Peer reviewed article

Testing strategies and follow-up for coeliac disease in a general internal medicine outpatient department from 2000 to 2005

A retrospective analysis and proposal for clinical practice

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Summary

Principles: Coeliac disease (gluten sensitive enteropathy) is a genetically determined disorder with an incidence in the general population that is comparable to type 2 diabetes mellitus. Awareness of this fact and of the often atypical and oligosymptomatic manifestations is only now gaining ground in the medical profession. A high index of suspicion is important in order to minimise diagnostic and therapeutic delay.

Methods: Testing patterns and follow-up for coeliac disease in our institution have been analysed retrospectively for the past five years. The current literature was reviewed with respect to recommendations for clinical practice.

Results: A total of 271 patients were tested for coeliac disease over a period of five years. Only in 24 patients were positive results found; after further work-up, the final number of cases with certain or presumed coeliac disease was four. Follow-up was often difficult, many patients being lost after a single visit.

Conclusions: This study showed that the number of tests ordered in our institution, more often for abdominal than atypical symptoms, has started to increase in the past two years. It also showed that screening tests have found their place in general clinical practice, while the final choice of tests needs to be determined in accordance with available guidelines and local resources. Upper endoscopy with small bowel biopsy remains the gold standard for diagnosis, but its place in follow-up is less certain.

Coeliac disease is a disorder for which there is a definite treatment (gluten free diet); if it is left untreated diminished quality of life and potentially serious complications may ensue. Further education of the medical profession regarding coeliac disease, its incidence, presentation and treatment, is clearly indicated.

Key words: coeliac disease; sprue; gluten; tissue transglutaminase; testing strategy; screening

Introduction

Coeliac disease (CD) is a genetically determined disorder characterised by an enteral T-cell-mediated hypersensitivity reaction following ingestion of gluten (gliadin and glutenin). Once considered a disease with a classic, predominantly gastrointestinal presentation in childhood, it has been increasingly recognised that CD has a higher prevalence (comparable to type 2 diabetes) throughout the population and often presents atypical symptoms, giving rise to the expression "coeliac iceberg". The incidence may be as high as 1:100–200 [1]. Only in a minority of cases do patients actually present with gastrointestinal symp-

List of abbreviations

CD	coeliac disease
GFD	gluten-free diet
UE	upper endoscopy
SBB	small bowel biopsy
IEL	intraepithelial lymphocytes
TTG	tissue transglutaminase
IgA tTG	IgA antitissue transglutaminase antibodies
IgA EMA	IgA antiendomysial antibodies
IgA AGA	IgA antigliadin antibodies
IgG AGA	IgG antigliadin antibodies

No financial support declared.

toms such as diarrhoea, bloating or cramping pain. Disorders of malabsorption such as iron deficiency and osteoporosis, as well as unspecific symptoms such as fatigue, may be the only sign of the disease. There are a number of associated autoimmune disorders, ranging from diabetes mellitus type 1 to thyroid disorders, dermatitis herpetiformis of Duhring and Sjögren's syndrome [2, 3]. Up to 10% of patients exhibit deficiency of IgA antibodies.

Pathophysiology of CD

Gluten proteins derived from wheat, rye and barley contain large quantities of glutamine. After digestion, peptides are transported into the mucosa, where key glutamine residues are deamidated by tissue transglutaminase (tTG), a ubiquitous enzyme with a high concentration in the gastrointestinal mucosa. Deamidation results in a negative charge, and subsequently the deamidated epitopes are more efficiently bound to the specific HLA DQ2 or DQ8 receptors on the surface of antigen-presenting cells which are positively charged. Intestinal DQ2- or DQ8-restricted $CD4^+$ T cells then recognise the deamidated gliadin peptides and produce inflammatory cytokines. Formation of antibodies against tTG is thought to occur via intermolecular epitope spreading due to recognition of tTG-catalysed cross-links between gliadin and tTG [4, 5].

Figure 1

Representative view of denudated duodenal mucosa.

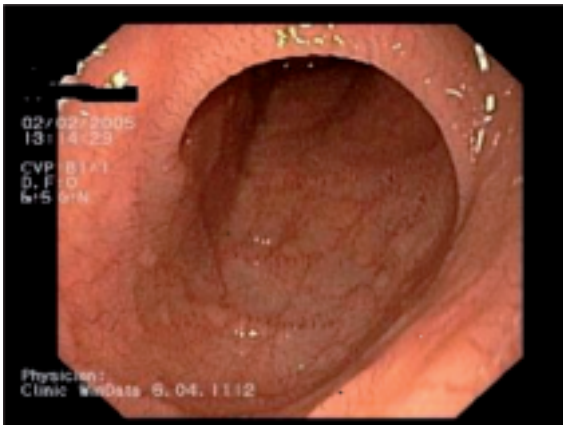

Figure 2

Representative histological specimen of duodenal mucosa with severely shortened villi, hyperplastic crypts and massive intraepithelial lymphocytosis.

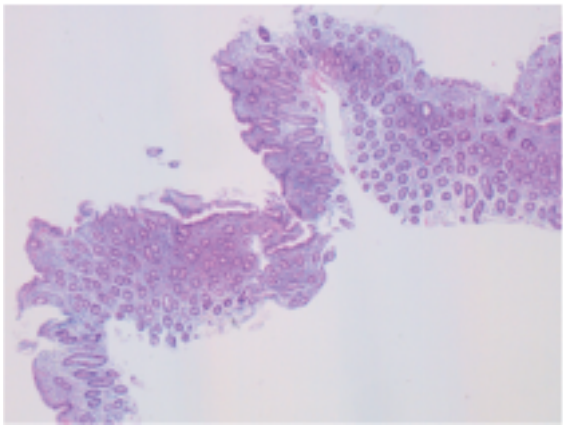

Table 1

Intestinal disease states that can cause histomorphological lesions similar to those seen in coeliac disease.

HIV enteropathy
Combined immunodeficiency states
Radiation damage
Recent chemotherapy
Crohn's disease
Eosinophilic gastroenteritis
Zollinger-Ellison syndrome
Giardiasis
Graft-versus-host disease
Chronic ischaemia of the small intestine
Tropical sprue
Enteropathy-associated T-cell lymphoma (EATL)

Testing and diagnosis of CD

Testing for CD starts with history and physical examination. Unless clinical suspicion is very strong, in which case endoscopy can be performed immediately, testing for CD usually continues with evaluation of laboratory data. In CD, autoantibodies are formed against gliadin, endomysium and tissue transglutaminase. Historically, the first autoantibodies to be measured were antigliadin IgA (IgA AGA) and IgG (IgG AGA) with relatively high sensitivity but low specificity [6, 7]. They were followed by IgA antiendomysial autoantibodies (IgA EMA), measured by direct immunofluorescence, with both high sensitivity and specificity [6, 7]. In 1997, tTG was identified as the antigen for antiendomysial antibodies. Anti-tTG IgA (IgA tTG) can be measured by ELISA. Specialised laboratories can measure IgG tTG and IgG EMA in cases of IgA deficiency.

Several kits are commercially available which differ with regard to the origin of the antigen (for tTG, e.g. guinea pig, human, recombinant human). In cases of selective IgA deficiency, as mentioned above, results for IgA antibodies may be falsely negative.

For confirmation of the diagnosis upper endoscopy (UE) is required. In severe cases the denudated mucosa will be apparent macroscopically (fig. 1). The examination should include representative small bowel biopsies (SBB) demonstrating the typical lesions in duodenal mucosa, including shortening or atrophy of villi, hypertrophy of crypts and increased intraepithelial lymphocytes (IEL) (fig. 2). The lesions are classified in stages as described by Marsh [8]. The lesions are characteristic of, but not diagnostic for, CD and can also be seen in numerous other intestinal disorders (table 1).

Patients are classified into categories according to symptoms and the results of serology and UE/SBB: symptomatic patients who have the classic pathological lesions are defined as symptomatic CD, whether or not they are antibody-positive [2, 9]. Patients with the classic pathological lesions who are asymptomatic are defined as silent CD, whether or not antibodies can be found. Patients with no pathological lesions and who are asympto-

matic but antibody-positive are considered to have latent CD. It is not currently known whether patients with latent CD will progress inadvertently towards symptomatic CD, or will suffer from other negative consequences if not treated by strict gluten-free diet (GFD) [10]. It must be stressed that at present the majority of patients are oligosymptomatic, asymptomatic or present with atypical symptoms; the diagnostic process and classification are difficult and fraught with uncertainty, and the index of suspicion must be high.

Aim and setting of the study

Despite the fact that coeliac disease is one of the most common genetically determined diseases and has an incidence close to or even higher than type 2 diabetes mellitus, knowledge of the disease and its implications is not widespread in the medical profession, as opposed to the broad coverage diabetes has received. This lack of awareness will lead to missed diagnoses or an unacceptably long latency from the first atypical symptoms until the final institution of therapy.

The aim of our study was to identify diagnostic strategies for coeliac disease as employed in our general internal medicine outpatient department in recent years. We wished to document not only the methods employed, but also the reasons which led to testing in the first place, i.e. why a possible diagnosis of CD was considered. Consequently, we wished to garner information on the follow-up in patients with positive test results.

Methods

From the laboratory database we extracted all test results for measurements of IgA AGA, IgG AGA, IgA EMA and IgA tTG which had been ordered for patients from the general internal medicine outpatient department for the period starting 1 Jan. 2000 to 5 May 2005. The data included patient name, date of birth, date of the test, type of test and result in numerical values. Positive results were identified on the basis of established cutoff values. Data were analysed regarding trends in tests ordered, frequency of tests in certain time periods and overall number of tests.

Tests from venous blood samples used in our institution were as follows:

IgA AGA and IgG AGA: UniCAP Specific IgA resp. IgG, Pharmacia Diagnostics, Uppsala, Sweden

IgA EMA: Monkey Oesophagus IFA Kit, Binding Site, Birmingham, England

IgA tTG: Quanta Lite h-tTG IgA ELISA, Inova Diagnostics, San Diego, USA (starting in Jan 2003)

Positive tests were analysed separately and further information for patients with at least one positive test result was extracted from the hospital database. It included details of history, results of physical examination, additional laboratory data and information on other diagnostic and therapeutic procedures. Special attention was paid to endoscopy and histology information.

No further follow-up was attempted to verify the outcome in patients no longer attending the outpatient department.

Statistical analysis

Quantitative variables were described in terms of appropriate measures of localisation and dispersion; qualitative variables were presented by counts and percentages.

Results

Total number and distribution of test patterns

From January 2000 to May 2005, a total of 271 individual patients were tested serologically for CD on a total of 284 different occasions. The average age of these patients was 37.5 ± 14.9 years at the time of testing. The percentage of female patients was 55% (n = 149).

The serological tests that were ordered showed definite trends over time. When only IgA AGA, IgG AGA and IgA EMA were available, they were most often ordered in combination. In 2002, fewer tests were ordered, and the combinations were more evenly distributed. In 2003, with the availability of IgA tTG, use shifted towards either all four available tests or combination of IgA EMA and IgA tTG, this combination becoming more common in later years (table 2a). The total frequency of tests and the frequency of positive results are shown in table 2b.

Positive serological tests

Out of 271 patients tested, 24 (8.9%) (14 women) had at least one positive result in one or other of the tests during the study period (patient characteristics given in table 3). The most frequent was an isolated positive finding of IgA AGA (15 times in 13 patients). Next came the combination of positive IgA AGA and IgG AGA (5 times in 5 patients), followed by an isolated positive finding for IgG AGA (4 times in 3 patients). In one patient there was an isolated positive result for IgA tTG, and one patient had positive results for all four tests. One patient who was tested four times during the study period had one combination of positive results for IgA EMA and IgA tTG, two combinations of positive IgA tTG and IgG AGA with negative IgA EMA and IgA AGA, and one instance with negative results for all four tests.

The primary reason for testing as well as information follow-up and additional procedures

Table 2a

Frequency of serological tests and combinations of tests for CD from 2000 to 2005 (for abbreviations see list at beginning of article).

	2000	2001	2002	2003	2004	2005
AGA/AGG	–	1	7	2	–	3
EMA	7	4	4	16	1	–
AGA/AGG + EMA	29	27	10	23	8	–
TTG	–	–	–	–	4	2
EMA + TTG	–	–	–	7	38	15
All four	–	–	–	20	47	9

Table 2b

Frequency of positive results of serological tests for CD.

	Total number of tests	Positive results (% of total number)	Number of patients with positive results
AGA	186	21 (11%)	19
AGG	186	12 (6%)	10
EMA	264	2 (0.8%)	2
TTG	142	5 (3.5%)	3
Any of the above	778	40 (5%)	24

was ascertainable from the available documents in all patients.

Signs and symptoms

Of the 24 patients with at least one positive result, gastrointestinal symptoms (pain, cramping, bloating, flatulence, diarrhoea, changes in stool habits) were present in 17 (70%), while 7 had no abdominal symptoms. Fatigue was a symptom in 15 patients. Signs of iron deficiency were present in 7 patients. None had pathological thyrotropin values. The mean haemoglobin concentration was 131.8 ± 18.5 g/L, and mean corpuscular volume was 85.4 ± 9.4 fl. One patient had known CD at the time of the investigation.

Main reason for testing

When abdominal symptoms were present they were the main reason for testing for coeliac disease. In the 7 patients who had no abdominal symptoms, the reasons for testing for CD were iron deficiency with or without anaemia (n = 3), low body weight and fatigue (n = 1), weight loss, fatigue and polyarthritic pain (n = 1), suspicious ileal mucosa seen during colonoscopy for another reason (n = 1), and known CD under GFD (n = 1).

Upper endoscopy and small bowel biopsy – reasons for and against

Upper endoscopy was performed in 12 patients (50% of all patients with at least one positive test result). Eight of 17 patients (47%) in whom abdominal symptoms were present underwent UE.

In patients without abdominal symptoms (n = 7), 4 (57%) underwent UE. One of these 4 patients had known CD on GFD, and UE was undertaken in view of concern about the presence of refractory CD in the presence of weight loss, fatigue and positive antibodies (IgA AGA and IgG AGA). Two other patients without abdominal symptoms had iron deficiency and one had low body weight with suspected malassimilation, and thus in their case UE was probably part of the work-up for this condition as opposed to work-up for CD. The 3 patients without abdominal symptoms who did not undergo UE were only seen on the one occasion when the serological tests were ordered.

Results of UE and SBB

The duodenum was macroscopically normal in all patients but one. Two patients had signs of erythematous gastritis. Duodenal biopsies were examined in all 12 patients: 7 (58%) had no histomorphological signs of CD; these included the patient with known CD on GFD. A further 2 patients had normal villi and a slight increase in IEL, which did not allow diagnosis of CD on these grounds alone. One patient each exhibited normal villi with a marked increase in IEL (judged as possible latent CD), and villous shortening with increased IEL (judged highly suspect for CD). One patient without abdominal symptoms at the time of presentation exhibited a completely denudated duodenal mucosa with complete villous atrophy and a massive increase in IEL, corresponding to Marsh IIIc lesions.

The total number of patients newly identified in the period 2000–2005 as suffering from CD is as follows:

- one definite case with severe CD
- one case with very probable CD
- one with probable latent CD
- one case with presumed oligosymptomatic CD

Table 3

Characteristics of patients with at least one positive result in a serological screening test (n = 24). Results are given as mean, standard deviation and percent, where applicable.

Age (yrs)	41 ± 16.5
Female	14 (58%)
Gastrointestinal symptoms	17 (71%)
Documented iron deficiency	7 (29%)
Upper endoscopy during follow-up	12 (50%)

Only in one patient were the results unequivocal and led to an immediate change in treatment and management, and subsequently to an improvement in patient status.

Patients lost to follow-up

Overall, seven patients were effectively lost to follow-up. Four of them were male (57%) compared to five males (29%) in the group followed up successfully. The patients lost were younger (37.9 ± 10.1 vs. 42.4 ± 18.6 years); three of them had not presented with gastrointestinal symptoms, compared to four out of 17 followed up. The two patients who underwent upper endoscopy, in whom CD was judged strongly suspect and likely respectively, were both lost to follow-up.

Discussion

In our patient population with at least one positive test result, testing for CD was most often undertaken for abdominal symptoms. There is a definite trend over time with regard to the serological tests used. While the tests for "dietary" antibodies to gliadin were popular to begin with, the advent of the "autoantibody" tTG led to a shift towards this modality. The tendency to order a panel of all four tests very probably reflects the intuitive wish to increase diagnostic yield by ordering the full range of possible tests – a strategy not borne out by the evidence.

In half of the patients with positive results in serological tests for CD, upper endoscopy was part of the further workup. Interestingly, the absence of abdominal symptoms did not preclude UE. Obviously the decision for or against UE was not based solely on either serological tests or single clinical symptoms, but represents a choice made after incorporating all the available information.

The low overall number of tests performed and the small number of patients actually diagnosed with CD in our department are a striking and unexpected result, considering the large number of patients seen annually. The numbers began to increase in 2003, which may well be due to increasing awareness among medical staff of the true prevalence of CD in the general population and its often atypical clinical presentation. The results show that further attempts to raise awareness of this issue are indicated. Physicians should have a low threshold for evaluation of patients with a suggestive history.

The true prevalence of CD in the patient population seen in our outpatient department cannot be determined, but this was not the aim of the study. The prevalence would probably be higher than in the general population because of a selective bias due to referral of patients who are symptomatic or have diffuse symptoms, where primary workup did not yield a diagnosis. Unfortunately, the number of patients in our clinic belonging to the submerged part of the coeliac iceberg (undiagnosed) will probably be higher than the visible part. There may also be patients with known CD in whom testing for antibodies was not deemed necessary or who had negative results due to adherence to GFD. There may also be patients who tested false negative, though their number is likely to be small.

In general, follow-up was often difficult. More than a quarter of patients were lost before newly gained crucial information could be discussed with them. Some patients never returned for further consultations midway through the diagnostic process. This is probably owing to the special circumstances under which our outpatient department operates, and probably reflects the experience of other tertiary care centres but not those of office-based primary care physicians. We have no sure way of knowing whether patients with suspected CD were eventually or even simultaneously

Table 4

Suggestions for screening of at-risk populations for coeliac disease in adults (adapted from [10]).

Screening recommended	Screening recommended when subtle symptoms consistent with CD are present	Screening unnecessary
Malabsorption, isolated iron deficiency[a]	Family history of CD	General population
Osteoporosis	Autoimmune thyroid disease Sjögren's syndrome	Acute or short-term gastrointestinal symptoms
Ataxia and polyneuropathy	Type I diabetes[b]	Atopic symptoms
Arthritis of unknown aetiology	Addison's disease	Type I diabetes[c]
Chronic liver disease of unknown aetiology	Autoimmune endocrinological disease in general	
Suspicion of dermatitis herpetiformis (consider skin biopsy)	Any chronic gastrointestinal symptoms[a]	
Irritable bowel syndrome[a]		
Lactose intolerance		

[a] Consider small intestinal biopsy when screening test is negative
[b] With symptoms indicative of CD
[c] Without symptoms indicative of CD

seen by other physicians, hospitals or outpatient departments. To date, no integrated patient data management system exists which would help to identify previous contacts with the health system and help to prevent multiple examinations.

The number of patients who underwent UE (50%) seems large compared with that reported by Pearce and Sinclair [11], where only 12 of 63 IgA EMA-positive patients from a group of 1450 patients screened for CD ultimately underwent UE with SBB. After these authors had added a comment on the laboratory report form concerning recommendation of gastroenterology referral, the rate increased dramatically to 80% [12]. Thus far no such comment has been added to the report forms in our hospital.

Test characteristics and choice of tests

The present study did not address the question of test performance. The current literature suggests that the pooled specificities of IgA-EMA and IgA-tTG were between 95% and 100% in adults and children, while sensitivities ranged from 90% to 99%. The performances of antigliadin antibodies were inferior to those of EMA and tTG [6, 7].

Testing for CD and interpretation of the results depends on the diagnostic accuracy of the tests used, which is in turn determined by the prevalence of the disease in the population examined. Several reviews address these questions and report that, overall, the tests' sensitivity and specificity are high, but may differ markedly between populations and age groups.

The sensitivity of these tests appears to be lower than reported when milder histological grades are used to define CD (below 90%). If true, the nearly perfect negative predictive value of these tests would be lower. Their positive predictive value is probably lower than reported where the tests are conducted in low-prevalence populations [6].

There was no evidence that a combination of tests was better than a single test using either the IgA EMA or IgA tTG. Either of these tests is useful for identifying individuals with CD, while screening with IgA AGA was discouraged [7, 13].

Pitfalls in using serological tests include the inadvertent or intuitive institution of a GFD by the patient, which would result in a more or less rapid decrease in antibody levels [14].

Available guidelines and recommendations for clinical practice

The British Society of Gastroenterology [15], the American Gastroenterological Association [16] and the World Gastroenterological Organisation [17] have all published very useful, exhaustive guidelines on the approach to patients with CD. While UE with SBB is unequivocally the gold standard for diagnosis of CD, the use of serological tests is considered part of the workup as well. Recently researchers have questioned the role of histology as a stand-alone tool; one study found that the quality of histological specimens was too poor to be considered for diagnosis in up to 10% [18]. New diagnostic algorithms including histology, serological tests, quantitative morphometry, immunohistochemistry and HLA typing are currently under discussion [19].

The data available at present does not support mass screening of asymptomatic adults. Even though a substantial number of persons would probably be identified by such an approach, it is not clear whether they would actually benefit from being detected. There are no data on the long-term consequences of untreated asymptomatic CD, or on the effect of GFD on these consequences. Also, no data on the cost-effectiveness of such a strategy are available [10].

Another approach is currently favoured and should be implemented in clinical practice where appropriate. It involves screening at-risk populations (table 4 [adapted from [10]). At present more than half of all new diagnoses of CD result from screening of high-risk populations. The presence of any chronic gastrointestinal symptoms should prompt testing for CD when subtle symptoms consistent with CD are present. In patients with negative serological tests an SBB should be considered, especially if UE forms part of the workup.

The choice of test should no longer include a panel of all available tests, but rather only IgA tTG or IgA EMA. A positive result for IgA tTG should be confirmed by a test for IgA EMA and vice versa. Any positive test result merits further inquiry and, ideally, referral to a gastroenterologist. If test results are positive, UE with SBB should be pursued aggressively. The practice of adding a comment to the laboratory report form concerning recommended referral to a gastroenterologist has been shown to increase the percentage of patients referred and biopsied by a dramatic margin [12] and should be considered for implementation in all laboratories offering such tests.

Conclusion

The incidence of coeliac disease in the general population is comparable to type 2 diabetes mellitus. Awareness of this fact and of the often atypical and oligosymptomatic presentation is only now gaining ground in the medical profession. A high index of suspicion is important in order to minimise diagnostic and therapeutic delay. This study showed that the number of tests ordered in our institution, more often in cases of abdominal symptoms than atypical symptoms, has started to increase in the past two years. It also showed that screening tests have found their place in general clinical practice, while the final choice of tests needs to be determined in accordance with available guidelines and local resources. Coeliac disease is a disorder with a definite treatment (gluten free diet); if left untreated, a diminished quality of life and potentially serious complications may ensue. Further education of the medical profession concerning coeliac disease, its incidence, presentation and treatment, is clearly indicated.

Special thanks go to Z. Beleznay and R. Pavlovic (Institute of Immunology, University Hospital Bern) for their help with data extraction and technical information on the serological tests. Special thanks are also due to E. Stauffer (Institute of Pathology, University of Bern) for the preparation of the histological illustrations. The endoscopy images were provided by P. Netzer (Department of Gastroenterology, University Hospital Bern).

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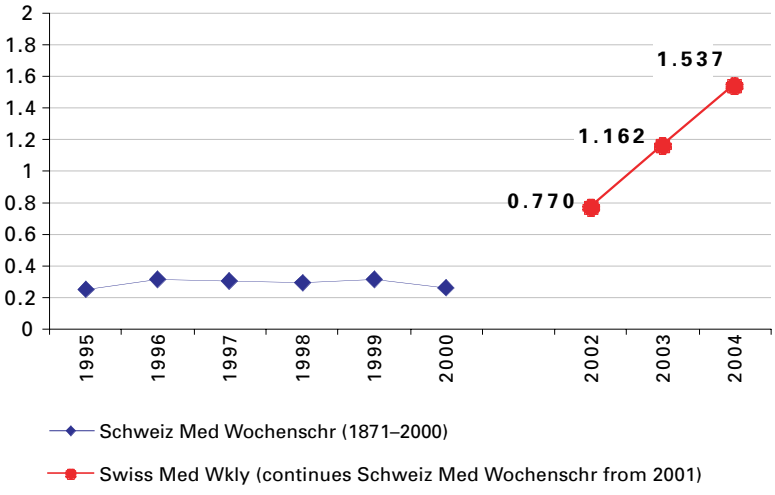

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