Burden of celiac disease in the Mediterranean area

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AIM: To estimate the burden of undiagnosed celiac disease (CD) in the Mediterranean area in terms of morbidity, mortality and health cost.

METHODS: For statistics regarding the population of each country in the Mediterranean area, we accessed authoritative international sources (World Bank, World Health Organization and United Nations). The prevalence of CD was obtained for most countries from published reports. An overall prevalence rate of 1% cases/total population was finally estimated to represent the frequency of the disease in the area, since none of the available confidence intervals of the reported rates significantly excluded this rate. The distribution of symptoms and complications was obtained from reliable reports in the same cohort. A standardized mortality rate of 1.8 was obtained from recent reports. Crude health cost was estimated for the years between symptoms and diagnosis for adults and children, and was standardized for purchasing power parity to account for the different economic profiles amongst Mediterranean countries.

RESULTS: In the next 10 years, the Mediterranean area will have about half a billion inhabitants, of which 120 million will be children. The projected number of CD diagnoses in 2020 is 5 million cases (1 million celiac children), with a relative increase of 11% compared to 2010. Based on the 2010 rate, there will be about 550 000 symptomatic adults and about 240 000 sick children: 85% of the symptomatic patients will suffer from gastrointestinal complaints, 40% are likely to have anemia, 30% will likely have osteopenia, 20% of children will have short stature, and 10% will have abnormal liver enzymes. The estimated standardized medical costs for symptomatic celiac patients during the delay between symptom onset and diagnosis (mean 6 years for adults, 2 years for children) will be about €4 billion (€387 million for children) over the next 10 years. A delay in diagnosis is expected to increase mortal-
CONCLUSION: In the near future, the burden of CD will increase tremendously. Few Mediterranean countries are able to face this expanding epidemic alone.

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Key words: Pediatric; Celiac disease; Short stature; Anemia; Osteopenia; Purchasing power parity; Standardized mortality rate; Mediterranean area

INTRODUCTION

Recent epidemiological studies show that the prevalence of celiac disease (CD) is underestimated not only in Europe, but also among the populations of Mediterranean regions such as the Middle East and North Africa[2,3], where its prevalence is similar to that recently observed in Western countries[4]. Indeed, in these two regions, a very high prevalence of CD has recently been reported both in the general population and in at-risk groups[5]. These high frequencies are associated with the widespread consumption of wheat and barley[6,7] and the high frequency of the DR3-DQ2 CD-predisposing haplotypes in these populations[8,9]. But these factors alone do not satisfactorily account for the spread of the CD epidemic in recent years[5,9]. The prevalence of CD among the general population varies from 0.14% to 1.17%[10-25], 1%-1.3% in Turkey[10,12], 0.6%-0.96% in Iran[13,14], 0.5% in Egypt[15], 0.6% in Tunisia and Israel[16,19], and < 0.5% in Jordan, Lebanon and Kuwait[25,26]. Among high-risk groups including patients with a positive family history, insulin-dependent diabetes mellitus (IDDM), thyroiditis[13,14] the prevalence of CD ranges from 2.4% to 44%, assessed by serological markers and biopsyp[15,25,26].

Egypt, and indeed all North African countries, were significant producers of wheat, and largely used barley for beer brewing; they were considered the “granary” of Romans for over 4 centuries. Bread, mostly made of wheat flour and called “the survival” in some local languages[15], has been a staple food for thousands of years. Similarly, the widespread use of couscous [from grossly milled durum wheat (Triticum durum)] dates back over 2000 years. But the use of wheat and other gluten-containing cereals is also increasing in the countries where it has been a staple for centuries[5,26].

The diffusion of pasta across all the Mediterranean countries is relatively recent and stems from the industrial development of grain processing. Unfortunately, a side effect of this positive dispersal may be the enormous increase in gluten intolerance, which is at a truly epidemic level. CD is now a widespread public health problem that also involves the populations of developing countries, as well as China and India[25,24]. However, this epidemic is not fully recognized since a sizeable number of cases are neither diagnosed nor cared for. In many Mediterranean countries, few cases are diagnosed because of the low level of awareness, knowledge and skill to deal with the problem, the lack of diagnostic resources and the attribution of CD symptoms to other, similar, illnesses[5,20]. The low awareness of CD often leads to a delay in diagnosis, which contributes to an excess of medical costs (CD includes growth failure, infant malnutrition, gastrointestinal diseases, anemia and more than 20 associated symptoms and conditions) and mortality.

All partners taking part in this study agreed that, to date, the best available estimation of CD-associated medical cost was that reported by Long et al[29], and supported by Herschovici et al[31]. The annual medical cost in the year preceding the diagnosis of CD, excluding diagnostic costs, was estimated to be $5023/patient, $1764 more than the cost of the same patients in the year after diagnosis[29]. In the four years preceding the diagnosis of symptomatic CD, the direct medical cost was estimated to be $11 037/patient. For a symptomatic- and age-matched control individual, not affected by CD, the cost after 4 years was estimated at $7073, with a difference of $3964 (about $1000/patient per year). This difference is due to increased in-patients admissions, out-patient cost, laboratory tests, radiology, and office visits[29]. The diagnosis of CD resulted in a 30% reduction in direct medical expenditure. A similar 30% reduction in direct medical costs after diagnosis of CD was reported by Green et al[30], the mean medical expenditure decreased from $8502 per capita to $7133 for the 2 years after diagnosis of CD.

The CD epidemic is the largest epidemic of food-induced permanent disease in the Euro-Mediterranean region. Very few countries of this region are able to face this expanding problem. The aim of this study was to estimate what the burden of CD will be in the near future, and how the CD epidemic will affect morbidity, mortality and health costs. We aim to provide stakeholders with a reliable prediction of the incoming picture of CD in the Mediterranean area, and so enable them to take action to face this epidemic.

MATERIALS AND METHODS

Population statistics

For statistics regarding each country in the Mediterra-
Celiac disease

The prevalence of CD among the populations of Mediterranean countries, such as the Middle East and North Africa\cite{32,33,35,37}, is similar to that recently observed in Western countries\cite{4}. The prevalence of CD among the general population varies from 0.14% to 1.17%\cite{10,20}: 1%-1.3% in Turkey\cite{10,12}, 0.6%-0.96% in Iran\cite{31,34,36}, 0.5% in Egypt\cite{13}, 0.6% in Tunisia and Israel\cite{16,19}, and <0.5% in Jordan, Lebanon and Kuwait\cite{17}. An overall prevalence rate of 1% cases/total population was finally estimated to better represent the frequency of the disease in the area, since none of the available confidence intervals of the reported rates significantly excluded this 1% rate. The rate of symptomatic vs asymptomatic patients was obtained from several reliable reports from the area\cite{5,13,20,32-35,37}. In summary, 85% of symptomatic patients are likely to suffer from gastrointestinal symptoms, which include diarrhea, abdominal pain, vomiting, irritable bowel, and gastritis\cite{5,13,20,32-35,37}. Among the non-gastrointestinal complaints, the available estimates suggest 20% of children are affected by short stature\cite{10,20,30-35,37}, 40% of all cases are affected by anemia\cite{5,20,32,34,37}, 30% are affected by osteopenia\cite{5,32,35,37}, and 10% by abnormal liver enzymes\cite{32,34}. Mortality has been reported in excess of 1.8 compared to age- and sex-matched controls\cite{41,42,43-46,47}. The risk of cancer in undiagnosed adults is significantly increased and the mortality is almost doubled in the total cohort of affected persons compared with the general population\cite{1,44}.

Crude medical costs

Crude health costs were estimated for the years between symptoms and diagnosis only for symptomatic adults and children, and were standardized for purchasing power parity (PPP) to account for the different economic profile among Mediterranean countries. Since gross national product is different across countries, the PPP is based on the law of one price; in the absence of transaction costs, identical goods will have the same price in different markets. The PPP equalizes the purchasing power of different currencies for a given basket of goods, thereby providing a standardized estimate of cost across countries.

We assume that the cohort of CD without symptoms does not increase the average medical cost compared to non CD individuals (but this should also be revised, since a significant number of patients identified by screening had a posteriori clinical symptoms). Therefore, medical costs are estimated only for 1:7 adults and 1:5 children with CD symptoms.

For each individual adult we assigned (on the basis of the reports cited and the clinical experience of the study partners), a minimal period of 6 years of delay between symptom onset and diagnosis of the disease\cite{41,42}, while this delay was two years for each assigned child with CD\cite{5,20}. During that period an adult with CD required, in excess of age- and sex-matched controls, at least: 2 inpatient admissions, 1 out-patient admission, 3 primary medical consultations, 2 specialized consultations, and 4 laboratory tests. Similarly, children needed at least: 1 inpatient admission and 1 out-patient admission, 3 medical consultations, 1 specialized consultation and 2 laboratory tests (Table 1).

Estimated medical costs

The costs of health services were estimated based on the 2007 costs of the Italian National Health Service (NHS) which is similar to that of several European countries. We summed the total costs of the medical services required for each child or adult patient to obtain a standardized cost/per patient before the diagnosis of CD was made (Table 1). In this way, we obtained an estimation of the financial load (only for medical expenses) of symptomatic patients. The estimated cost according to the Italian NHS was then standardized for each country according to its PPP index. The total load of medical expenses for each country was calculated by multiplying the individual cost by the number of symptomatic patients estimated (adults and children).

Summary of reference data

(1) CD prevalence = 1%; incidence: new cases/year estimated at 1% of the live births, corrected for infant mortality rate; (2) symptomatic adults: 1 of every 7 cases, children 1:5 cases; (3) mortality of the total CD cohort: standardized mortality rate 1.8 compared to age- and sex-matched population; (4) delay between symptoms and diagnosis: adults 6 years, children 2 years; (5) associated conditions: 10%-15% of the total cohort - autoimmune disorders 30% (Turkey 1.9%, Iran 33%) and IDDM 10% (6.7%-18.5%); (6) complications: 16% of symptomatic CD patients; and (7) non gastrointestinal

| Table 1 Excess need of health resources before the diagnosis of celiac disease |
|---|
| n | Adult cost (€) | n | Child cost (€) |
|---|
| In-patient admission | 2 | 9818 | 1 | 2254 |
| Out-patient admission | 1 | 879 | 1 | 586 |
| Medical consultations | 3 | 100 | 3 | 150 |
| Specialist consultations | 2 | 150 | 1 | 50 |
| Lab test | 4 | 446 | 2 | 297 |
| Total per patient | 11393 | 3337 |
Table 2 Populations now and after 10 years

| Country     | Population 2010 | Children 0-14 | Median age | Population growth rate | Children 0-14 in 2020 | Total population in 2020 |
|-------------|-----------------|---------------|------------|------------------------|-----------------------|--------------------------|
| Albania     | 3,619,778       | 853,883       | 29.9       | 0.5                    | 4,017,368             | 3,822,345                |
| Algeria     | 33,769,669      | 8,878,665     | 26.6       | 1.2                    | 8,999,566             | 38,032,972               |
| Bosnia      | 4,590,310       | 673,770       | 39.8       | 0.3                    | 696,962               | 4,748,317                |
| Cyprus      | 792,604         | 154,445       | 35.5       | 1.7                    | 182,623               | 937,214                  |
| Croatia     | 4,491,543       | 708,683       | 41         | -0.1                   | 705,006               | 4,468,242                |
| Egypt       | 81,713,517      | 25,983,672    | 24.8       | 2                      | 31,775,575            | 99,931,053               |
| France      | 64,057,790      | 11,894,698    | 39.4       | 0.5                    | 12,564,088            | 67,662,729               |
| Greece      | 10,722,816      | 1,531,606     | 41.8       | 1                      | 1,551,169             | 10,859,777               |
| Israel      | 7,312,359       | 1,989,313     | 29.1       | 1.7                    | 2,347,869             | 8,394,203                |
| Italy       | 58,126,212      | 7,870,226     | 43.3       | 0                      | 7,833,314             | 57,855,956               |
| Lebanon     | 3,971,941       | 1,032,888     | 29.3       | 1.1                    | 1,153,096             | 4,434,197                |
| Malta       | 6,173,579       | 2,048,548     | 23.9       | 2.2                    | 2,539,599             | 7,653,242                |
| Morocco     | 34,343,219      | 10,473,478    | 25         | 1.1                    | 11,683,138            | 8,309,775                |
| Syria       | 19,747,586      | 7,146,569     | 21.7       | 2                      | 8,716,754             | 24,086,361               |
| Slovenia    | 2,007,711       | 273,464       | 41.5       | 0                      | 273,655               | 2,009,117                |
| Spain       | 40,525,002      | 5,864,419     | 41.1       | 0.1                    | 5,906,780             | 40,817,729               |
| Tunisia     | 10,383,577      | 2,413,484     | 29.2       | 1                      | 2,660,713             | 11,447,256               |
| Turkey      | 71,892,807      | 17,545,890    | 27.7       | 1.3                    | 19,965,025            | 81,805,009               |
| Mediterranean | 458,445,552    | 107,403,812   | 33.2       | 0.9                    | 121,526,405           | 507,693,365              |

Table 3 Prevalence of celiac disease in the next 10 years

| Country     | Estimated celiacs today | Estimated celiac children today at 1% | Projected prevalence of CD in next 10 yr | Projected celiac children in next 10 yr |
|-------------|-------------------------|--------------------------------------|-----------------------------------------|---------------------------------------|
| Albania     | 36,198                  | 853,883                              | 38,223                                  | 4,017,368                             |
| Algeria     | 337,697                 | 8,878,665                            | 38,223                                  | 8,999,566                             |
| Bosnia      | 45,903                  | 673,770                              | 38,223                                  | 696,962                               |
| Cyprus      | 792,604                 | 154,445                              | 38,223                                  | 182,623                               |
| Croatia     | 44,915                  | 708,683                              | 38,223                                  | 705,006                               |
| Egypt       | 817,135                 | 25,983,672                           | 38,223                                  | 31,775,575                           |
| France      | 64,057,790              | 11,894,698                           | 38,223                                  | 67,662,729                           |
| Greece      | 10,722,816              | 1,531,606                            | 38,223                                  | 10,859,777                           |
| Israel      | 7,312,359               | 1,989,313                            | 38,223                                  | 8,394,203                            |
| Italy       | 58,126,212              | 7,870,226                            | 38,223                                  | 57,855,956                           |
| Lebanon     | 3,971,941               | 1,032,888                            | 38,223                                  | 4,434,197                            |
| Malta       | 6,173,579               | 2,048,548                            | 38,223                                  | 7,653,242                            |
| Morocco     | 34,343,219              | 10,473,478                           | 38,223                                  | 8,309,775                            |
| Syria       | 19,747,586              | 7,146,569                            | 38,223                                  | 24,086,361                           |
| Slovenia    | 2,007,711               | 273,464                              | 38,223                                  | 2,009,117                            |
| Spain       | 40,525,002              | 5,864,419                            | 38,223                                  | 40,817,729                           |
| Tunisia     | 10,383,577              | 2,413,484                            | 38,223                                  | 11,447,256                           |
| Turkey      | 71,892,807              | 17,545,890                           | 38,223                                  | 81,805,009                           |
| Mediterranean | 458,445,552           | 107,403,812                          | 38,223                                  | 507,693,365                          |

RESULTS

Table 2 shows the population growth, number of children aged 0-14 years and the predicted figures for the year 2020, calculated based on a constant growth rate. The Mediterranean area will have about half a billion individuals by the year 2020, more than 100 million of which will be children aged 0-14 years. This estimate is likely to be in the low range, since some countries with a large population are likely to grow at a higher rate than this estimate before the year 2010.

Table 3 shows the prevalence of CD in each country in 2010 and the predicted prevalence in 2020. Within 10 years, the Mediterranean area will have to face more than 5 million cases of CD, one million of which will be in children. The large majority will not have clear symptoms and their diagnosis and care will be significantly delayed. Among the adult CD population, about 550 000 will present symptoms, while only 240 000 out of the 1 million estimated celiac children will be symptomatic. Table 4 shows the estimated number of clinical complaints associated with the CD epidemic. It is likely that more than 48 000 children will be affected by growth failure as a result of growth failure, they will be 317,000 cases of anemia and 238,000 individuals will be afflicted with osteopenia. Table 5 shows the estimated financial burden of the CD epidemic. There is no scope for a detailed calculation of costs, which will be related more to the availability of and access to medical services than to the actual cost of the service, but these figures help to understand the financial burden of the undiagnosed disease. European countries may not be impressed by these estimates but, for several other Mediterranean countries, these predicted costs might be a consistent load to the gross national product. More than €4 billion is a prudent estimate; only crude medical costs are included, not individual or social cost.

Table 6 shows the estimated number of deaths in the celiac disease cohort and the excess of deaths compared to age- and sex-matched controls. At the present rate, there will be more than 250 000 CD-related deaths in the Mediterranean area in 2020.

DISCUSSION

Celiac disease is a very common chronic disease that...
affects adults and children in all wheat-consuming countries. It has also recently been reported in countries where its prevalence was previously unknown, such as China[27]. For more than two decades, we have been discussing the difference in the prevalence of CD among countries in Europe, North America and South America, and the conclusion is that there is no country where CD prevalence is significantly different from the overall prevalence of about 1%. Interestingly, the prevalence, at a global level, is not related either to the amount of wheat consumed by each country or to the prevalence of the human leukocyte antigen (HLA) DR3-DQ2 and DR4-DQ8 haplotype worldwide[27].

An excess prevalence of CD has been reported in an isolated population in North Africa and in a large population in Sweden, but again it is plausible that this excess prevalence reflects a bias related to the cohort rather than a true excess. The prevalence of CD is increasing worldwide, including in Europe[4], China[27] and India[28]. The only region where it has not yet been described is Central Africa, and this may be explained by the absence in this region of HLA predisposing haplotypes, and of polymorphisms of the major non-HLA genes, namely \textit{HLA-B3}, \textit{IL12A}, \textit{IL18R}, \textit{IL4RAP}, and \textit{IL1RL1}, among others[27,28]. Recently, Barada et al[23] from Lebanon produced a comprehensive report of the situation in the

| Table 4 | Symptoms and diseases associated with symptomatic cases |
|---------|---------------------------------------------------------|
|         | Symptomatic adults next 10 yr 1:7 | Symptomatic children next 10 yr 1:5 | Gastrointestinal symptoms | Anemia | Osteopenia | Abnormal liver | Children with short stature |
| Albania | 4172 | 1803 | 5079 | 2390 | 1793 | 598 | 361 |
| Algeria | 40 048 | 19 999 | 51 040 | 24 019 | 18 014 | 6005 | 4000 |
| Bosnia  | 5788 | 1394 | 6104 | 2873 | 2154 | 718 | 279 |
| Cyprus  | 1078 | 365 | 1227 | 577 | 433 | 144 | 73 |
| Croatia | 5576 | 1410 | 5768 | 2714 | 2056 | 679 | 282 |
| Egypt   | 97 364 | 63 553 | 136 779 | 64 367 | 48 275 | 16 092 | 12 711 |
| France  | 78 712 | 25 128 | 88 264 | 41 536 | 31 152 | 10 384 | 5026 |
| Greece  | 13 298 | 3102 | 13 940 | 6560 | 4920 | 1640 | 620 |
| Israel  | 8638 | 4696 | 11 333 | 5333 | 4000 | 1333 | 939 |
| Italy   | 71 458 | 15 667 | 74 056 | 34 850 | 26 137 | 8712 | 3133 |
| Lebanon | 4687 | 2306 | 5944 | 2797 | 2098 | 699 | 461 |
| Libya   | 7305 | 5079 | 10 527 | 4954 | 3715 | 1238 | 1016 |
| Malta   | 502 | 138 | 543 | 256 | 192 | 64 | 28 |
| Morocco | 38 038 | 23 366 | 52 194 | 24 562 | 18 421 | 6140 | 4673 |
| Syria   | 21 957 | 17 434 | 31 482 | 15 756 | 11 817 | 3939 | 3487 |
| Slovenia | 2479 | 547 | 2573 | 1211 | 908 | 303 | 109 |
| Spain   | 49 873 | 11 814 | 52 433 | 24 675 | 18 506 | 6169 | 2363 |
| Tunisia | 12 552 | 5321 | 15 193 | 7149 | 5362 | 1787 | 1064 |
| Turkey  | 88 343 | 39 930 | 109 032 | 31 788 | 23 846 | 7942 | 7986 |
| Mediter | 551 667 | 243 053 | 675 512 | 317 888 | 238 416 | 7942 | 48 611 |

| Table 5 | Excess cost of undiagnosed symptomatic celiac patients |
|---------|---------------------------------------------------------|
| Purchasing power parity | Standardized cost for an adult in 6 yr of delay, € | Standardized cost for a child in 2 yr of delay, € | Total cost for adults in the next 10 yr, € | Total cost for children in the next 10 yr, € | Total cost of symptomatic in the next 10 yr, € |
| Albania | 7.164 | 2804 | 821 | 11 698 575 | 1 481 020 | 13 179 595 |
| Algeria | 6.869 | 2688 | 787 | 107 662 084 | 15 748 296 | 123 410 460 |
| Bosnia  | 7.561 | 2881 | 844 | 16 673 654 | 1 176 265 | 17 849 919 |
| Cyprus  | 17.7 | 6928 | 2029 | 7 468 819 | 741 246 | 8 210 065 |
| Croatia | 28.54 | 11 171 | 3272 | 60 057 866 | 4 613 886 | 64 671 751 |
| Egypt   | 6.123 | 2396 | 702 | 233 320 214 | 44 699 799 | 277 930 013 |
| France  | 33.68 | 13 181 | 3861 | 1 037 513 563 | 97 017 277 | 1 134 530 840 |
| Greece  | 29.88 | 11 695 | 3426 | 155 520 664 | 10 726 416 | 166 148 080 |
| Israel  | 28.39 | 11 112 | 3255 | 95 987 202 | 15 284 247 | 111 269 450 |
| Italy   | 29.11 | 11 393 | 3337 | 814 080 186 | 17 779 338 | 866 359 425 |
| Lebanon | 14.23 | 5568 | 1631 | 26 097 336 | 3 761 033 | 29 858 369 |
| Libya   | 14.33 | 5608 | 1643 | 40 966 178 | 8 342 757 | 49 308 935 |
| Malta   | 23.58 | 9230 | 2704 | 4 630 407 | 372 044 | 5 002 450 |
| Morocco | 4.604 | 1802 | 528 | 68 540 194 | 12 332 575 | 80 872 769 |
| Syria   | 4.7 | 1839 | 539 | 40 388 186 | 9 393 156 | 49 781 342 |
| Slovenia | 29.69 | 11 619 | 3403 | 28 807 411 | 1 862 767 | 30 670 178 |
| Spain   | 33.7 | 13 189 | 3863 | 657 796 976 | 45 639 366 | 703 426 342 |
| Tunisia | 8.254 | 3230 | 946 | 40 548 541 | 5 035 253 | 45 583 796 |
| Turkey  | 12.48 | 4883 | 1430 | 431 358 582 | 57 108 945 | 488 467 527 |
| Mediter | 17.92 | 7012 | 2054 | 3 879 104 619 | 387 426 887 | 4 266 531 506 |
countries that face the Mediterranean Sea, thereby increasing the awareness of CD in the area.

The EUROMED program supports several health-promoting activities across the Mediterranean, such as the surveillance of infectious diseases program and the Program for Transplants and Oncology EuroMed (Cancer Registries Network, Cancer screening and early diagnosis program, Mediterranean Transplant Network). Italy has requested that the CD epidemic be included in these programs (www.eeas.europa.eu/euromed/index_en.htm). The first step in facing this epidemic is to estimate the burden of CD in the area. Here we provide a reliable and simple picture of the present situation and a prediction of the development of the CD epidemic in the next 10 years, up to 2021.

The prediction obtained by simple straightforward calculations is impressive. Mediterranean countries will have to be prepared to deal with a considerable number of CD patients in the near future. There will be more than 5 million cases, one million of which will be children. But, more than the overall figures, each country will be especially concerned about the national figures. Our estimates are conservative figures, since we estimated a constant population growth over the next ten years, whereas the faster growing countries may have a more rapid growth rate than slower growing countries. Data on symptoms and common clinical problems are available only for symptomatic individuals, while a considerable percentage of so-called “asymptomatic” subjects notoriously report significant complaints a posteriori. A limitation of this study is related to the uncertainties inherent in any prediction given the wide confidence intervals of rates. However, the starting 1% prevalence rate is not only very robust, because of innumerable replications, but it also probably underestimates rather than overestimates the problem. The rate of symptomatic versus asymptomatic individuals is also fairly conservative.

The financial burden estimate is not aimed to acquire more precision; we provide a gross figure for the spectrum of resources needed in each country for the services required by symptomatic patients. The priority issue is the availability of services; in many African countries, services are mostly only available in large cities and specialized health institutions. In the rural areas, the availability of services can be far less than that required. Hence, the cost of these services should, sadly, be subtracted from the total financial burden. This impending cohort of CD patients does require, and moreover will require, access to health services as inpatients or outpatients, for medical consultations, laboratory tests and, after diagnosis, financial support for a lifelong gluten-free diet. There is universal concern and many countries demand the expertise and support for dissemination of know-how and capacity building for the management of CD.

The EuroMed - MEDICEL project (www.medicel.unina.it) offers a platform to analyze the problem and develop strategies, but active national plans are required to face the burgeoning epidemic, and the heavy burden that it will place on the health and the finances of the population.

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Table 6  Excess mortality in undiagnosed cases

| Country     | Projected prevalence of CD in the next 10 yr | Death rate, deaths/1000 individuals | Population expected deaths (next 10 yr) | Celiac deaths in next 10 yr | Excess celiac deaths in next 10 yr |
|-------------|---------------------------------------------|------------------------------------|---------------------------------------|---------------------------|-----------------------------------|
| Albania     | 38 223                                      | 5.1                                | 193 793                               | 3488                      | 1550                              |
| Algeria     | 380 330                                     | 4.6                                | 1 764 730                             | 31 765                    | 14 118                            |
| Bosnia      | 47 483                                      | 8.6                                | 409 780                               | 7376                      | 3278                              |
| Cyprus      | 9372                                        | 6.4                                | 59 982                                | 1080                      | 480                               |
| Croatia     | 44 682                                      | 11.8                               | 525 018                               | 9450                      | 4200                              |
| Egypt       | 999 511                                     | 4.9                                | 4 876 635                             | 87 779                    | 39 013                            |
| France      | 676 627                                     | 8.6                                | 5 791 930                             | 104 255                   | 46 335                            |
| Greece      | 108 598                                     | 10.5                               | 1 141 363                             | 20 545                    | 9131                              |
| Israel      | 83 943                                      | 5.4                                | 455 811                               | 8205                      | 3646                              |
| Italy       | 578 536                                     | 10.7                               | 6 201 905                             | 111 634                   | 49 615                            |
| Lebanon     | 44 342                                      | 6                                  | 267 382                               | 4813                      | 2139                              |
| Libya       | 76 534                                      | 3.4                                | 260 982                               | 4698                      | 2088                              |
| Malta       | 4200                                        | 8.4                                | 35 193                                | 633                       | 282                               |
| Morocco     | 383 098                                     | 4.7                                | 1 815 883                             | 32 686                    | 14 527                            |
| Syria       | 240 864                                     | 3.7                                | 896 013                               | 16 128                    | 7168                              |
| Slovenia    | 20 091                                      | 9.2                                | 184 839                               | 3327                      | 1479                              |
| Spain       | 408 177                                     | 10                                 | 4 077 691                             | 73 398                    | 32 622                            |
| Tunisia     | 114 472                                     | 5.2                                | 595 256                               | 10 715                    | 4762                              |
| Turkey      | 818 050                                     | 6                                  | 4 908 301                             | 88 349                    | 39 266                            |
| Mediter     | 5 076 934                                   | 7                                  | 34 462 486                            | 620 325                   | 275 700                           |

1Undiagnosed celiac patients have 1.8 standard mortality rate. CD: Celiac disease.
increasing in all countries in which there is awareness of this intolerance. In all Western countries, including the United States and South America, the observed prevalence of the disease went from 1:1000 individuals to more than 1:100 individuals in two decades. However, large series of cases have recently been reported from “new” countries like India, China, North Africa and the Middle East. Celiac disease is expanding over and above any predicted trend, and has taken on the semblance of a real epidemic.

Research frontiers

This expanding “epidemic” raises a series of unanswered research questions related to the following hot topics: (1) the weight of environmental factors in the increase of CD; (2) the genetic profile associated with predisposition to CD; (3) population differences in terms of genetic and environmental factors; and (4) the development of “sensitivity” to gluten.

Innovations and breakthroughs

In next 10 years, the Mediterranean area will have about half a billion inhabitants, 120 million of whom will be children. The projected number of CD cases in 2020 will be 5 million cases (1 million celiac children), with a relative increase of 11% compared to 2010. At a 2010 constant rate, there will be about 550 000 symptomatic adults and 240 000 sick children: 85% of patients will suffer from gastrointestinal complaints, 40% are likely to have anemia, 30% will be affected with osteopenia, 20% of children will have short stature and 10% will have abnormal liver enzymes. The estimated standardized medical costs for symptomatic celiac disease during the years of delay between onset of symptoms and diagnosis (mean: 6 years for adults, 2 years for children) will be about €4 billion ($3.87 million for the next 10 years). A delay in diagnosis is expected to increase mortality; about 600 000 deaths will occur among individuals affected by CD in the next 10 years, with an excess of 44.4% compared to age- and sex-matched controls.

Applications

The data produced in this study provide a picture of the cohort of patients affected by CD that will develop over the next 10 years in each country of the Mediterranean Basin. Stakeholders and health professionals in each country now have the figures with which it is possible to base adequate plans to face this epidemic. The diagnostic protocol must be simplified and made available not only in specialized centers, usually in large cities, but it should be especially important in rural districts.

Terminology

CD: Celiac disease is a permanent intolerance to gluten based on a genetic predisposition; Projected prevalence: The number of celiac cases that are expected to be present over the next 10 years; Excess mortality: Undiagnosed celiac cases have twice the risk of death compared to age- and sex-matched controls. If the expected cases are not diagnosed, there will be more than 200 000 excess deaths in the Mediterranean area; Growth failure: 20% of children (about 50 000) with undiagnosed CD are affected by weight loss and short stature, due to a growth failure.

Peer review

The paper is well written and deals with an important patient problem are continuously facing.

REFERENCES

1 Cataldo F, Montalto G. Celiac disease in the developing countries: a new and challenging public health problem. World J Gastroenterol 2007; 13: 2153-2159
2 Barada K, Bitar A, Mokadem MA, Hashash JG, Green P. Celiac disease in Middle Eastern and North African countries: a new burden? World J Gastroenterol 2010; 16: 1449-1457
3 Rostami K, Malekzadeh R, Shahbazkhani B, Akbari MR, Catassi C. Celiac disease in Middle Eastern countries: a challenge for the evolutionary history of thin complex disorder? Dig Liver Dis 2004; 36: 694-697
4 Mustalahi K, Catassi C, Reunanan A, Fabiani E, Heier M, McMillan S, Murray L, Metzger MH, Gasparin M, Bravi E, Mäki M. The prevalence of celiac disease in Europe: results of a centralized, international mass screening project. Ann Med 2010; 42: 587-595
5 Rawashdeh MO, Khalil B, Raveily E. Celiac disease in Arabs. J Pediatr Gastroenterol Nutr 1996; 23: 415-418
6 Bouguerra F, Babron MC, Eliaouf JF, Debbabi A, Clot J, Khaldi F, Greco L, Clerget-Darpoux F. Synergistic effect of two HLA heterodimers in the susceptibility to celiac disease in Tunisia. Genet Epidemiol 1997; 14: 413-422
7 Catassi C, Rätsch IM, Gandolfi L, Pratesi R, Fabiani E, Al Asmar R, Frijia M, Beirazi I, Vizzoni L. Why is celiac disease endemic in the people of the Sahara? Lancet 1999; 354: 647-648
8 Lohi S, Mustalahi K, Kaukinen K, Laurila K, Collin P, Risangan H, Lohi O, Bravi E, Gasparin M, Reunanen A, Mäki M. Increasing prevalence of celiac disease over time. Aliment Pharmacol Ther 2007; 26: 1217-1225
9 Roma E, Panayiotou J, Karantana H, Constantiniou C, Siakavellas SI, Kini M, Siropoulou VP, Baniadis G. Changing pattern in the clinical presentation of pediatric celiac disease: a 30-year study. Digestion 2009; 80: 185-191
10 Guroysu S, Guven K, Simsek T, Yurci A, Koca N, Patiroglu TE, Ozbakir O, Yuceyosu M. The prevalence of unrecognized adult celiac disease in Central Anatolia. J Clin Gastroenterol 2005; 39: 508-511
11 Tatar G, Elsurier R, Simsek H, Balaban YH, Hascelik G, Ozcebe OI, Buyukcayik Y, Sokmensuer C. Screening of tissue transglutaminase antibody in healthy blood donors for celiac disease screening in the Turkish population. Dig Dis Sci 2004; 49: 1479-1484
12 Ertekin V, Selimoğlu MA, Kardaş F, Ağaç E. Prevalence of celiac disease in Turkish children. J Clin Gastroenterol 2005; 39: 669-691
13 Akbari MR, Mohammadhkani A, Fakheri H, Javad Zahedi M, Shahbazkhani B, Nouraie M, Sotoudeh M, Shakeri R, Malekzadeh R. Screening of the adult population in Iran for celiac disease: comparison of the tissue-transglutaminase antibody and anti-endomysial antibody tests. Eur J Gastroenterol Hepatol 2006; 18: 1181-1186
14 Shahbazkhani B, Malekzadeh R, Sotoudeh M, Moghadam KF, Farhadi M, Ansari R, Elahyfar A, Rostami K. High prevalence of celiac disease in apparently healthy Iranian blood donors. Eur J Gastroenterol Hepatol 2003; 15: 475-478
15 Abu-Zekry M, Kryszyk D, Diab M, Catassi C, Fasano A. Prevalence of celiac disease in Egyptian children disputes the east-west agriculture-dependent spread of the disease. J Pediatr Gastroenterol Nutr 2008; 47: 136-140
16 Manai A, Landolfo H, Chahed A, Gueddah L, Limem M, Ben Abdessalem M, Yacoub-Jemni S, Ghanem H, Jeddi M, Chedira I. Celiac disease in Tunisia: serological screening in healthy blood donors. Pathol Biol (Paris) 2006; 54: 10-13
17 Ben Hariz M, Kallet-Sellami M, Kallet L, Lahmer A, Halouii S, Bourouai S, Laater A, Sliti A, Mahjoub A, Zouari B, Makni S, Mahzeri A. Prevalence of celiac disease in Tunisia: mass-screening study in schoolchildren. Eur J Gastroenterol Hepatol 2007; 19: 687-694
18 Bdiouf S, Sakly N, Hassine M, Saffar H. Prevalence of celiac disease in Tunisian blood donors. Gastroenterol Clin Biol 2006; 30: 33-36
19 Shamir R, Lerner A, Shinar E, Labat N, Sobel E, Bar-or R, Kerner H, Elakim R. The use of a single serological marker underestimates the prevalence of celiac disease in Israel: a study of blood donors. Am J Gastroenterol 2002; 97: 2589-2594
20 Khuffash FA, Barakat MH, Shaltout AA, Farwana SS, Adnan MS, Tungekar MF. Coeliac disease among children in Kuwait: difficulties in diagnosis and management. Gut 1987; 28: 1595-1599
21 Bouguerra R, Ben Salem L, Chaâbouni H, Laadhar L, Esais O, Zitouni M, Haouet S, Ben Slama C, Ben Ammar A, Zouari B, Makni S. Celiac disease in adult patients with type 1 diabetes mellitus in Tunisia. Diabetes Metab 2005; 31: 83-86
22 Ashabani A, Abushofu A, Abureswili S, Abdelazeem M, Tucková L, Tlaskalová-Hogenová H. The prevalence of celiac disease in Libyan children with type 1 diabetes mellitus. Diabetes Metab Res Rev 2003; 19: 69-75
Greco L et al. Celiac burden

23 Boudraa G, Hachelaif W, Benbouabdellah M, Belkadi M, Benmansour FZ, Touhami M. Prevalence of coeliac disease in diabetic children and their first-degree relatives in west Algeria: screening with serological markers. Acta Paediatr Suppl 1996; 412: 58-60

24 Shahbazkhan B, Faezi T, Akbari MR, Mohamadnejad M, Sotoudeh M, Rajab A, Tahaghoghi S, Malekzadeh R. Coeliac disease in Iranian type I diabetic patients. Dig Liver Dis 2004; 36: 191-194

25 Byerlee D, Hesse de Polanco E. Wheat in the world food economy: increasing role in developing countries. Food Policy 1983; 8: 67-75

26 Defra Food and Farming Group. OECD-FAO agricultural outlook 2010-2019 Summary by Defra. Available from: URL: http://www.agri-outlook.org/

27 Wu J, Xia B, von Blomberg BM, Zhao C, Yang XW, Crusius JB, Peña AS. Coeliac disease: emerging in China? Gut 2010; 59: 418-419

28 Makharia GK, Verma AK, Amarchand R, Bhatnagar S, Das P, Goswami A, Bhatia V, Ahuja V, Datta Gupta S, Anand K. Prevalence of celiac disease in the northern part of India: a community based study. J Gastroenterol Hepatol 2011; 26: 894-900

29 Long KH, Rubio-Tapia A, Wage AE, Melton LJ, Lahr BD, Van Dyke CT, Murray JA. The economics of coeliac disease: a population-based study. Aliment Pharmacol Ther 2010; 32: 261-269

30 Green PH, Neugut AI, Nayer AJ, Edwards ZC, Gabinelle S, Mansuer C, Fasano A. Celiac disease pathogenesis. Annu Rev Immunol 2011; 29: 493-525

31 Hershcovici T, Leshno M, Goldin E, Shamir R, Israeli E. Cost effectiveness of mass screening for coeliac disease is determined by time-delay to diagnosis and quality of life on a gluten-free diet. Aliment Pharmacol Ther 2010; 31: 901-910

32 Elsurer R, Tatar G, Simsek H, Balaban YH, Aydinli M, Sокmensuer C. Celiac disease in the Turkish population. Dig Dis Sci 2005; 50: 136-142

33 Masjedizadeh R, Hajiani E, Hashemi J, Shyayesteh AA, Moula K, Rajabi T. Celiac disease in South-West of Iran. World J Gastroenterol 2006; 12: 4416-4419

34 Fayad SB, Aref MI, Fathy HM, Abd El Dayem SM, Emara NA, Maklof A, Shafik A. Prevalence of celiac disease, Helicobacter pylori and gastroesophageal reflux in patients with refractory iron deficiency anemia. J Trop Pediatr 2008; 54: 43-53

35 Qari FA. Clinical presentation of adult celiac disease in Western Saudi Arabia. Saudi Med J 2002; 23: 1514-1517

36 Doganci T, Bozkurt S. Celiac disease with various presentata-
tions. Pediatr Int 2004; 46: 693-696

37 Kuloğlu Z, Kirsagçılóğlu CT, Kansu A, Ensari A, Girgin N. Celiac disease: presentation of 109 children. Yonsei Med J 2009; 50: 617-623

38 Novacek G, Miehsler W, Wrba F, Ferenci P, Penner N, Vogelsang H. Prevalence and clinical importance of hypertransaminasemia in coeliac disease. Eur J Gastroenterol Hepatol 1999; 11: 283-288

39 Biagi F, Corazza GR. Mortality in celiac disease. Nat Rev Gastroenterol Hepatol 2010; 7: 158-162

40 Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. Gastroenterology 2006; 131: 1981-2002

41 Logan RF, Rifkind EA, Turner ID, Ferguson A. Mortality in celiac disease. Gastroenterology 1989; 97: 265-271

42 Cottone M, Termini A, Oliva L, Magliocco A, Marrone C, Orlando A, Pinzone F, Di Mitri R, Rosselli M, Rizzo A, Pagliaro L. Mortality and causes of death in celiac disease in a Mediterranean area. Dig Dis Sci 1999; 44: 2538-2541

43 Corrao G, Corazza GR, Bagnard V, Brusco G, Ciacci C, Cotton M, Sategna Guidetti C, Usai P, Cesari P, Pelli MA, Lopezido S, Volta U, Calabró A, Certo M. Mortality in patients with coeliac disease and their relatives: a cohort study. Lancet 2001; 358: 356-361

44 Rubio-Tapia A, Kyle RA, Kaplan EL, Johnson DR, Page W, Erdtmann F, Brantner TL, Kim WR, Phelps TK, Lahr BD, Zinsmeister AR, Melton LJ, Murray JA. Increased prevalence and mortality in undiagnosed celiac disease. Gastroenterology 2009; 137: 88-93

45 Sanders DS, Hurlstone DP, Stokes RO, Rashid F, Milford-Ward A, Hadjivassiliou M, Lobo AJ. Changing face of adult coeliac disease: experience of a single university hospital in South Yorkshire. Postgrad Med J 2002; 78: 31-33

46 Jones S, D’Souza C, Haboubi NY. Patterns of clinical presentation of adult coeliac disease in a rural setting. Natr J 2006; 5: 24

47 Abadie V, Sollid LM, Barreiro LB, Jabri B. Integration of genetic and immunological insights into a model of celiac disease pathogenesis. Annu Rev Immunol 2011; 29: 493-525

48 Cataldo F, Lio D, Simpore J, Musumeci S. Consumption of wheat foodstuffs not a risk for celiac disease occurrence in burkina faso. J Pediatr Gastroenterol Nutr 2002; 35: 233-240

49 Fasano A. Celiac disease—how to handle a clinical chameleon. N Engl J Med 2000; 343: 2568-2570

50 Martinelli P, Troncone R, Paparo F, Torre P, Trapanesi E, Fasano C, Lamberti A, Budillon G, Nardone G, Greco L. Celiac disease and unfavourable outcome of pregnancy. Gut 2000; 46: 332-335

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