

Prevalence and progression of monoclonal gammopathy of undetermined significance and light-chain MGUS in Germany

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Abstract We determined the prevalence and progression rate of monoclonal gammopathy of undetermined significance (MGUS) and light-chain MGUS (LCMGUS) in Germany utilizing the biobank of the population-based Heinz Nixdorf Recall Study. The Heinz Nixdorf Recall Study comprises 4,814 men and women aged 45–75 years. To detect monoclonal proteins, standard serum electrophoresis was combined with parallel screening immunofixation using pentavalent antisera. Additionally, free light chains (FLC) were measured in all samples. Definition of MGUS included M-protein concentration, laboratory results, and disease history. LCMGUS was defined as abnormal FLC

ratio, increase in FLC causing the abnormal ratio, and lack of intact immunoglobulin. One hundred sixty-five MGUS cases were identified among 4,702 screened samples (prevalence 3.5%, 95% confidence interval (CI) 3.0–4.1; median age 63 years, range 47–75 years; 103 (62%) male; IgG 59%, IgA 17%, IgM 17%, biclonal 4.8%, kappa 56%, and lambda 44%). Five cases progressed (0.6%/year, 95% CI 0.2–1.4). An abnormal FLC ratio was detected in 220 samples. Thirty-nine of these showed intact immunoglobulin. Thirty-four of the remaining met LCMGUS criteria (prevalence 0.7%, 95% CI 0.5–1.0). None of the LCMGUS cases progressed. We demonstrate a MGUS prevalence of 3.5% and a LCMGUS prevalence of 0.7% in the general population aged 45–75 years in Germany using a sensitive screening approach.

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Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is characterized by the presence of a monoclonal immunoglobulin in individuals lacking evidence of an existing lymphoproliferative disease [1]. In a recently published, large population-based study in the USA, the prevalence of MGUS was estimated to be 3.2% in the Caucasian general population 50 years of age or older [2]. Long-term follow-up studies of MGUS cases demonstrated an average risk of 1%/year of developing multiple myeloma (MM) or a related lymphoproliferative malignancy [3, 4].

This risk did not diminish even after more than three decades of follow-up. Isotype and concentration of the monoclonal protein were consistently identified as biological factors influencing the risk of progression [3].

Further evidence of the strong association of MGUS with MM came from two recently published studies, where serially collected blood samples several years prior to cancer diagnosis were available [5, 6]. Virtually all MM cases were preceded by a monoclonal gammopathy in these studies establishing the role of MGUS as the precursor condition leading to MM.

The plasma cell clones of about 20% of MM cases produce only immunoglobulin light chains (light-chain multiple myeloma, LCMM). Recently, it was suggested that—similar to MGUS—there exists a light-chain MGUS (LCMGUS) as precursor condition leading to LCMM [2]. Indeed, in a large population-based study, the prevalence of LCMGUS, which was defined by use of the free light-chain (FLC) ratio, was found to be 0.8% in the general population 50 years of age or older [7].

The aim of this study was to determine for the first time estimates of prevalence and progression rate of MGUS and LCMGUS in a well-defined population in Germany. To this end, we utilized the biobank of the ongoing, population-based Heinz Nixdorf Recall Study to identify MGUS and LCMGUS cases. We used a sensitive screening approach by combining standard serum electrophoresis (SPE) with screening immunofixation and free light-chain κ and λ measurements in all available samples.

Methods

The study population of the Heinz Nixdorf Recall Study has been described in detail elsewhere [8]. Approved by the relevant institutional ethics committees, the study follows strict internal and external quality assurance protocols. Briefly, the study cohort comprises 4,814 men and women aged 45–75 years from three large adjacent cities in Germany (Essen, Bochum, Mülheim an der Ruhr). The study area covers a region of approximately 600 km² with almost 1.2 million inhabitants. Subjects were randomly selected from statutory lists of residence and gave informed consent. The response, calculated as recruitment efficacy proportion, was 55.8% [9].

Serum samples collected at baseline examination which took place from 2000 until 2003 were stored at -80°C . Standard serum electrophoresis was combined with parallel screening immunofixation electrophoresis (scIFE) using pentavalent antisera (Hydragel 12 IF, Penta-Kit, Sebia, Fulda, Germany). Where a monoclonal band was visible or suspected confirmatory IFE using antisera against γ , α , μ , κ , and λ immunoglobulin chains followed. Samples containing

monoclonal light chains but no monoclonal heavy chains were also tested with δ and ϵ antisera. All gels were evaluated independently by LE and AH. The gels of discrepant cases were reviewed again by LE, AH, and JD. Definition of MGUS cases was based on common criteria including detectable monoclonal protein on SPE and/or IFE, monoclonal protein concentration, laboratory results, and disease history [1].

FLC measurements were performed on a Dade Behring BNII automated nephelometer (Siemens, Germany) utilizing a commercially available kit (FREELITE, The Binding Site Ltd, Birmingham, UK). Published reference ranges for κ and λ FLC were used (3.3–19.4 and 5.7–26.3, respectively). An abnormal κ/λ FLC ratio was defined as <0.26 or >1.65 [10].

To quantify the impact of scIFE on detection of monoclonal proteins, we re-evaluated standard electrophoresis strips using a mask covering the pentavalent tracks on the gels (see [Supplementary Material](#)). Re-evaluations were done by RA blinded for the results of the previous evaluation.

Follow-up information was provided by questionnaires sent to the study participants annually since their enrollment in the Heinz Nixdorf Recall Study. Health changes indicated by the returning questionnaires were validated by asking treating general practitioners and hospitals to provide medical information. For deceased participants, the cause of death was determined from death certificates. Diagnoses were coded using International classification of diseases, 10th revision.

Statistical analysis

Exact 95% confidence intervals (CI) for prevalence and progression rate were computed using the binomial and Poisson distribution, respectively. To compare the results with the prevalence reported for Olmsted County, USA [2], the age-standardized prevalence was obtained by direct standardization according to the US 2000 population [12] using age intervals 50–59, 60–69, and 70–79 years. When p values were computed, values <0.05 were considered significant. All analyzes were performed with SAS 9.1 (SAS Institute, Cary, NC, USA). Plots were produced with R Statistical Software 2.12. (<http://www.r-project.org>).

Results

MGUS prevalence by serum protein electrophoresis and screening immunofixation

Using combined SPE and scIFE, monoclonal proteins were detected in 171 out of a total of 4,708 samples. Reviewing clinical and laboratory data revealed that in six cases, a lymphoproliferative disease was known at the time of blood

sampling (four MM, one MALT lymphoma, one T-prolymphocytic leukemia). These cases were excluded for further analysis. Therefore, 165 MGUS cases were identified, translating into a prevalence of 3.5% (95% CI 3.0–4.1). The median age of MGUS cases was 63 years (range 47–75), and 103 (62%) were of male gender. Prevalence increased with increasing age (Table 1; Fig. 1). The age-standardized total prevalence was 3.9% (95% CI 3.2–4.5). Comparison with the age-standardized prevalence in individuals 50–79 years of age in the Olmsted County cohort (2.8%, 95% CI 2.5–3.0), which was calculated using the published data [2], showed a significant higher MGUS prevalence in the Heinz Nixdorf Recall cohort ($p < 0.05$).

Table 2 and Fig. 2 summarize characteristics of MGUS cases. Twelve samples had no detectable whole immunoglobulin in IFE and were counted in the kappa ($n=2$) and lambda ($n=10$) categories only. None of these samples met LCMGUS criteria. One sample with an IgA isotype had no detectable light chain in IFE. Concentrations of the monoclonal proteins ranged from unquantifiable–22.4 g/l with a median of 5.3 g/l. The M-protein was unquantifiable in 88 cases (53%).

After a median observation time of 5 years, four MGUS cases had progressed to multiple myeloma and one case developed Waldenström's macroglobulinemia with subsequent transformation into a diffuse large B cell lymphoma. This represents a progression rate of 0.6%/year (95% CI 0.2–1.4). Table 3 gives characteristics of the identified five progressive MGUS cases.

Risk profile of MGUS cases

The FLC ratio together with monoclonal protein isotype and concentration can be used to assess the risk of progression of MGUS cases [13]. In a retrospective study, the risk was the highest in cases with an abnormal ratio, non-IgG isotype, and high serum levels of the monoclonal protein and the lowest in those cases with none of these risk

factors [13]. In our cohort, 65 of 165 MGUS cases (39%) showed a low risk profile, whereas the remainder showed at least one ($n=87$, 53%) or two ($n=12$, 7%) risk factors. We did not observe cases representing a high-risk profile. However, of the five MGUS cases that progressed during the observation time, three showed an abnormal FLC ratio including the IgM MGUS progressing to WM and subsequent DLBCL (Table 3).

Prevalence of light-chain MGUS

FLC κ and λ measurements were available for 4,697 and 4,696 samples, respectively. Median FLC κ and λ concentrations were 14.9 mg/l (range 1.51–1,220.0) and 15 mg/l (range 2.09–936.0), respectively. Calculation of the FLC ratio was possible in 4,694 samples, and an abnormal ratio was detected in 220 (4.7%) samples. SPE and scIFE showed IgH expression in 39 (17.7%) of these 220 samples, thus indicating presence of conventional MGUS. A total of 34 (19%) of the 181 individuals with abnormal free light-chain ratios, and no IgH expression had an increase in concentration of the light chain that was the cause of the abnormal ratio and thus met criteria for LCMGUS. The overall prevalence of LCMGUS was 0.7% (95% CI 0.5–1.0), the age-standardized prevalence was 0.8 (95% CI 0.5–1.1) (Table 1). Similar to MGUS, the prevalence of LCMGUS increased with age and was higher in males (Fig. 1). The median age of individuals with LCMGUS was 67 years (range 47–74). Twenty-eight individuals with LCMGUS had κ and six had λ predominance (4.7:1). None of the LCMGUS cases showed a progression during a median observation time of 5 years.

Of the 220 individuals showing a pathologic FLC ratio, 147 (66.8%) did neither meet criteria of MGUS nor LCMGUS. The minimum and maximum ratio in these cases was 0.16 and 5.01, respectively. Median age was 57 years (range 46–74). Serum creatinine showed values

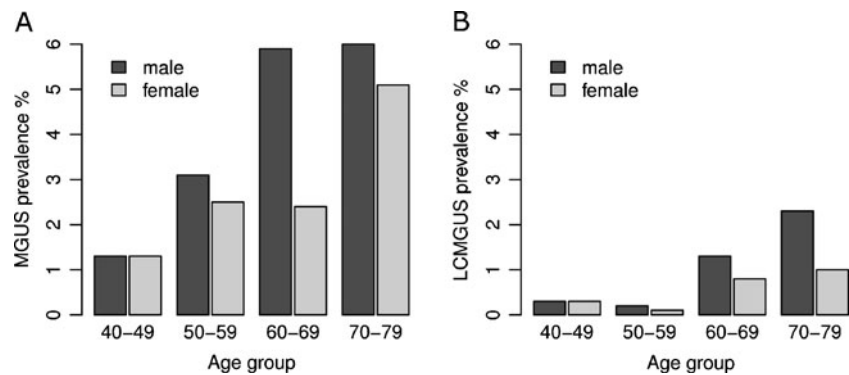
Table 1 MGUS and LCMGUS prevalence

Age (years)	Male	%	Female	%	Total	%
MGUS						
40–49	4/299	1.3	4/297	1.3	8/596	1.3
50–59	26/831	3.1	21/847	2.5	47/1,678	2.8
60–69	55/934	5.9	22/899	2.4	77/1,832	4.2
70–79	18/299	6.0	15/297	5.1	33/596	5.5
Total	103/2,363	4.4 ^a	62/2,339	2.7 ^a	165/4,702	3.5 ^a
LCMGUS						
40–49	1/299	0.3	1/297	0.3	2/596	0.3
50–59	2/829	0.2	1/843	0.1	3/1,672	0.2
60–69	12/934	1.3	7/897	0.8	19/1,831	1.0
70–79	7/299	2.3	3/297	1.0	10/596	1.7
Total	22/2,361	0.9 ^b	12/2,334	0.5 ^b	34/4,695	0.7 ^b

^a 95% confidence intervals 3.6–5.3, 2.0–3.4, and 3.0–4.1 for male, female, and total prevalence, respectively

^b 95% confidence intervals 0.6–1.4, 0.3–0.9, and 0.5–1.1 for male, female, and total prevalence, respectively

Fig. 1 MGUS (a) and LCMGUS (b) prevalence by sex and age groups



within the reference range, and median high-sensitivity C-reactive protein was 0.12 mg/l (range 0.01–8.44; reference ≤ 0.5) in these individuals. A self-reported history of pneumonia, chronic bronchitis, or chronic arthritis was documented in 14, 15, and 9 cases, respectively.

Using the published reference range of 0.26–1.65 to define an abnormal FLC ratio [10] can lead to false-positive results in individuals with impaired renal function [14]. Therefore, an alternative reference range (0.37–3.17) was suggested when renal impairment is present [15].

When the GFR was estimated using the Cockcroft–Gault formula [16] and the alternative reference range was employed for GFR < 60 ml/min, four previously identified cases failed to meet LCMGUS criteria. These cases had ratios between 1.7 and 2.8. Among them were the two previously identified cases with the most severe renal impairment in terms of estimated GFR (12 and 15 ml/min, respectively).

Discussion

We utilized the biobank of the ongoing population-based Heinz Nixdorf Recall study to determine the prevalence and progression rate of MGUS and LCMGUS in a well-defined population in Germany. Kyle et al. previously reported results from a population-based study from the USA. They found a prevalence of 3.2% in individuals 50 years or older [2]. Using screening immunofixation in addition to standard serum electrophoresis, we found the prevalence of MGUS to be 3.5% in the Heinz Nixdorf cohort. Taking into account the younger age structure compared to the Mayo clinic cohort, this prevalence was significantly higher than that

Table 2 Characteristics of MGUS and LCMGUS cases

Characteristic		MGUS		LCMGUS
		SPE + scIFE ^b N=165	SPE only ^b N=120	N=34
Sex (%)	Male	103 (62.4)	72 (60.0)	22 (64.7)
	Female	62 (37.6)	48 (40.0)	12 (35.3)
Age, years	Median (range)	63 (47–75)	62.5 (48–75)	67 (47–74)
Isotype (%) ^a	IgG	97 (58.8)	77 (64.2)	–
	IgA	28 (17.0)	9 (7.5)	–
	IgM	28 (17.0)	21 (17.5)	–
	Biclonal	8 (4.8)	7 (5.8)	–
	Kappa	92 (55.8)	67 (55.8)	–
	Lambda	72 (43.6)	41 (34.2)	–
M-protein (g/dl)	Median (range)	0.53 (n.a. ^c –2.24)	0.53 (n.a. ^c –2.24)	–

SPE standard serum electrophoresis, n.a. not available

^a Immunoglobulin isotype, with SPE + scIFE, 12 samples had no detectable complete immunoglobulin in IFE and were counted kappa ($n=2$) and lambda ($n=10$) only. One sample with an IgA isotype had no detectable light chain in IFE. With SPE only, 12 samples had no IFE available

^b MGUS cases identified by SPE combined with screening immunofixation (SPE + scIFE) or SPE only

^c In cases identified by SPE + scIFE and SPE only, the M-protein was unquantifiable densitometrically in 88 (53%) and 48 (40%) cases, respectively

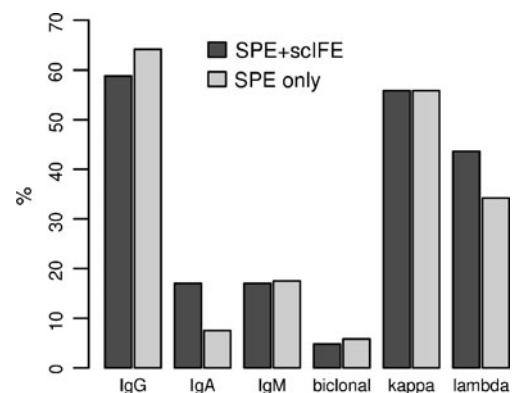


Fig. 2 Immunoglobulin isotype distribution by serum electrophoresis combined with screening immunofixation (SPE + scIFE) and serum electrophoresis only (SPE only)

Table 3 Characteristics of progressive MGUS cases

Case	Age	Sex	M-protein	M-concentration ^a (g/dl)	FLCR ^b	Observation ^c (years)	BLPD
1	62	M	IgG1	2.24	0.055	5.4	Multiple myeloma
2	67	M	IgGk	0.55	1.03	4.4	Multiple myeloma
3	60	M	IgGk	1.56	12.27	4.5	Multiple myeloma, subsequent diagnosis of Hodgkin's lymphoma
4	68	M	IgG1	1.16	1.10	3.7	Multiple myeloma
5	55	M	IgMk	<1.5	2.38	2.5	M. Waldenström, with subsequent transformation to DLBCL

FLCR free light chain ratio, BLPD B-lymphoproliferative disease, DLBCL diffuse large B cell lymphoma

^a Concentration of monoclonal protein

^b Reference range 0.26–1.65

^c Time from base line evaluation to diagnosis of BLPD in years

reported by Kyle et al. However, this is not an unexpected finding as immunofixation is known to be more sensitive in detecting monoclonal proteins.

To better quantify the impact of the pentavalent tracks on the detection of monoclonal bands, we developed cover sheets that made it possible to completely mask the pentavalent tracks while leaving the standard electrophoresis strips visible for evaluation. When we re-evaluated the gels without the additional information added by the pentavalent lanes, we found that 57 previously identified MGUS cases were missed (Table 2, Fig. 2; for details, see [Supplementary material](#)). These 57 discrepant cases included a high proportion of IgA isotype MGUS (19 of 57). Additionally, in 29 of these cases, the monoclonal protein appeared only weak on SPE adding to the number of densitometrically unquantifiable monoclonal proteins. As the concentration of the monoclonal protein is a known risk factor of progression, these cases may never experience the development of a hematological malignancy. The increase of IgA isotype MGUS is of note because non-IgG MGUS cases are believed to have an increased risk of progression [3]. However, as MGUS screening of the general population is currently not recommended outside of studies [16], clinical and economical implications of this finding are limited at the moment.

Compared to the study of Dispenzieri et al. [7], we observed a higher fraction of samples showing a pathologic FLC ratio (4.7% vs. 3.3%). Inherent imprecision in the measurement of individual FLCs are enhanced by forming the FLC ratio, and ratios close to the reference limits are particularly prone to misclassification [11]. Thus, this discrepancy may in part be explained by random fluctuation. Additionally, we observed pathologic ratios where one FLC was below the lower reference limit while the other showed values within the reference range. None of these samples met LCMGUS criteria, however, because LCMGUS requires an abnormal FLC ratio together with an absolute elevation of

the FLC that caused the abnormal ratio [7]. Clinical and laboratory data of individuals with an abnormal ratio not meeting MGUS or LCMGUS criteria were uninformative. Thus, these ratios may include false-positive results and underscore the importance of additional criteria in defining LCMGUS. In keeping with the study of Dispenzieri et al., we found a prevalence of LCMGUS of 0.7% in the general population. That none of the LCMGUS cases progressed during the observation period is consistent with the reported low progression rate of this entity [7].

The prospective population-based approach of the Heinz Nixdorf Recall Study and the associated high internal and external validity represent strengths of our study. We can therefore present the first population-based data with regard to MGUS prevalence in Germany. There are, however, also limitations to our study. The Heinz Nixdorf Recall Study was primarily designed to answer research questions from cardiology and inclusion criteria limited the age of study participants to 45–75 years. Additionally, we did not analyze urine samples and therefore a small fraction of MGUS cases and rare plasma cell dyscrasias might have been missed [17]. Furthermore, as we did not have bone marrow aspirates available, there remains an uncertainty whether some of the progressive MGUS cases would have been judged myelomas already at baseline. However, the long time between the baseline evaluation and progression to myeloma (>3.7 years, Table 3) argues against this possibility.

Taken together, we demonstrate a MGUS prevalence of 3.5% among individuals aged 45–75 years old in the general population in Germany using a sensitive screening approach including immunofixation. The estimated progression rate of MGUS is in line with the published 1%/year. Notably, all the MM cases that developed during the observation period showed MGUS at baseline, thus further corroborating previous results that MGUS consistently precedes MM [5, 6].

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