individuals with an intact serum monoclonal protein concentration (both immunoglobulin heavy-chain and light-chain detectable) lower than 30 g/L and with less than 10% plasma cells in bone marrow.^{2,17,18} MGUS was shown to be the precursor lesion for intact immunoglobulin multiple myeloma.¹⁹ Roughly 80% of patients with multiple myeloma have IgH expression (ie, IgG, IgA, IgM, IgD, and IgE); no IgH is expressed in the remaining 20%. Before our original description of light-chain MGUS,²⁰ a premalignant lesion for light-chain multiple myeloma corresponding to MGUS had not been systematically described. However, a disorder called idiopathic Bence-Jones proteinuria was defined in seven patients who had urinary excretion of monoclonal protein of at least 1 g in 24 h without evidence of multiple myeloma or related disorders.²¹ In view of our present work, these patients could be considered the first cases of light-chain MGUS, but prevalence was not addressed. We have shown that 19% of cases of MGUS are of light-chain type, which is consistent with the proportion of light-chain only cases

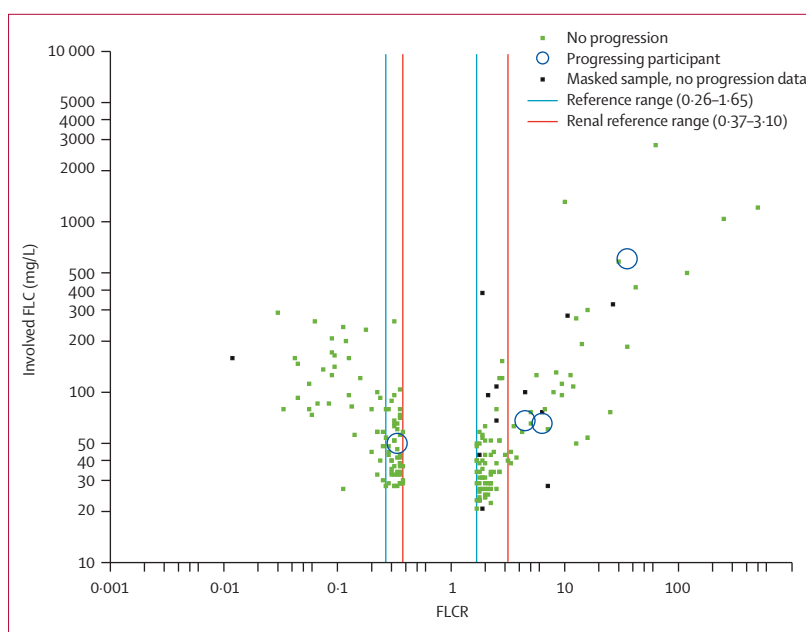


Figure 3: Definition of light-chain MGUS with the normal versus the renal reference range for FLCR
MGUS=monoclonal gammopathy of undetermined significance. FLC=free light chain. FLCR=free light-chain ratio.

among newly diagnosed cases of multiple myeloma,²² and our estimate that 0.8% of the general population aged 50 years and older have light-chain MGUS.

Recognition and description of this entity is important for two reasons. First, it provides insight into an additional

	n	Renal disease (%)		
		Before FLC measurement*	After FLC measurement†	Total
Patients with light-chain MGUS (a)	129	11 (8.5%)	19 (14.7%)	30 (23.3%)
Patients with MGUS (b)	566	35 (6.2%)	133 (23.5%)	168 (29.7%)
Patients without MGUS or light-chain MGUS, but abnormal FLCR (c)	211	2 (0.9%)	11 (5.2%)	13 (6.2%)
Patients without MGUS or light-chain MGUS, and normal FLCR (d)	15 349	531 (3.5%)	1965 (12.8%)	2496 (16%)
All patients with diagnostic data	16 255	579 (3.6%)	2128 (13.1%)	2707 (16.7%)

Data are number (%). MGUS=monoclonal gammopathy of undetermined significance. FLC=free light chain. FLCR=free light-chain ratio. *By χ^2 analysis: groups a and b versus c and d, $p<0.0001$; a versus b versus c and d, $p<0.0001$. †With a Cox model excluding patients with previous renal diagnosis: a versus c and d, hazard ratio 1.3, $p=0.2$; a and b versus c and d, hazard ratio 2.1, $p<0.0001$; a versus b, hazard ratio 0.60, $p=0.03$.

Table 5: Association between light-chain MGUS and renal disease

precursor lesion for multiple myeloma, which is a devastating malignant disease. Second, the natural history of light-chain MGUS needs to be understood to promote appropriate testing for patients with this fairly benign disorder. Patients with light-chain MGUS had a progression rate of only 0.3% per year—which was lower than that of their counterparts with conventional MGUS, who had an overall yearly risk of progression of 1.0%—but 23% of this group have or will develop renal disease. The low progression rate was perhaps unexpected in the context of our previous finding that patients who have intact immunoglobulin MGUS, but who also have an abnormal free light-chain ratio, are at higher risk of progression than are their counterparts with a normal ratio.¹² We have shown, however, that progression rates of patients with low-risk conventional MGUS (ie, without coexisting abnormal free light-chain ratios) and those with light-chain MGUS were similar.

Whether these differential risks of progression are a function of tumour burden, biology, or a combination of the two is unknown. The transforming events producing light-chain and conventional heavy-chain MGUS (with a normal free light-chain ratio) could conceivably be the same, whereas conventional MGUS combined with an abnormal ratio might be a manifestation of an additional effect that is one step closer to full transformation to active multiple myeloma.²³ Light-chain MGUS might be detected earlier than is conventional MGUS (ie, at a point of earlier tumour burden) since the serum free light-chain ratio (which can detect involved free light-chain concentrations lower than 10–30 mg/L) is more sensitive than serum protein electrophoresis screening (1–2 g/L).^{3,8} In this study, we detected an additional 57 patients with previously unrecognised MGUS by use of the free light-chain assay, increasing the prevalence of conventional MGUS in this population from 3.2%² to 3.4% and defining the prevalence of MGUS overall as 4.2%. A final explanation could be that a small proportion of our light-chain MGUS cohort—ie, patients with the least abnormal ratios—do not have a true clonal disorder, but rather renal dysfunction or polyclonal activation.

Our description of light-chain MGUS is substantiated by three recent reports. Landgren and colleagues,²⁴ in

collaboration with our group, showed that either conventional or light-chain MGUS is present in more than 96% of patients with multiple myeloma more than 6 years before diagnosis of malignant disease. If light-chain MGUS were excluded, only 93% of patients with multiple myeloma had premalignant MGUS before diagnosis. Thus, in a small subset of patients with multiple myeloma the precursor lesion is not MGUS, but rather light-chain MGUS. Results of a second similar study²⁵ showed that light-chain MGUS was the preceding premalignant lesion for light-chain multiple myeloma. These results substantiate our previous report that heavy-chain MGUS progresses only to multiple myeloma with heavy-chain immunoglobulin expression. Taken together, they lend strong support to our findings. Finally, in a slightly different vein, Tsai and co-workers²⁶ showed that in 109 patients with chronic lymphocytic leukaemia, prevalence of an abnormal free light-chain ratio before diagnosis was 38% (95% CI 29–47); none of the patients with light-chain MGUS in our cohort has yet developed chronic lymphocytic leukaemia.

For the purposes of disease definition, we excluded from the light-chain MGUS category those individuals with an abnormal free light-chain ratio who had no increase in the involved light chain. This group, constituting 63% of all individuals with an abnormal ratio and no IgH expression, might include a subset of patients with true light-chain MGUS, but were regarded as false positives for two reasons. First, since an abnormal ratio in the context of B-cell disorders is used as a surrogate for clonality, abnormality in the ratio caused by only relative suppression of the other immunoglobulin free light chain seems insufficient evidence for a clone. Second, when we explored the prevalence of abnormal ratios with neither raised κ nor λ concentrations, the age distribution was the inverse of that seen in MGUS.

A more specific definition of light-chain MGUS could include only the subset of patients who were immunofixation positive (26 of 146 cases), but such a definition would have missed all three patients with light-chain MGUS who progressed to multiple myeloma in this series. Since the free light-chain ratio is more sensitive for detection of free light chains than is serum

immunofixation,^{4-7,9} reliance on immunofixation alone would also greatly underestimate the true prevalence of light-chain MGUS. Our trust in the free light-chain assay to detect clonal disorders in the setting of negative immunofixation is lent support by Weiss and colleagues.²⁵ Their series included 30 patients with multiple myeloma for whom prediagnostic serum (taken 2.2 to 15.3 years before diagnosis) was available for retrospective testing for monoclonal gammopathy. In six of these patients, the first evidence of a plasma-cell clone was the free light-chain ratio alone, and two subsequently had an IgH detected by immunofixation before diagnosis of non-light-chain multiple myeloma.

Another more specific definition of light-chain MGUS might use the renal reference range.¹⁶ This exercise increased the number of λ cases by 57 and decreased the number of κ cases by 69, which did not substantially change the prevalence rate, but did affect the population at risk. Because the definition of renal range does not take into account degrees of renal dysfunction,¹⁶ we could not select patients to whom the renal reference range should have been applied. Use of the normal reference range rather than the renal range, albeit imperfect, allowed for the greatest consistency in the setting of this large population study. Another confounder of our prevalence estimates is that recognition of MGUS—be it conventional or light-chain type—depends on the screening method used. As the sensitivity of screening technology increases, the prevalence of an entity also seems to increase. For conventional MGUS, detection rates have risen with increasing sensitivity of the screening method from paper electrophoresis²⁷ to agarose gel electrophoresis² to free light-chain measurements.

An important limitation of this study is the absence of African American participants in the Olmsted County cohort. Conventional MGUS is two to three times more common in the African American population than it is in white people, and our population study does not provide information about the prevalence of light-chain MGUS in this group.²⁷ We also noted an association with renal disease that needs further study. We do not recommend screening for this disorder; however, we expect patients to be identified incidentally when a free light-chain assay is ordered as part of a diagnostic assessment for various symptoms and laboratory abnormalities such as anaemia, hypercalcaemia, or renal failure. If light-chain MGUS is identified in the context of one of these abnormalities, as with conventional MGUS we recommend that a diagnosis of multiple myeloma, amyloidosis, and related disorders is excluded by use of a bone marrow examination and clonality testing, imaging studies, renal biopsy, and Congo red staining of fat or other tissue as clinically appropriate. If no malignant disorder is recognised, the free light-chain assay should be repeated in 6 months and yearly thereafter; no therapy is needed as long as there is no progression. Our data suggest that periodic monitoring of renal function is prudent, since 23% of

these patients either have or will develop renal disease. Patients with light-chain MGUS are at risk of light-chain multiple myeloma, amyloidosis, and renal disorders and hence will need further assessment if symptoms suggesting these disorders are encountered during follow-up. We postulate that light-chain MGUS occurs as a consequence of translocations involving the immunoglobulin heavy-chain region at chromosome 14q32, which results in total suppression of heavy-chain production.²⁸

Contributors

AD, JAK, RAK, SKK, and SVR designed the study. AD, JAK, RAK, SKK, DRL, LJM, CLC, TMT, RC, and SVR gathered and analysed the data. AD, JAK, RAK, SKK, DRL, LJM, TT, AB, RF, DFJ, and SVR wrote the report. AD and SVR vouch for the data and the analyses. All authors agreed to publishing of the report.

Conflicts of interest

JAK, DRL, CLC, LJM, TMT, RC, SKK, RF, DFJ, and SVR declare that they have no conflicts of interest. AD and RAK have received honoraria from The Binding Site, UK. AB is a director of The Binding Site, which manufactures and sells the free light-chain immunoassay kits.

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Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Dispenzieri A, Katzmann JA, Kyle RA, et al. Prevalence and risk of progression of light-chain monoclonal gammopathy of undetermined significance: a retrospective population-based cohort study. *Lancet* 2010; **375**: 1721–28.

Web only appendix for manuscript: THELANCET-D-09-07011R1, Prevalence and Risk of Progression of Light-Chain Monoclonal Gammopathy of Undetermined Significance (LC-MGUS): A newly defined entity.

Supplemental Table 1. Combinations of serum immunoglobulin free light chain (FLC) kappa (κ) and lambda (λ) levels leading to an abnormal free light chain ratio (FLC-R) in Olmsted County, Minnesota, residents without intact immunoglobulin (IgH) Monoclonal Gammopathy of Undetermined Significance (MGUS)

	Abnormal FLC-R, n (%)		
	κ predominant	λ predominant	All cases
High κ and high λ *	17 (6•3)	5 (3•9)	22 (5•4)
One FLC high; other normal*	83 (30•7)	30 (23•6)	113 (28•5)
One FLC high; other low *	8 (3•0)	3 (2•4)	11 (2•8)
Normal κ and λ	32 (11•9)	14 (11•0)	46 (11•6)
One FLC normal; other low	125 (46•3)	73 (57•5)	198 (49•9)
Low κ and λ	5 (1•9)	2 (1•6)	7 (1•8)
Total	270 (68)	127 (32)	397 (100)

*Considered light chain monoclonal gammopathy of undetermined significance (LC-MGUS)

Supplemental Table 2. Characteristics of Olmsted County, Minnesota residents with light chain-monoclonal gammopathy of undetermined significance (LC-MGUS), conventional MGUS, and no MGUS

	LC MGUS (N=146)	MGUS (N=623)	No MGUS (N=17588)	p value
Age, median (range), years	68 (50•0-96•0)	70 (50•0-96•0)	63 (50•0-109•0)	<0•0001
Female Gender	65 (44•5%)	314 (50•4%)	9789 (55•7%)	0•0010
Race				0•2
White	119 (81•5%)	566 (90•9%)	14081 (80•0%)	
Non-White	2 (1•4%)	4 (0•6%)	241 (1•4%)	
Unknown	25 (17•1 %)	53 (8•5%)	3266 (18•6%)	
κ cases, n	108	385	163	
κ, median (range), mg/L	43 (20-2700)	20 (1-1320)	10 (1•0-19)	<0•0001
FLC-R, median (range)	2•4 (1•7-511•0)	1•4 (0•4-258•8)	2•2 (1•7-40•9)	<0•0001
λ cases, n	38	229	89	
λ, median (range), mg/L	91 (27-283)	23 (3•0-1650)	12 (5•0-23)	<0•0001
FLC-R, median (range)	0•1 (0•0-0•3)	0•5 (0•0-1•5)	0•2 (0•0-0•3)	<0•0001

The effect of employing the renal (dialysis) FLC-R reference range rather than the normal patient population FLC-R reference range to define LC-MGUS

The definition of LC-MGUS is dependent on using FLC-R values outside of the normal reference range. It has been recognized that patients with severe renal insufficiency (i.e. dialysis patients) may have skewed FLC-R; therefore, we assessed how using the “renal reference range” (0.37 to 3.1)¹ rather than the normal population reference range (0.26-1.65)² would affect the number and progression rates of patients classified as LC-MGUS. This analysis was recognized as being an extreme case example, since creatinine measurements performed within 30 days of FLC sampling were available for 75% of participants, and only 51 of all patients (0.3%) and 9 (1.4%) of LC-MGUS patients had a serum creatinine greater than 354 µmol/L.

As anticipated, the use of the renal range definition reduced the number of patients with an abnormal kappa-biased FLC-R and increased the number of patients with an abnormal lambda-biased FLC-R. Of the 146 patients with LC-MGUS defined by normal population reference range 133 had follow-up information and were included in the progression analysis. Of the 134 LC-MGUS (renal) participants, 127 had follow-up information and were included in the progression analyses. Seventy-one individuals were included in both groups. There were 3 progressions to multiple myeloma among the LC-MGUS patients and 4 progressions to multiple myeloma among the LC-MGUS (renal) participants. As demonstrated in supplemental Table 3, the progression rates were not significantly different based whether the standard definition or the renal definition of LC-MGUS was used.

Supplemental Table 3. Comparative progression rates, employing different definitions of light chain monoclonal gammopathy of undetermined significance (LC-MGUS)

	LC-MGUS	LC-MGUS-renal
Progressions/person years (in hundreds)	3/11.1	4/10.3
Progression rate/100 person years (95%CI)	0.27 (0.06, 0.79)	0.39 (0.11, 0.99)
Progression to MM, LC-MGUS*		
At 1 year	0 (0, 0)	0 (0, 0)
At 2 years	1.72 (0, 4.1)	1.84 (0, 4.3)
At 5 years	1.72 (0, 4.1)	1.84 (0, 4.3)
At 10 years	2.98 (0, 6.3)	4.31 (0, 8.4)

*According to the methods of Kaplan-Meier

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