Epidemiology of Diabetes and its Non-Coronary Complications

Alberto Goday

Servicio de Endocrinología. Hospital Universitario del Mar. Barcelona.

Diabetes mellitus is among the diseases with great impact on health and society, not only for its high prevalence but also for its chronic complications and high mortality. The most precise method to investigate the prevalence of diabetes is by oral glucose tolerance testing. In Spain, the prevalence of diabetes in the 30-65 year-old population is estimated to be 6.5% among 30-to-65- year old, and 10.3% among the 30-to-89 year-old population. The ratio of known to unknown diabetes ranges from 1:3 to 2:3. The incidence of diabetes mellitus type 2 in Spain is 8/1000 persons per year, and the incidence of type 1 is 11 to 12 cases per 100,000 persons per year. The prevalence of chronic complications varies according to type of diabetes, time since onset and degree of metabolic control: neuropathy 25%, retinopathy 32% and nephropathy 23%. Diabetes is one of the most important causes of death in Spain, occupying third place for women and seventh for men.

Key words: *Diabetes mellitus. Incidence. Prevalence. Spain.*

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Epidemiología de la diabetes y sus complicaciones no coronarias

La diabetes mellitus (DM) es una de las enfermedades con mayor impacto sociosanitario, no sólo por su alta prevalencia, sino también por las complicaciones crónicas que produce y por su elevada tasa de mortalidad. La forma más exacta de estimar la prevalencia de la DM es la práctica de un test de tolerancia oral a la glucosa. En España, la prevalencia de la DM se estima en un 6,2% para los grupos de edad 30-65 años, y del 10% para 30-89 años. La proporción de DM conocida frente a la ignorada oscila entre 1:3 y 2:3 del total. Los factores de riesgo de las DM más importantes son la edad, la obesidad y la historia familiar de DM. La incidencia de la DM tipo 2 se estima en 8/1.000 habitantes año, y la de DM tipo 1 en 11-12 casos por 100.000 habitantes y año. La prevalencia de las distintas complicaciones crónicas varía en función del tipo de DM, tiempo de evolución y grado de control metabólico, estimándose globalmente en la siguiente: neuropatía, un 25%; retinopatía, un 32%, y nefropatía, un 23%. La DM es una de las principales causas de mortalidad en España, ocupando el tercer lugar en mujeres y el séptimo en varones.

Palabras clave: *Diabetes mellitus. Incidencia. Prevalencia. España.*

INTRODUCTION

Diabetes mellitus (DM) is one of the most prevalent diseases and has major societal health consequences, not just because of its high prevalence rate, but also because it causes chronic complications and is a risk factor for cardiovascular disease. When data on certain diseases are cited, they are often given in the context of U.S. or other Anglo-Saxon countries´ values because of the lack of data in this country (Spain); or in some instances because the Anglo-Saxon data are considered more trustworthy than Spanish data. It is evident that if we want to know the impact of an illness in our country, we would have epidemiological data available on our population.

Over the last few years, epidemiological studies have been performed in Spain that have provided solid data on the most relevant aspects of the epidemiology of diabetes in this country.

Correspondence: Dr. Alberto Goday.
Servicio de Endocrinología. Hospital del Mar.
P.º Marítimo, 25-29. 08003 Barcelona. Spain.

METHODS OF ESTIMATING THE PREVELANCE OF DIABETES MELLITUS

The prevalence of diabetes can by estimated by a number of methods: medical records, prescription drug use, random interviews of sample populations, and clinical tests (fasting or random) or by use of glucose tolerance testing (OGTT). The results of the

OGTT vary according to the criteria applied,[2,3] and different methods provide different information. A survey of the population, therefore, provides information on DM that had been diagnosed; a survey of physicians provides information on DM that is diagnosed and controlled; a sample of clinical histories provides information on DM that is diagnosed and documented in the population receiving treatment and the drugs used; information on the use of drugs provides information on DM diagnosed and pharmacologically treated; random glucose testing provided information on diabetes that is diagnosed and overlooked; and finally, the OGTT identifies DM that is known and untreated, as well as identifying those at risk for DM.

For years the only known data on the prevalence of DM in Spain were from self-declared cases in the population surveyed or those reported by physicians[4,5] based on estimates of diabetes treated with drugs using the defined daily dose method[6] (consisting of the mean dose established by previous standardized studies on an international scale) or the prescribed daily dose method (based on calculating the mean dose used in the area in question by a sample of prescribing physicians).[7,8] All these studies are undoubtedly of interest, particularly due to the lack of OGTT studies in the general population. Nevertheless, the prevalence of DM is under-reported because studies do not include cases treated by diet alone, disease that is untreated, or disease that it not recorded. We documented, therefore, studies that used OGTT to document the prevalence of diabetes in the general population.

PREVALENCE OF KNOWN AND UNTREATED TYPE 2 DIABETES IN SPAIN

Table 1 is a summary of the data published in Spain.[9-17] Recently, excellent studies on the overall prevalence of diabetes in our country have been performed that offer data from the general public on known and untreated DM, as well as altered glucose tolerance (AGT). In the province of León (population 530 983) there is a cross-sectional study on the adult population (older than 18 years of age) performed by a random multiple sample of 572 individuals who were given a questionnaire that dealt with hypoglycemic medication, baseline capillary glycemia, and OGTT.[9] The criteria used for evaluation were in accordance with those proposed by the World Health Organization (WHO) in 1985. The overall prevalence of diabetes was 5.6% (95% confidence interval [CI], 3.7% to 7.5%), diagnosed diabetes was 3.9% (95% CI, 2.3% to 5.5%), and undiagnosed diabetes, 1.7% (95% CI, 0.7% to 2.9%), with a ratio of known to unknown diabetes of 2.2:1, respectively. Risk factors for diabetes were age, family history of diabetes, and obesity.[9]

A cross-sectional study was performed in Lejona (Vizcaya) between 1984 and 1985 to establish the prevalence of type 2 diabetes mellitus (DM2) in a sample of 862 inhabitants over the age of 30 years randomly selected from a population of 11 515 inhabitants.[10] The prevalence of DM was 6.4%; 3.6% was undiagnosed DM and 2.8%, diagnosed. The prevalence of AGT, also known as glucose intolerance or hydrocarbon intolerance, was 10.4%. The most significant risk factors associated with DM2 prevalence were age, body mass index (BMI), and systolic arterial pressure (SAP).[11,12]

The prevalence of DM2 in Cataluña[13] was established by double sampling the population for age and sex groups representative of the general population of Cataluña. The sample consisted of 3839 individuals aged 30 to 89 years. An OGTT was administered to detect diagnosed, undiagnosed, and AGT diabetes, using the 1985 WHO criteria. The total prevalence of diabetes for the group aged 30 to 89 years was 10.3% (95% CI, 9.1% to 11.6%), with a diagnosed rate of 6.4%, an undiagnosed rate if 3.9%, and an AGT rate of 11.9% for males, and an diagnosed rate of 6.9%, undiagnosed rate of 3.4%, and AGT rate of 11.9% for women. The adjusted prevalence for the group 30 to 64 years of age was 6.1% (7.1% in men and 5.2% in women). Risk factors associated with DM were age, obesity, arterial hypertension, and family history of

TABLE 1. **Prevalence of DM2 and glucose intolerance in Spain**

Author, year	Area	Age, years	Sample	Prevalence DM2	Prevalence AGT	Diagnostic criteria
Franch et al,[9] 1992	León	>18	572	5.6%	10.3%	1985
Bayo et al,[10] 1993	Lejona (Vizcaya)	>30	862	6.4%	10.4%	1985
Vila et a,l[18] 1994	Cerdaña (Cataluña)	>6	692	5.5%	No	1985
Muñiz et al,[24] 1995	Galicia	40-69	1275	7.5%	No	1985
Tamayo et al,[14] 1997	Aragón	10-74	995	6.1%	7.2%	1985
Castell et al,[13] 1999	Cataluña	30-89	3839	10.3%	11.9%	1985
Botas et al,[17] 2001	Asturias	30-75	1034	9.9%	13.2%	1985
De Pablos et al,[16] 2001	Guía (Canary Islands)	>30	691	18.7%	17.1%	1985
				15.9%		1997

diabetes. With regard to age, prevalence was lowest in the group aged 30 to 49 years, with a rate of 2.5% (95% CI, 1.4% to 3.6%), and highest in the group aged 70 to 89 years, with a rate of 24% (95% CI, 19.7% to 28.3%). It is important to note that when a prevalence rate is given, it is fundamental to specify the age group in question.

The Guía study was performed in Nuestra Señora de Guía, which is located in the northwestern part of Gran Canaria island.[16] The particulars are that the majority of the population are natives of the Canary Islands, defined as 3 of 4 grandparents born in the Canary Islands; there is very little foreign population. The town has 12 383 inhabitants. In addition to the municipal sample, a stratified random sample was taken by sex and increments of 5-years in age groups beginning with 30 and grouping those 85 years and over into a single group. The number of people to be sampled at each 5-year level was calculated, with the population considered finite, estimating a 10% prevalence and a margin of error of less than 6% with a 95% CI, using the SAMPLE program. Six hundred and ninety-one inhabitants participated in the study, which represented a median response rate of 76.4%. The response rate was similar in all age and sex groups. DM prevalence was 15.9% (according to 1997 ADA criteria)[3] and 18.7% (according to 1985 WHO criteria)[2]; baseline glucose intolerance prevalence was 8.8% and AGT was 17.1%. DM prevalence adjusted per Segi world population was 12.4% (1985 WHO criteria). This represents a higher prevalence than in the rest of Europe.[16]

The most recent DM prevalence study was performed in Asturias.[17] With the goal of determining the prevalence of DM2 and AGT in the adult population of Asturias, a cross-sectional population study was designed with 1034 randomly selected individuals (54.1% women) of 30 to 75 years of age. A questionnaire was filled out, a physical examination performed, and an oral glucose overload test was performed with baseline blood draw at 2 hours. The diagnostic criteria established by WHO in 1985 were used. The overall prevalence of DM2 was 9.9% (95% CI, 8.2% to 11.7%); known diabetes 4% (95% CI, 2.8% to 5.1%); untreated DM 5.9% (95% CI, 4.5% to 7.4%), with a ratio of known to unknown diabetes of 1.5:1. The prevalence of AGT was 13.3% (95% CI, 11.3% to 15.2%). DM2 prevalence for the Segi population (30 and 64 years of age) was 8.2% in men and 5.2% in women. Dependent factors associated with DM were age, arterial hypertension, family history of diabetes, obesity, and hypertriglyceridemia. According to these results, the prevalence of DM2 in the adult population of Asturias (9.9%) is moderately elevated and similar to that observed previously in Spain[9-15] and other white world populations. In population-based studies performed with OGTT on total DM2 prevalence, the rate of known DM and DM unknown prior to the study can be calculated. In the past, the ratio of known to unknown DM was thought to be 1:1. In the Aragón,[14] Lejona,[10] León,[9] Cataluña,[13] and Asturias[17] studies, known DM prevalence rates were 3.1:3.0; 2.8:3.6; 3.9:1.7; 6.7:3.6 and 4:5.9, respectively. In any case, a large number of people who present with DM in Spain are unaware that they have the disease, so that strategies for early diagnosis in high-risk populations.

There are other studies on DM2 prevalence in smaller sample population groups with or without the use of AGTT that, although the results are based on local data, they are nevertheless interesting.[18-24]

WORLDWIDE PREVALENCE OF TYPE 2 DIABETES

The prevalence of DM worldwide varies widely (Table 2).[25-27] In many parts of the world, DM2 occurs in epidemic proportions. The groups know to have a higher prevalence rate are the Pima Indians living on a reservation in Arizona, the population of Nauru, Oceania, where the illness affects more than 20% of its inhabitants (rates adjusted to the world population).[25] Nevertheless, other populations also have elevated rates of the illness. In general, the populations most affected are those where traditional lifestyles have given way to Western ones, or those that have been rapidly industrialized in a relatively short period of time.[26,27] This is especially evident in certain countries of Southeast Asia and Oceania, and on Native American reservations in North America. Nevertheless, DM2 is considered one of the epidemics of the 21st century.

There are many possible reasons for the variability found in DM prevalence, including: longevity, family history, race, urbanization, migration, obesity, diet, physical activity, and fetal and neonatal nutrition.[28] DM2 incidence reaches its highest rate in groups of individuals of advanced age. For this reason, in populations with shorter lifespans, the prevalence may appear to be deceptively low. There is a racial predisposition to DM2, with certain ethic groups such as Melanesians being somewhat protected; these differences are apparent when different races in the same country are compared.[29] There is also a genetic component involved for all the racial groups. Consequently, having an immediate family member with DM2 diabetes confers up to a 40% risk, and in identical twins the risk rate for DM2 is nearly 100%, much greater than for DM1. The majority of studies show that urbanization doubles the risk of developing DM2.[30] Obesity is probably the most often studied risk factor since the pioneering study of West et al,[31] although it is proposed as a precipitating factor rather than a fundamental cause for diabetes.

TABLE 2. **Prevalence of DM2: different world populations**

Population	Age group, years	Adjusted Prevalence by age, %
Solomon Islands (Melanesia)	20+	0.7
Papua New Guinea (Melanesia)	20+	0.7
Tanzania (black population)	15+	0.9
Nigeria (black race) (Rotimi et al, 1999)	25-75	1
Cameroon (black race) (Mbanya et al, 1997)	24-74	1.1
United Kingdom (Poole area) (Gatling et al, 1998)	15+	1.44
Indonesia	15+	1.7
Iceland (Vilbergsson et al, 1997)	30-79	2.5
Australia (white population)	25+	3.3
Singapore (Chinese population)	18+	4.0
India (native Indian) (Ramachandran et al, 1999)	20+	5.9
USA (white population)	20-74	6.1
Spain (Cataluña) (Castell et al, 1999)	30+	6.1
Tanzania (Muslim population)	15+	7.1
Europe (DECODE Study Group, 1999)	30+	7.2
Singapore (Malaysian population)	18+	7.6
Singapore (Indian population)	18+	8.9
South Africa (Mamre city) (Levitt et al, 1999)	15+	10.8
Mauritius (Chinese population)	25+	11.9
Jamaica (Rotimi et al, 1999)	25-74	12
Mauritius (Indian population)	25+	12.4
USA (Mexican population)	20-74	12.6
USA (black population) (Rotimi et al, 1999)	25-74	13
India (Trivandrum city) (Raman et al, 1999)	30-64	13.7
Kuwait (Abdella et al, 1998)	20+	14.8b
Germany (Kohler et al, 1999)	40-70	15.1b
Australia (indigenous)	20+	15.6
Taiwan (Penghu Islets) (Chen et al, 1999a)	40+	16.8
Nauru	20+	24.3
Canada (Sandy Lake natives) (Harris et al, 1997)	18+	26.1
USA (Pima Indians)	20+	34.1

[a]Using ADA (American Diabetes Association) (1997), WHO (World Health Organization) (1985), or NDDG (National Diabetes Data Group) (1979) diagnostic criteria. [b]Gross rates. The prevalence rates not expressly referenced been extracted from Bennet et al, 1992, and Alberti and Taylor, 1989.

INCIDENCE OF DIABETES TYPE 2

Given than DM2 is a disease with a silent course, without a sudden beginning or an exact date of onset, it is difficult to design studies regarding incidence rate for this disease. Studies are needed to that asymptomatic diabetes can be detected by using specific tests such as glycemia, and OGTT, or both, repeated annually or after a pre-determined amount of time in the general population. The sample population involved in the Lejona (Vizcaya)[10] DM prevalence study included a second OGTT test 10 years after the study initiation, enabling a determination of the accumulated 10-year incidence of DM: at 8 cases per 1000 inhabitants in 10 years.[12] Overall, the annual incidence of DM2 in European studies varied between 1.2 and 4.1 cases per 1000 persons.[32-45] This study, given its methodology and results, deserves to be examined in depth. The incidence rate for the Lejona study, although it coincides with these studies by being less than 1% annually, could be somewhat elevated in relation to other countries as it gives an overall estimate of 8.2 cases per 1000 people per year, particularly in the group of male subjects. In subjects with AGT, the estimated 2% annual rate was actually close to 2.9% and 1.5% annually in the British studies of Whitehall[32] and Bedford,[45] respectively. Although some followup studies revealed an annual incidence rate of more than 10%,[46] the majority of the larger prospective studies indicate that, in general, the annual incidence rate for subjects with AGT is between 2% and 5%.[47] The annual AGT incidence rate adjusted for age in the cohort of subjects with normal glucose tolerance (NGT) was 2%, with a greater incidence noted in men as compared to women. Nevertheless, 49.2% of the cohort of subjects with AGT at the beginning of the study reverted to NGT at the end of 10 years, a reversal that is similar to that estimated by Warram et al of 37% at 8-years followup.[48] As expected, age was also confirmed as a significant factor by the Lejona study, showing a greater increase in risk after 60 years of age. Therefore, as life expectancy continues to increase, the incidence of DM2 will also increase. The role of sex in the progression of DM2 is still controversial, with evidence as much for[44] as against[49] its possible implication as a risk factor. The Lejona study demonstrated a risk 3 times higher in men than in women, somewhat higher than the risk estimated for men by Haffner et al (odds ratio [OR]=1.56; 95% CI, 0.91% to 2.68%), very close to statistical significance after adjustment for several variables, including the ethnic origin of the participants.[50] Baseline glycemia was an important predictor in subjects with NGT, especially when glycemia was greater than 82 mg/dL, which quadrupled the risk factor, coinciding with the results of the Finnmark study for both men and women.[46] When the cohort of subjects with AGT is included in the analysis, baseline diagnostics are highly predictive of the subsequent progression to DM, thus eliminating the need for obtaining baseline glycemia values. Therefore, in subjects with AGT the risk is 4 times higher, which is an estimate somewhat higher than that proposed by Haffner et al (OR=3.0; 95% CI, 1.85% to 4.88%), and lower than that obtained in the Paris study (OR=9.6; 95% CI, 5.5% to 16.8%).[51] The diagnosis of AGT is generally recognized as a risk factor in the de-

velopment of DM. Nevertheless, it is not clear up to what point the diagnosis of AGT should be considered a risk factor in triggering DM, or whether it is detectable in the etiopathogenesis of DM. In any case, the elevated risk of progression to DM in subjects diagnosed with AGT could be used for instituting intervention and prevention measures. As far as the presence of family antecedents is concerned, the study demonstrated that, although the statistical significance was probably limited by sample size, the presence of family history constituted a risk factor. This result corroborates the importance of the hereditary component in the etiopathogenesis of this process is pointed out in previous studies.[52] Obesity is 1 of the factors most consistently associated with the risk of DM in prevalence studies,[53] and also in incidence studies.[54] Although analysis of the mean percentage of BMI indicates a certain statistical association between a greater BMI and DM progression, in the Lejona study baseline BMI did not appear to be an independent risk factor in progression to DM. It also did not appear significant in a combined baseline analysis;[49] in fact, the estimated baseline BMI effect was practically null (OR=1.03) for increments of 1 kg/m^2. In conclusion, the results of the Lejona[10-12] study do not indicate that this population should be considered at greater risk than others in the same environment. The risk factors for DM appear to be similar to those in other populations, including populations at greater risk than those studied, which underlines the fact that, in addition to a lesser or greater genetic predisposition, the etiopathogenic mechanism is generally a common one.

INCIDENCE OF DIABETES TYPE 1

A few years ago there were no data for the incidence of diabetes type 1 (DM1) in Spain or most other countries, with the exception of several Scandinavian, British, and North American studies. Several consensus meetings have been held over the past decade to begin epidemiological investigations with standardized and validated methodology in order to obtain results that can be compared in the international arena.[55]

The first data published following the aforementioned methodology was that obtained on DM1 incidence in Cataluña[56] and in the autonomous community of Madrid. The Catalan DM1 registry is a prospective study on the population of the entire autonomous community during the period from 1987 to 1990, including all new cases of DM1 in individuals aged 0 to 14 years and aged 15 to 29 years (risk population 0 to 29 years of age of 2 690 394 inhabitants). The thoroughness of the study, calculated by the capture-recapture method, was 90.1%. The incidence rate observed by Goday et al[56] for the group of patients 0 to 14 years of age was 11.3 per 100 000 inhabitants per year (95% CI, 10.3% to 12.4%), and for the group of patients age 15 to 29 years 9.9 per 100 000 inhabitants per year (95% CI, 9.8% to 10.8%). The incidence rate was lowest between in the group between 0 and 5 years of age, and highest between the group 13 and 14 years of age. In the group of patients 0 to 14 years of age there was no differences in the incidence rate between the 2 sexes, while between 15 and 30 years of age a clear predominance in males was observed. As in other countries, the incidence rate of DM1 followed a seasonal pattern, with peaks in the cold months of the year. The study of the Autonomous Community of Madrid[57] included all patients younger than 15 years of age in an at-risk population (age younger than 15 years age) of 1 105 243 inhabitants, retrospectively, from 1985 to 1988. The veracity or depth of the study according to the capture-recapture method was 90%, and incidence was estimated at 11.3 of 100 000 inhabitants per year (95% CI, 10.3% to 12.4%).

Recently, other studies carried out in Málaga,[58,59] Navarra,[60] Extremadura,[61] and the Canary Islands,[62] including groups 0 to 14 years of age and using the capture-recapture method, have obtained results that are very similar to those previously mentioned[63,64] (Table 3). Comparison of these studies permits an estimate of the incidence rate of DM1 for Spain in its entirety, by province, and by autonomous community.[63] From these studies, four points stand out. First, this is the first adequately validated data on DM1 obtained for the Mediterranean area. Secondly, there is a great similarity of incidence rates found among the various studies with regard to the group of patients 0 to 14 years of age, and the extraordinary worldwide homogeneity in the incidence of the disease. In the third place, the high incidence observed in Spain, much greater than that estimated in other European countries, destroys the hypothesis of a North-South gradient for diabetes incidence of diabetes that was postulated during the last decade. Finally, although the existence of a clear North-South gradient was not demonstrated, the cause of the great heterogeneity in the incidence of diabetes, with a rate 10 to 40 times different (Finland as compared to France or Japan), constitutes 1 of the great challenges of current investigation.

There is evidence that the incidence of DM1 has increased.[65] Given that DM1 is 1 of the reasons for exemption from military service, some authors have used this information to investigate possible increases in the incidence of DM1. In reality, exemption from military service due to diabetes does not exactly identify the incidence (new cases) of DM1, but the accumulated incidence at the age at which the individual presents for military service (17 to 20 years of age), or a study of cohorts by year of birth, obviously only in males. The study strategy has certain limitations and biases, but is undoubtedly of interest in the absence of other more exact sources. This methodology is used in Spain country to evaluate male cohorts born between

TABLE 3. **DM1 incidence in Spain**

Authors, year	Age group	Risk population	Study period	Incidence (CI)/100 000 inhabitants/year
Serrano-Ríos et al,[57] 1990	0-14	1 105 243 Madrid	1985-1988	11.3 (10.3-12.4)
Goday et al,[56] 1992	0-14	1 295 763 Cataluña	1987-1990	11.5 (10.6-12.5)
Goday et al,[56] 1992	15-29	1 394 631 Cataluña	1987-1990	9.9 (9.8-10.8)
Calle-Pascual et al,[7] 1992	0-14	33 679 Ávila	1987-1990	14.9 (9.6-23.7)
López Siguero et al,[59] 1992	0-14	Málaga	1982-1988	11.4 (9.7-13.1)
Chueca et al,[60] 1997	0-14	Navarra	1975-1991	9.5 (8.2-11.1)
Morales-Pérez et al,[61] 2000	0-29	Badajoz	1992-1996	12.8 (11.0-14.7)
Carrillo,[62] 2000	0-29	Canary Islands	1995-1996	15.0 (13.0-17.0)

1964 and 1974 in the entire state, and it demonstrates a progressive and practically linear increase in the accumulated incidence of diabetes at 17 years of age, that was greater than 0.918 in those born in 1964 and 1.825 in those born in 1974.[66] In 10 years the accumulated incidence rate has practically doubled, with an absolute rate of greater than 315 cases in the 1964 cohort to 671 cases in the 1974 cohort. The authors did not find inter-territorial geographic differences during the period analyzed.[66]

On the other hand, some incidence studies have grouped one collection phase of retrospective cases with another prospective study, studying them together over extensive periods of time; these have revealed a progressive increase in the incidence of DM1. The most recent data from the DM1 register in Málaga shows an clear increase in the incidence of the illness, revealing that although in initial published results the rate during the period from 1982 to 1988 was fixed at 11 cases per 100 000 inhabitants per year,[58] studies of more recent periods of time have fixed the rate at a much higher number: close to 18 cases per 100 000 inhabitants per year.[59] A similar situation was observed in Navarra.[60] On the other hand, the Catalan DM1 register, developed prospectively since 1987, based on a population of 2 million and individuals less than 30 years of age, a relatively constant incidence rate has been demonstrated, without an index indicative of epidemic outbreaks or an increase in incidence or tendency toward attenuation of the numerical impact of the illness.[56] They also have not detected important changes in DM1 incidence in Badajoz during the period 1992 to 1996.[61]

When considering data on the epidemiology of DM1 it is worth noting that, although this is a disease that occurs relatively frequently, the incidence rates are low. This means that in order to investigate its occurrence with some precision, epidemic outbreaks, secular changes in incidence, or geographical differences, it is necessary to analyze wide population bases during prolonged periods of time, which is particularly difficult with a disease is not required to be reported. Cases are detected, therefore, by physicians dedicated to the study of diabetes. Maintaining an active diabetes register may be difficult, but it is fundamental, and we must obtain long-term collaboration and cooperation of physicians and patients. In addition, prospective studies are intrinsically superior to retrospective studies. For all these reasons, prospective epidemiological studies of DM1 that include extensive population bases and cover prolonged periods of time are of great interest, as they allow the detection of data that is not evident in smaller studies. An example is the collaborative European study in the Biomed program called EURODIAB TIGER, which for 10 years has analyzed the incidence of DM1 in an intensive sample of the European population.[67] In a recent publication, studies have demonstrated that the incidence of DM1 in Europe is increasing, although unequally, by age and by country.[68] The most obvious change has been observed in the population group of individuals of less than 5 years of age, an age group which had been characterized up until now by a lesser incidence of the disease, in comparison with groups of age 5 to 9 years, 10 to 14 years of age, and 15 to 29 years of age. In the lowest age group (0 to 4 years of age), the incidence rate increased by 6.3% from 1989 to 1994, while in the group of 5 to 9 years of age it was 3.1% and in the group of 10 to 14 years of age 2.4%. With regard to countries, the most spectacular change was observed in Eastern and Central Europe, with initially low rates in countries which have undergone significant socioeconomic changes. On the contrary, one of the participating centers with the most constant incidence rates during the period of 6 years analyzed (from 1989 to 1994) was Spain (Cataluña), with an annual relative risk of exactly 1.00 (95% CI, 0.96% to 1.04%), while in most countries this rate was greater.

PREVALENCE OF DIABETES MELLITUS TYPE 1

The results of the 1987 National Health Questionnaire study performed by the Ministry of Health and Consumption showed a prevalence of declared diabetes in persons aged 1 to 15 years of 0.3% (0.5% in persons aged 1 to 4 years; 0.2% in persons aged 5 to 14 years; 0.3% in males, and 0.2% in females). Although the type of diabetes was not specified, the age range restricts the cases almost totally to DM1.[69]

EPIDEMIOLOGY OF THE CHRONIC COMPLICATIONS OF DIABETES MELLITUS

There are very few epidemiological studies in Spain on the chronic complications of DM, and there are basically 2 fundamental problems with this type of study. First, it is difficult to establish the exact parameters, given the different sensitivities, specifics, and complexity of the diagnostic methods involved. In the second place, the majority of studies are not performed on a well-defined geographical population base, a diabetic register, or for more than one cohort, but rather as the function of patients who have received treatment in the center that is performing the study, thus introducing confusing biases and variables that are difficult to correct and to control.

Diabetic retinopathy

Diabetic retinopathy affects 15% to 50% of patients with DM2, with approximately 10% presenting with proliferative retinopathy. Twenty to 30 percent of recorded blindness is a result of diabetic retinopathy.[70] Among the affiliates of the Spanish National Organization of Blind People (SNOBP), DM is the third most common pathological cause of visual deficiency. DM presents a relative risk of vision loss 20 times greater than in the non-diabetic population. Cataracts occur 1.6 times more frequently in the diabetic population. Open-angle glaucoma occurs 1.4 times more frequently in diabetics.[71] Twenty years after the diagnosis of diabetes, nearly 100% of patients with DM1 and 60% of patients with DM2 develop diabetic retinopathy.[72]

Diabetic nephropathy

Nephropathy is present in between 3% and 35% of patients with DM2. The relative risk of suffering renal insufficiency is 25 times greater in subjects with DM. From 30% to 50% of individuals who have developed the disease over 10 to 20 years, have some degree of renal involvement. At present, DM is the primary cause for inclusion in hemodialysis programs in Spain.[73] Studies have been performed on prevalence in the various phases of diabetic nephropathy, as well as the autonomic environment of Cataluña,[74,75] the Canary Islands,[76] and Extremadura,[77] and in Spain as a whole.[78,79] In the samples studied, the prevalence of microalbuminuria was 13% for DM1 and 23% for DM2; for macroproteinuria it was 4.6% to 5%, and for renal insufficiency it was 4.8% to 8.4%.[74-79]

Diabetic neuropathy

Diabetic retinopathy is the most common complication with DM2, and it is estimated that approximately 40% of diabetics have some type of neuropathic change at the time of diagnosis. Prevalence varies from one study to another, depending on the diagnostic criteria used and the sensitivity of the tests utilized. Prevalence rates increase with the amount of time diabetes has been present, and the age of the patient.[80] The relative risk of neuropathy for people with diabetes is 7 times that for the general population. Diabetic polyneuropathy will affect more than 40% of the patient population with diabetes for more than 10 years.[80]

A collaborative study by Figuerola et al provided an overall approximation of the prevalence of chronic complications of diabetes in Spain.[81] In a sample of 1 430 diabetic patients, from 4 different levels of health care (ambulatory endocrinology clinics, regional hospitals, university hospitals, and private diabetic clinics) they observed, in patients with insulin-dependent diabetes, a 32% prevalence of retinopathy (21% non-proliferative, 9% proliferative, and 2% amaurosis), 14% prevalence of neuropathy, 14% nephropathy, and 2% diabetic foot symptoms. In the group of non-insulin-dependent patients, the prevalence of retinopathy was 42% (31% non-proliferative, 9% proliferative, 2% amaurosis), 30% neuropathy, 18% nephropathy, and 14% with diabetic foot symptoms. As the authors noted, this study contains some biases: family and internal medicine physicians were excluded, the centers that participated in the study were not selected randomly, and, finally, the criteria for defining the chronic complications were primarily clinical, and not strictly standardized for all the centers included in the study. Even so, we believe that the size of the sample, the overall spectrum of data obtained for each patient, and the lamentable lack of Spanish population-based studies from diabetes registers, make the results of this study valuable. Another study performed by the health service in Vizcaya had similar results.[82]

In any case, the increased prevalence of chronic complications of DM means that this disease had a strong impact on general health[83,84] and hospitalization costs.[85]

We will not discuss the data concerning the epide-

miology of macroangiopathic complications of DM as these will be the subject of a future manuscript.

MORTALITY RATES FOR DIABETES

Hyperglycemia alone is associated with an increased mortality rate, which has been described as being in direct proportion to the higher baseline glycemia levels.[86] Also, age, hypertension, and the presence of proteinuria are independently associated with an increase in death by any cause in DM2.[87] In the United States, it is estimated that DM2 represents 15% to 20% of all deaths in the population older than 25 years of age. The mortality rate is 2 to 3 times higher in patients diagnosed with the disease after 40 years of age.[88,89] In the majority of developed countries, diabetes is the 4th to the 8th most common cause of death. In European countries, the mortality rate varies from 8 to 33 people per 100 000 inhabitants, with the current rate in Spain being approximately 23 per 100 000.[90] In most studies, the mortality rates are greater for women than men (in Spain, 29 vs 16 per 100 000).

The estimated mortality rate in Spain was established by the General Subdivision of Preventive Medicine of the Ministry of Health and Social Security for the period 1951 to 1974, and published in their *Weekly Epidemiological Bulletin*.[91] This data was obtained from death certificates. The trustworthiness of this method has been questions as, in general, a large percentage of death certificates do not list diabetes as the cause of death. In any case, the information available is of interest as certain Spanish studies do confirm the validity of the data obtained from death certificates. The mortality rate (per 100 000 inhabitants increases for both sexes during the course of the observation period, so that it was 6.76 in the period from 1951 to 1956 (per 100 000 inhabitant) and increased to 16.09 from 1969 to 1974. In 1978, the mortality rate was estimated to be 18.4 per 100 000 inhabitants. This increase was observed to be greater in the female population, and to increase for both sexes after the age of 65. Regidor et al reported the principal causes of death in Spain between 1975 and 1988,[92] and the mortality rate for diabetes was 14.8 to 13.8 for men and 19.2 to 17.2 in women (per 100 000 inhabitant, adjusted by age as a function of standard population in 1970). Diabetes is the third most common cause of death for women in Spain (after cardiovascular disease and ischemic heart disease) and seventh most common cause of death in men.[92] These data clearly need to be corrected as a function of the role diabetes plays as a predisposing factor in the development of cardiovascular or heart disease. When analyzed by province, the mortality rates show a geographic aggregation in the south, southwest, and insular provinces of Spain.[93]

RISK FACTORS FOR DIABETES

Risk factors for DM2 include advanced age,[94] obesity,[9-14] family history of diabetes,[95,96] ethnicity,[97-99] socioeconomic level,[100,101] and Western lifestyle (principally with reference to obesity, diet, and physical inactivity). Each of these is probably a reflection of underlying causative factors. In the natural history of DM2 a prior state of glucose intolerance and altered baseline glycemia is described,[102-105] states that confirm that the risk of developing DM2 increases as glycemia levels increase. Gestational diabetes can also be a marker for a pre-diabetic state.

Many studies support the role of physiological factors and lifestyle in the etiology of DM2. These factors include, among others, in first place, obesity,[9-14] which is accompanied by insulin resistance. Prolonged obesity[106,107] and central obesity[108] have also been associated with a greater incidence of DM2. More divisive is the question of whether diet alone can precipitate diabetes independently of obesity. Recent studies indicate that important changes in glucose tolerance occur with the change from a traditional to a Western diet, and vice versa.[109-111] Other studies describe the protective effects of a diet rich in fiber, whole cereals, magnesium,[112] although in 1 study greater protection was observed with greater serum levels of magnesium, but not with increased ingestion,[113] in fruits and vegetables,[114] and including, though it may seem paradoxical, the protective effect of the moderate consumption of alcohol,[115,116] or a greater risk with low plasma concentrations of vitamin E.

Physical in activity also plays an important role in the risk of developing glucose intolerance and DM2.[118-124]

Other studies have described an increased incidence of DM2 in smokers,[116,125] in certain professions[126] and work conditions,[127] or in the presence of depressive symptoms[128] or hypertension.[129] Recent studies in Europe and the United States have described low birth rate[130] and other changes in fetal growth in full-term neonates[131] may be associated with a greater prevalence of glucose intolerance and consequent DM2. The mechanisms are unknown, but it appears that changes there are changes in the neuroendocrine development of the fetus. These hormonal changes could contribute to a predisposition for diabetes and the metabolic syndrome.[132] Along the same lines, the treatment of children and adolescents with growth hormone has been described as accelerating the appearance of DM2 in individuals predisposed to the illness.[133]

PREVENTION OF DIABETES

Although many markers and risk factors for the development of DM2 have been identified, little is known regarding what interventions could prevent or

reverse the pathology in cases that have already been diagnosed.[134] Some studies have been informed on intervention and others are currently trying to prove the hypothesis that DM2 (and its cardiovascular risks) can be prevented with drugs[135-137] or lifestyle changes. Below we detail the most interesting studies in this last group.

The incidence of DM2 is growing worldwide, probably due to changes in lifestyle, related to the adoption of more western habits such as being sedentary, obesity, or an unbalanced diet. On the other hand, today we know that obese individuals and glucose intolerance have an increased risk of developing DM2. Based on this fact, Toumilehto et al[138] proposed that it is possible to avoid the development of DM2 in these individuals by making lifestyle changes. With the aim of investigating whether DM2 could be prevented with lifestyle changes in people at a high risk for developing the disease, they designed a randomized study in Finland that assigned 522 obese middle-aged people (172 men and 350 women; average age, 55 years; BMI, 31) with glucose intolerance to either a group receiving therapeutic intervention or a control group. The intervention consisted of individual counseling for weight reduction, a decrease in the total ingestion of saturated fats, an increase in the ingestion of fiber, and an increase in physical activity. An oral glucose tolerance test was performed annually. The diagnosis of DM2 was confirmed by a second test. Mean follow-up was 3.2 years. Weight loss during the first year was 4.2+5.1 kg in the intervention group vs 0.8+3.7 kg in the control group. The net weight loss at the end of the second year was 3.5+5.5 kg in the intervention group vs 0.8+4.4 kg in the control group (significant differences with $P<.001$ in both comparisons of the 2 groups). The accumulated incidence of diabetes at 4 years was 11% in the intervention group (95% CI, 6% to 15%) vs 23% in the control group (95% CI, 17% to 29%). During the study, the risk of developing DM2 was reduced by 58% ($P<.001$) in the intervention group. The reduction in the incidence of diabetes was directly related to lifestyle changes. The results of this excellent study were spectacular, as by losing weight, changing diet (decrease in the total consumption of fat, the percentage of saturated fats, and the amount of sugar, and an increase in the consumption of vegetables) and an increase in exercise decreased the occurrence of DM2 by more than half.

Of note, these optimal results also achieved a moderate weight loss of an average of 4.2 kg, or a 4.7% weight reduction. In a parallel manner, the intervention group also showed a significant reduction in both fasting glycemia and 2 hours after an oral glucose tolerance test, in insulinemia, triglycerides, and PAS and PAD. All these reductions in values are probably related to an improvement in insulin resistance. It is difficult to achieve weight loss and changes in eating habits in daily medical practice. In fact, in the study a weight loss of more than 5% was only achieved in 43% of the intervention group (vs 13% in the control group). According to this study, to prevent 1 case of DM2 requires intervention in 22 subjects for 1 year, or 5 subjects for 5 years.[138] Therefore, in subjects with a high risk of developing DM2, medical counseling regarding a moderate weight loss (much less than what would be required to reach normal weight) prevents the development of DM2. DM2 can be prevented with lifestyle changes.

With regard to exercise, various epidemiological studies have shown a positive relationship between insulin sensitivity and physical activity, but the consistency of this association among populations with a distinct ponderal state is uncertain. One multicenter epidemiological study examined whether physical activity is related to insulin concentrations in 2 populations at high risk for diabetes but located in different geographical areas, of different ethnic groups, and different BMI.[139] The population studies were 2321 non-diabetic Pima Indians from 15 to 59 years of age and 2716 non-diabetic inhabitants of the Mauritius Islands. Insulin sensitivity was estimated by the baseline and postprandial insulin concentration in the blood and physical activity by questionnaire. The results demonstrated that in the Pima Indians, people with more physical activity had significantly lower concentration of insulin than those who were less active (179 vs 200 and 237 vs 268 pmol/L). Similar results were found in the Mauritius Islands (94 vs 122 and 127 vs 148 pmol/L). In both populations, physical activity was significantly associated with insulin concentrations, controlled by age, BMI, waist to hip index, and glycemia. In accordance with the preceding physical activity is negatively associated with insulin concentrations both in the Pima Indians, who tend to be overweight, and in the inhabitants of the Mauritius Islands, who tend to be thin. These results indicate that the benefits of physical activity on insulin sensitivity are independent of the influence of physical activity body composition. The development of DM2 is associated with obesity, fat distribution, and being sedentary. All these factors are associated with insulin resistance. Nevertheless, given that being sedentary is a factor associated with obesity and the distribution of body fat, it could simply be a reflection of this association. On the other hand, the relationship between insulin resistance, greater BMI, and greater waist to hip index is often occurs in overweight and obesity, but not as clearly in thin people. What is interesting about this study is that it investigates these associations both in a population with a tendency to obesity, the Pima Indians, with an average BMI between 28 and 35, a waist to hip index between 1.5 and 1.9, and in a population without a tendency to obesity, the inhabitants of Mauritius, with an average BMI between 24

and 25, and a waist to hip index of 0.8 to 0.9. As expected, the Pima population with its tendency toward obesity and less physical activity, had greater insulinemia (greater insulin resistance). What is interesting is that this relationship was nearly the same for the normal weight population of the Mauritius Islands. Therefore, physical activity and insulin sensitivity are consistently related in distinct populations. This correlation is maintained when the possible effect of the ponderal state, the waist to hip index, and ethnicity are controlled. Therefore, this relationship is not dependent on the hypothetical fact that people who are more physically active weigh more, but on the intrinsic effect of exercise on insulin sensitivity.[139]

Obesity and an increase in weight are independent risk factors for the development of DM2. Glucose tolerance is known to improve with a decrease in weight and to worsen with an increase in weight. Nevertheless, whether loss of weight is therapeutic raises questions on the action and secretion of insulin in the short, medium, and long term. Many studies show that the improvement in glucose tolerance due to weight reduction is attributable to a decrease in resistance to the action of insulin. A recent study of Pima Indians[140] provided information on the long-term effects of weight on the action and secretion of insulin, not only in normal subjects but also on those with AGT. The improvement in insulin sensitivity is proportionate to weight loss. Inversely, weight gain causes an equal worsening in insulin sensitivity. In an intermediate situation, if the weight loss is maintained, so is the insulin sensitivity. Weight gain can have consequences for people with AGT, in whom insulin secretion also decreases upon weight gain instead of increasing to compensate for the decrease in its peripheral action. More recently, the analysis of the results of 16 years of followup (from 1980 to 1996) in a cohort of American nurses that included 84 941 women, once again demonstrated that the most important predictor for DM2 is obesity and overweight.[141] The development of DM2 is also associated with being sedentary, diet, smoking, and the new and surprising factor of alcohol abstinence. In any case, all these factors are modifiable with lifestyle changes.

CONCLUSIONS

A review of the epidemiology of diabetes in Spain shows the social and health consequences of this disease. Obviously, information is still needed on such elemental data as the incidence and prevalence of different types of diabetes and its complications in many areas of Spain. An approximate calculation of the incidence and prevalence described and based on the most recent census reports the following data for Spain: prevalence of known diabetes: 1.1 to 1.4 million inhabitants; total prevalence of diabetes (both known and unknown): 2.1 million inhabitants; incidence of diabetes in individuals less than 15 years of age: 29 000 children; incidence of DM1 in individuals less than 15 years of age: 1104 new cases per year. Obviously, these data are not exact, given that they are based the scarce data that is available, assume homogeneous distribution for all Spain, do not include CI, seasonal changes, the progressive aging of the population, etc. In any case, they can serve as an index of the health importance of diabetes, as well as the priority of obtaining more exact epidemiological information.

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