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The Epidemiology of Type 1 Diabetes Mellitus

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1. Introduction

Type 1 diabetes mellitus (type 1 diabetes, insulin-dependent diabetes mellitus), one of the most common chronic diseases in childhood, is caused by insulin deficiency following auto-immune destruction of the pancreatic beta cells. Until the one and only therapeutic option – the life-long supplementation of insulin or its analogues – was established, affected children died within a short time. Although extensive investigations on the pathogenesis of type 1 diabetes have been performed, the underlying causes and mechanisms are still far from being completely understood. The consequence is a lack of prevention strategies or causal therapies.

Great efforts have been made to assess the incidence and prevalence of type 1 diabetes. The epidemiology of type 1 diabetes is estimated with different methods ranging from small cross-sectional studies to nationwide registries. Understanding the epidemiology of type 1 diabetes may identify risk factors, e.g. genetic predisposition or environmental factors, and may thereby elucidate the pathogenesis of type 1 diabetes. This could be one way to establish possible preventive or causal therapeutic strategies. However, the findings on the possible trigger factors of type 1 diabetes and its epidemiology are sometimes controversial or even contradictory.

In the present chapter, the incidence and prevalence of type 1 diabetes during the last decades will be described. Some fundamental facts about the estimation of type 1 diabetes epidemiology may facilitate understanding. The epidemiologic patterns of type 1 diabetes regarding geographic differences, gender and age of the patients, as well as seasonal and ethnic factors in populations are summarized. The expected changes in type 1 diabetes epidemiology and its implications on future research directions and health care are mentioned.

2. Estimating the epidemiology of type 1 diabetes mellitus

The epidemiology of type 1 diabetes can be estimated in different ways. In principle, there is the possibility of estimating epidemiologic data by self-report of the patients, longitudinal or cross-sectional studies or different-sized registries.

Data gained from self-reporting of diabetic patients have been shown to underestimate the true burden of diabetes (Forouhi, Merrick et al. 2006). Another possibility, but with similar limitations, is to assess data retrospectively (Mooney, Helms et al. 2004). Generally, longitudinal or cross-sectional studies are often locally or regionally performed. This limits the opportunity to get generalizable results because the epidemiology of type 1 diabetes is known to be heterogeneous regarding geography and ethnicity. Cross-sectional studies do not provide information on the time-dependent changes of the epidemiology. Additionally, many studies are limited to special settings, e.g. a general practice setting (Frese, Sandholzer et al. 2008), and although providing useful and necessary information, the reported data may not be representative for the epidemiology of type 1 diabetes.

Especially when estimating the incidence of type 1 diabetes, the latency of onset until diagnosis is important and influences the quality of estimated data. Also the validity of the chosen diagnosis should be critically reviewed. In a recent German investigation, 60 (10.3%) of 580 patients were reclassified at mean 2.4 years after the diagnosis of type 1 diabetes: 23 (38.3%) as type 1 diabetes; 9 (15%) as maturity onset diabetes of the young; 20 (33.3%) as "other specific diabetes forms", and 8 (13.3%) as "remission" of type 2 diabetes (Awa, Schobor et al. 2011). The validity of the chosen diagnosis may differ depending on the data source that affords a correct differential diagnosis, e.g. between type 1 diabetes and malnutrition diabetes in developing countries or type 1 diabetes, type 2 diabetes and maturity onset diabetes of the young in industrial countries, as well as a correct encoding of diagnosis. This is because usual classification systems such as the International Classification of Primary Care or International Classification of Diseases cannot be assumed to be sufficiently complete and valid (Gray, Orr et al. 2003; Wockenfuss, Frese et al. 2009; Frese, Herrmann et al. 2012).

It is conclusive that reliable and valid – and thereby comparable – data on type 1 diabetes epidemiology have to be based on a complete and detailed assessment. Disease registries can be assumed to be probably the best method to estimate and manage standardized data. However, the availability, completeness, quality and accuracy of diabetes registers are again very variable (Forouhi, Merrick et al. 2006). Type 1 diabetes registries were established on different levels: local (Howitt and Cheales 1993), regional (Galler, Stange et al. 2010), national or multinational.

Much of our knowledge of the epidemiology of type 1 diabetes in young people has been generated by large collaborative efforts based on standardized registry data: the EURODIAB study in Europe and the DIAMOND project worldwide (Dabelea, Mayer-Davis et al. 2010). In order to provide reliable information about the incidence and geographical variation of type 1 diabetes throughout Europe, EURODIAB was established as a collaborative research project (Fuller 1989; Green, Gale et al. 1992). During a 15-year period, 1989 to 2003, 20 popu-

lation-based EURODIAB registers in 17 countries registered 29,311 new cases of type 1 diabetes in children before their 15th birthday (Patterson, Dahlquist et al. 2009). The World Health Organization program, Multinational Project for Childhood Diabetes (Diabetes Mondiale or DIAMOND), has been developed to investigate and characterize global incidence and mortality of type 1 diabetes and the health care provided for type 1 diabetic patients. Both projects used similar ascertainment methodologies. However, DIAMOND ascertained some data retrospectively. This may have led to some underestimation of incidence rates. The completeness of case ascertainment varied from 35 to 100% in DIAMOND. Most European nations in DIAMOND had comparable (> 90%) rates of ascertainment to EURODIAB (Vehik and Dabelea 2010). DIAMOND reached the lowest completeness rates in Africa, Central and South America. This reflects a general problem when assessing type 1 diabetes epidemiology: data from developing countries are scarce and may not be fully representative due to low rates of completeness.

3. The incidence of type 1 diabetes mellitus

This section provides a comprehensive description of type 1 diabetes incidence, its changes over the last years, and its variability in populations and patient subgroups.

3.1. Geographic differences

Mean incidence rates of type 1 diabetes vary considerably depending on the geographic region (Galler, Stange et al. 2010). The worldwide incidence of type 1 diabetes is described to vary by at least 100- to 350-fold among different countries (Karvonen, Viik-Kajander et al. 2000). The highest incidence rates are found in Finland and Sardinia (Italy) and the lowest in South American countries, e.g. Venezuela and Brazil, and Asian countries, e.g. China or Thailand (Karvonen, Viik-Kajander et al. 2000; Borchers, Uibo et al. 2010; Panamonta, Thamjaroen et al. 2011). Apart from regions with low to intermediate incidence rates ranging between 5 and 20 per 100,000 children or adolescents per year, there are areas with incidence rates as high as 27 to 43 per 100,000 children or adolescents per year. Canada and Northern European countries, such as Finland and Sweden, have the highest incidence rates ranging between 30 and 40 per 100,000 children/adolescents per year. Incidence rates of countries in Central Europe (with the exception of Sardinia) vary from 8 to 18 per 100,000 children/adolescents per year. The incidence for type 1 diabetes in German children aged 0 to 14 years was estimated at 13 per 100,000 per year for 1987–1998 and at 15.5 per 100,000 per year for 1999–2003. The registry of the former German Democratic Republic, which was kept from 1960 until 1989, reported incidence rates between 7 and 14 per 100,000 children/adolescents per year (Galler, Stange et al. 2010). In Mediterranean countries, the incidence rates of type 1 diabetes also show wide variations, although for some of them, there are still no relevant and reliable data (Muntioni 1999). Summarizing the data on type 1 diabetes incidence, the polar-equatorial gradient does not seem to be as strong as previously assumed. The incidence of type 1 diabetes among different countries is presented in Table 1 and Table 2. When comparing the incidence of type 1 diabetes between countries, it is important to keep the size of the sample and the area of sampling in mind. This is because the incidence of type 1 diabetes may show

strong variations among different regions from many countries as United States or Italy. Also a Romanian study revealed a wide geographic variation (6.71-fold) between the highest and the lowest incidence rates in different districts of the country (Ionescu-Tirgoviste, Guja et al. 2004).

While genetic factors are thought to explain some of the geographic variability in type 1 diabetes occurrence, they cannot account for its rapidly increasing frequency. Instead, the declining proportion of newly diagnosed children with high-risk genotypes suggests that environmental pressures are now able to trigger type 1 diabetes in genotypes that previously would not have developed the disease during childhood (Borchers, Uibo et al. 2010). The importance of environmental factors towards manifestation of type 1 diabetes is also supported by migration studies: For example a recently published study revealed that being born in Sweden, a country with high type 1 diabetes incidence, increases the risk for type 1 diabetes in children with a genetic origin in low-incidence countries (Soderstrom, Aman et al. 2012).

Country	Sampling Region	Incidence	AI of Incidence
Algeria	Oran	4.7	7.9 (1.85 to 14.00)
Australia	West	14.9	6.3 (2.11 to 10.50)
Australia ^a	New South Wales	19.4	2.8 (1.9 to 3.8)
Canada	Prince Edward Island	23.5	3.2 (-0.33 to 6.38)
Canada	Montreal	9.3	1.6 (-0.67 to 3.82)
China	Shanghai	0.7	7.4 (2.3 to 12.5)
Iceland	n.s.	9.0	2.3 (-2.38 to 6.96)
Israel	Yemenite Jews	5.0	3.2 (2.51 to 3.88)
Japan	Hokkaido	1.7	5.9 (4.14 to 7.63)
Libya	n.s.	8.7	6.3 (0.69 to 11.8)
New Zealand	Auckland	10.1	6.4 (4.20 to 8.52)
New Zealand	Canterbury	12.7	2.7 (.005 to 10.50)
Peru	Lima	0.5	7.7 (-1.0 to 16.4)
Thailand ^b	Northeast Thailand	0.6	n.s.
United States ^c	Colorado	19.4	2.3 (1.6 to 3.1)
United States	Hawaii	7.8	7.8 (1.8 to 14.9)
United States	Allegheny County	14.7	1.5 (0.21 to 2.83)
United States	Colorado	12.3	-0.2 (-2.52 to 2.19)

^aTaplin, Craig et al. 2005

^bPanamonta, Thamjaroen et al. 2011

^cVehik, Hamman et al. 2007

n.s.: not specified

Table 1. The incidence (per 100,000 per year) of type 1 diabetes and its annual increase (AI; with 95% confidence interval) in different non-European countries. If not otherwise indicated, data were adopted from the review of Onkamo, Vaananen et al. (1999). The analyzed time period differed from country to country.

Country	Sample	1 st period	2 nd period	AI
Austria	whole nation	9.0	13.3	4.3 (3.3 to 5.3)
Belgium	Antwerp	10.9	15.4	3.1 (0.5 to 5.8)
Bosnia ^a	Tuzla canton	8.9	-	15 (6.0 to 25)
Croatia ^b	two sources	6.9	-	9.0 (5.8 to 12.2)
Czech Republic	whole nation	8.7	17.2	6.7 (5.9 to 7.5)
Denmark ^c	whole nation	22.0	-	3.4 (1.9 to 5.0)
Estonia ^d	whole nation	10.1	16.9	3.3 (n.s.)
Finland	two regions	39.9	52.6	2.7 (1.4 to 4.0)
Germany	BadenWürttemberg	13.0	15.5	3.7 (2.9 to 4.5)
Germany	Düsseldorf	12.5	18.3	4.7 (3.1 to 6.3)
Hungary	18 counties	8.8	11.5	2.9 (1.9 to 3.9)
Italy ^e	Sardinia	37.7	49.3	2.8 (1.0 to 4.7)
Lithuania	whole nation	7.3	10.3	3.8 (2.2 to 5.3)
Luxembourg	whole nation	11.4	15.5	2.4 (-1.4 to 6.3)
Malta ^f	n.s.	14.7	-	0.5 (-2.1 to 3.2)
Montenegro ^g	whole nation	10.8	16.3	4.6 (0.4 to 9.6)
Norway	eight counties	21.1	24.6	1.3 (0.1 to 2.6)
Poland	Katowice	5.2	13.3	9.3 (7.8 to 10.8)
Romania	Bucharest	4.7	11.3	8.4 (5.8 to 11.0)
Slovakia	whole nation	8.2	13.6	5.1 (4.0 to 6.3)
Slovenia	whole nation	7.9	11.1	3.6 (1.6 to 5.7)
Spain	Catalonia	12.4	13.0	0.6 (-0.4 to 0.6)
Sweden	Stockholm county	25.8	34.6	3.3 (2.0 to 4.6)
United Kingdom	Northern Ireland	20.0	29.8	4.2 (3.0 to 5.5)
United Kingdom	Yorkshire	17.1	22.4	2.2 (1.1 to 3.4)
United Kingdom	Oxford	16.0	23.3	3.6 (2.6 to 4.6)

^aStipancic, La Grasta Sabolic et al. 2008, 1995-2003

^bTahirovic and Toromanovic 2007, 1995-2004

^cSvensson, Lyngaae-Jorgensen et al. 2009, 1996-2005

^dTeeaar, Liivak et al. 2010, 1983-1990 vs. 1999-2006

^eCasu, Pascutto et al. 2004, 1989-1994 vs. 1995-1999

^fSchranz and Prikatsky 1989, 1980-1987

^gSamardzic, Marinkovic et al. 2010, 1997-2001 vs. 2002-2006

n.s.: not specified

Table 2. The incidence (per 100,000 per year) of type 1 diabetes and its annual increase (AI; with 95% confidence interval) in different European regions. If not otherwise indicated, data were adopted from Patterson, Dahlquist et al. (2009) and were estimated during the periods 1989-1993 and 1999-2003, respectively.

3.2. Changes over the last years

A global rise in the incidence of type 1 diabetes in children and adolescents has been reported over the past decades (Onkamo, Vaananen et al. 1999; Karvonen, Viik-Kajander et al. 2000; Soltesz 2003; Aamodt, Stene et al. 2007; Soltesz, Patterson et al. 2007). The world-wide annual increment of type 1 diabetes has already been summarized in the work of Onkamo, Vaananen et al. (1999). They found a statistically significant increase of incidence in 65% (24/37) of the examined populations. A non-statistically significant upward tendency was seen in another 12 populations, while a statistically significant decrease of type 1 diabetes incidence was not found. The global trend of the increase in the incidence of type 1 diabetes was 3.0% per year (95% CI 2.59-3.33; $p < 0.001$; Onkamo, Vaananen et al. 1999).

The United States stood apart from other nations in reporting a stable incidence of childhood type 1 diabetes in the 1970s through the 1990s (Vehik and Dabelea 2010). The multicenter Search for Diabetes in Youth Study (SEARCH) reported that the 2002 to 2005 incidence of type 1 diabetes in non-Hispanic White younger than 14 years of age was 27.5/100,000 per year (Bell, Mayer-Davis et al. 2009). This exceeded the incidence predicted for 2010 by earlier data from Allegheny County, Pennsylvania (Dokheel 1993). A similar development was noticed by estimated data from Colorado (Vehik and Dabelea 2010).

For Europe, data from the EURODIAB-register suggest an annual increment of incidence of about 0.6-15% (see Table 2 for details; Patterson, Dahlquist et al. 2009). Earlier data regarding type 1 diabetes incidence from all 36 EURODIAB-centers were published by Green and Patterson (2001).

Regarding the strong differences in the annual increase in the incidence of type 1 diabetes between the countries, it must be mentioned that, besides the geographic differences, the incidence trend was found not to be continuously linear. Furthermore, the incidence trend increases exponentially. Predictions made by Onkamo et al. for the incidence rates in 2010 pointed to large increases, but, in retrospect, were too conservative, especially regarding younger children (Knip 2012).

3.3. Sex-dependent differences of type 1 diabetes mellitus incidence

Despite matched-pair investigations suggested that for some early childhood risk factors the odds ratio in boys were different from those in girls (Svensson, Carstensen et al. 2005), most of the published studies reported no significant difference between the type 1 diabetes incidence in boys and girls (Shaltout, Qabazard et al. 1995; Abellana, Ascaso et al. 2009; Svensson, Lyngaae-Jorgensen et al. 2009; Samardzic, Marinkovic et al. 2010; Teeaar, Liivak et al. 2010). Other groups found small and thereby not relevant sex-related differences only for subgroups (Shaltout, Qabazard et al. 1995). A sex-related difference in incidence was found only in the 10- to 14-year age group with a significantly higher incidence in boys (18.77 vs. 14.7/100,000/year, $p = 0.015$; Bizzarri, Patera et al. 2010). However, a statistically significantly higher incidence in girls was reported by a Libyan (Kadiki and Roaeid 2002), a Thai (Panamonta, Thamjaroen et al. 2011), and an Australian group (Taplin, Craig et al. 2005). The lat-

ter also found the average annual increase of incidence to be significantly higher in boys (3.8% vs. 1.9%, $p = 0.046$).

Taken together the reported studies suggest no sex-dependent differences in the incidence of type 1 diabetes. Type 1 diabetes can be assumed to be the only major organ-specific autoimmune disease not to show a strong female bias. The overall sex ratio is roughly equal in children diagnosed under the age of 15 years (Gale and Gillespie 2001). After the age of puberty, males are more frequently affected than females (Nystrom, Dahlquist et al. 1992).

3.4. Age-dependent differences of type 1 diabetes mellitus incidence

The following sections are intended to answer two questions: 1) does the incidence of type 1 diabetes differ between distinct age groups, and 2) what changes of the incidence of type 1 diabetes within these age groups occurred over the last years.

3.4.1. The age-dependent pattern of type 1 diabetes mellitus incidence

The incidence of type 1 diabetes shows an age-dependent pattern. It was reported to be significantly lower in the 0– to 4-year-old group than in the other groups (Bizzarri, Patera et al. 2010). Many studies from different countries reported an increase of the incidence with increasing age. The highest incidences were found in the 10 to 14-year-old age group (Karvonen, Viik-Kajander et al. 2000; Michaelis et al., 1993; Neu, Eehalt et al. 2001; Taplin, Craig et al. 2005; Samardzic, Marinkovic et al. 2010).

3.4.2. The increase of incidence in different age groups

The increasing incidence of type 1 diabetes is evident. Although some groups found no age-dependent differences in the annual increment of type 1 diabetes incidence (Taplin, Craig et al. 2005; Svensson, Lyngaae-Jorgensen et al. 2009; Abduljabbar, Aljubeh et al. 2010), the majority of the published studies reported different increments of incidence after stratifying children and youths into different age groups: Michealis et. al (1993) found an increment of incidence of about 12.6% in 0- to 9-year-old children, in 10- to 19-year-old children the increment was 3.8%. Similar results were reported by other German groups (Neu, Eehalt et al. 2001; Eehalt, Blumenstock et al. 2008): the relative increment of type 1 diabetes incidence was 5.7% per year in 0- to 4-year-old children, the other age groups showed smaller increments. The incidence of childhood-onset type 1 diabetes in Estonian children under 15 years of age increased annually by an average of 3.3% with the most rapid annual increase (9.3%) occurring in the youngest age group (Teeaar, Liivak et al. 2010). The EURODIAB register repeatedly confirmed that in Europe the annual increase of incidence is higher in younger children (0 to 4 years of age; Green and Patterson 2001; Patterson, Dahlquist et al. 2009).

3.5. Seasonal differences of type 1 diabetes mellitus incidence

When discussing seasonal differences in the epidemiology of type 1 diabetes, two different aspects must be mentioned: 1) different frequency of type 1 diabetes regarding the season of birth, and 2) the changing onset or diagnosis of type 1 diabetes through the year.

3.5.1. Seasonal changes in the incidence of type 1 diabetes mellitus

The seasonality of onset or diagnosis of type 1 diabetes has been extensively studied and the results, so far, are conflicting (Moltchanova, Schreier et al. 2009). However, an increment of type 1 diabetes incidence during the winter has been reported by manifold studies (for details: Padaiga, Tuomilehto et al. 1999) from different countries, e.g. Australia (Elliott, Lucas et al. 2010), the United States (Gorham, Barrett-Connor et al. 2009), Chile (Durruty, Ruiz et al. 1979; Santos, Carrasco et al. 2001), Sweden (Samuelsson, Carstensen et al. 2007; Ostman, Lonnberg et al. 2008), Norway (Joner and Sovik 1981), Greece (Kalliora, Vazeou et al. 2011), and the Czech Republic (Cinek, Sumnik et al. 2003). Recently, Jarosz-Chobot et al. (2011) reported that a significant increase in type 1 diabetes incidence among children over 4 years of age was observed in the autumn–winter season ($p = 0.137$ for the age group 0–4 years and $p < 0.001$ for the age groups 5–9 and 10–14 years). These findings were confirmed by other studies in Poland (Pilecki, Robak-Kontna et al. 2003; Zubkiewicz-Kucharska and Noczynska 2010). Other, partially incomparable, studies revealed no seasonal pattern in the onset or diagnosis of type 1 diabetes mellitus (Levy-Marchal, Papoz et al. 1990; Muntoni and Songini 1992; Ye, Chen et al. 1998) or reported seasonal changes only for subgroups (Michalkova, Cernay et al. 1995; Douglas, McSporran et al. 1999; Padaiga, Tuomilehto et al. 1999). Moltchanova et al. (2009) analyzed data from 105 centers in 53 countries: however, only 42 centers exhibited significant seasonality ($p < 0.05$) in the incidence of type 1 diabetes when the data were pooled for age and sex (Moltchanova, Schreier et al. 2009). Centers further away from the equator were on average more likely to exhibit seasonality ($p < 0.001$). Although the majority of the published data suggests seasonal-dependent changes in the incidence of type 1 diabetes mellitus, further research is needed to complete the picture. Especially populations living below the 30th parallel north should be studied, the populations themselves should be investigated more deeply, and the sample sizes should be increased to gain adequate power to detect seasonal changes in low-incidence populations.

According to the published literature, the seasonal changes in the incidence of type 1 diabetes are likely to be caused by changes of the (auto-)immune activity. The first point is that a reduced ultraviolet radiation exposure during the winter months may lead to reduced vitamin D levels. Thereby, the inhibitory effect of vitamin D on Th1-lymphocytes decreases. The second point is the stimulation of the immune system especially by viral infections during the winter months. The result of both could be a higher (auto-)immune activity that causes β -cell destruction.

3.5.2. Effects of the season of birth on the incidence of type 1 diabetes mellitus

Possible influences of the season of birth are discussed for many autoimmune diseases, e.g. multiple sclerosis, Hashimoto thyreoditis, or Grave's disease (Krassas, Tziomalos et al. 2007). Spring births were associated with increased likelihood of type 1 diabetes, but possibly not in all United States regions (Kahn, Morgan et al. 2009). An Egyptian group reported that 48.3% of diabetic children were delivered during summer months (Ismail, Kasem et al. 2008). A German investigation showed children and adolescents with diabetes being significantly less often born during the months April–June and July–September (Neu, Kehrner et al. 2000). This seasonality pattern was different from those registered in Israel, Sardinia and Slovenia, in which the population with dia-

betes type 1 had most births during these months (1972; Neu, Kehrner et al. 2000). A Ukrainian group found that type 1 diabetes was some 30% more common among persons born in April than among persons born in December (Vaiserman, Carstensen et al. 2007). McKinney et al. analyzed data from 19 European countries, but found no uniform seasonal pattern of birth in childhood diabetes patients across European populations, either overall or according to sex and age (McKinney 2001). Small Turkish studies did not reveal any significant differences of the season of birth in type 1 diabetic vs. metabolically healthy children (Evliyaoglu, Ocal et al. 2002; Karaguzel, Ozer et al. 2007). The controversial results might be explained by the composition of most study samples: Laron et al. found a pattern in the seasonality of month of birth only in ethnically homogeneous populations (such as Ashkenazi Jews, Israeli Arabs, individuals in Sardinia and Canterbury, New Zealand, and Afro-Americans), but not in heterogeneous populations (such as in Sydney, Pittsburgh and Denver; Laron, Lewy et al. 2005). Thereby, it becomes likely that ethnically heterogeneous populations comprising a mixture of patients with various genetic backgrounds and environmental exposures mask the different seasonality pattern of month of birth that many children with diabetes present when compared to the general population (Laron, Lewy et al. 2005).

Authors describing a relationship between season of birth and susceptibility for type 1 diabetes have attributed this to intrauterine infections, dietary intake of certain nutrients and possible toxic food components, short duration of breastfeeding, early exposure to cows' milk proteins, and vitamin D deficiency (Vaiserman, Carstensen et al. 2007). Since most of these factors vary with season, one would expect a difference in the seasonal birth pattern between the general population and those children who develop diabetes. A possible link between environmental factors and type 1 diabetes mellitus manifestation was provided by Badenhoop et al. They found HLA susceptibility genes to be in different proportions of patients either born in different seasons of the year or having manifested their disease in different historical periods over time (Badenhoop, Kahles et al. 2009).

3.6. Ethnic differences

It has been proposed that much of the current variation in the incidence of type 1 diabetes is due in part to differing distributions of ethnicity throughout the world. Many large studies of type 1 diabetes have provided evidence that the ethnic background is one of the most important risk factors for type 1 diabetes (Vehik and Dabelea 2010). It can be assumed that there is a genetically founded – and thereby ethnically associated – varying susceptibility for type 1 diabetes. The onset of the disease is then triggered by ubiquitous environmental factors (Knip, Veijola et al. 2005; Knip and Simell 2012). In general, susceptibility to type 1 diabetes is attributable to genes that link disease progression to distinct steps in immune activation, expansion, and regulation (Nepom and Buckner 2012).

One half of the genetic susceptibility for type 1 diabetes is explained by the HLA (human leukocyte antigen) genes (Knip and Simell 2012). It becomes conclusive that the main research focus is on ethnic variances in HLA-haplotypes and its association with type 1 diabetes (Lipton, Drum et al. 2011; Noble, Johnson et al. 2011). Based on the presence of two high-risk HLA-DQA1/B1 haplotypes, an investigation in the United States revealed that

Caucasians are at the highest and Latinos are at the second-highest risk for developing type 1 diabetes compared to all other ethnic groups (Lipton, Drum et al. 2011). However, there is accumulating evidence that the proportion of subjects with newly diagnosed type 1 diabetes and high-risk HLA genotypes has decreased over the last decades, whereas the proportion of those with low-risk or even protective HLA genotypes has increased (Hermann, Knip et al. 2003; Gillespie, Bain et al. 2004).

The second half of the genetic susceptibility for type 1 diabetes is caused by more than 50 non-HLA genetic polymorphisms (Knip and Simell 2012). Nowadays, there are more than 60 gene loci contributing to the susceptibility of developing type 1 diabetes (Morahan 2012), but this overwhelming list of type 1 diabetes risk genes exerts little influence on the clinical management of children that are at high risk. Conclusively, it is necessary to place the genetics of type 1 diabetes in a more amenable clinical context (Morahan 2012).

Despite the fact that there is consensus about the different genetic type 1 diabetes susceptibility among different ethnic groups, these differences cannot explain the complete variance of type 1 diabetes incidence and prevalence. Furthermore, the annual increment of type 1 diabetes incidence cannot be explained by changing genetic susceptibility. Together with the fact that many individuals are genetically highly susceptible for type 1 diabetes, it becomes conclusive that environmental factors play a crucial role in the onset of the disease and its epidemiology (Knip and Simell 2012).

4. The prevalence of type 1 diabetes mellitus

This section provides a comprehensive description of the type 1 diabetes prevalence, current prevalence trends, and its variability depending among populations and individuals of different age.

4.1. The geographic differences of type 1 diabetes mellitus prevalence

Banting and Best introduced the treatment of type 1 diabetes with insulin injections in the year 1922. Although their first patient (Leonard Thompson) died at the age of 27 from suspected pneumonia, other patients, even from this first treatment series, lived a long time (Teddy Ryder died at the age of 76, Jim Havens at the age of 59 and Elisabeth Ewans Hughes at the age of 73 years; Pliska, Folkers et al. 2005). This observation led to the assumption that the life expectancy of type 1 diabetic patients may be near to normal if the disease is properly treated. It was proven that the life expectation of type 1 diabetic patients has increased over the last decades (Ioacara, Lichiardopol et al. 2009; Miller, Secrest et al. 2012). Therefore, it becomes conclusive that the changes in incidence imply similar trends in the prevalence rates of type 1 diabetes and lead to an accumulation of the disease burden caused by type 1 diabetes and its complications. Recent studies suggest a doubling of type 1 diabetes prevalence within a 20-year period (Akesen, Turan et al. 2011; Eehalt, Dietz et al. 2012). The International Diabetes Federation assumed that in 2011 about 490,100 children (aged 0 to 14 years) suffer from type 1 diabetes. This would correspond to a worldwide prevalence of (25.8 per 100,000 children aged 0 to 4 years). Following the Diabetes Atlas (Interna-

tional Diabetes Federation 2011), there 116,100 cases of type 1 diabetes in the Europe, 64,900 in the Middle East and North Africa region, 36,100 in the Africa, 94,700 in the North America and Caribbean, 36,100 in the South and Central America, 111,500 in the South-East Asia and 30,700 in the Western Pacific region. In accordance with incidence rates differing regionally within countries and also among different countries, the prevalence of type 1 diabetes mellitus varies in a broad range. The prevalence of type 1 diabetes in different countries is summarized in Table 3.

Country	Sampling Period	Prevalence
Finland	2000–2005	427.5
Sweden	2001–2005	270.5
Norway	1999–2003	182.4
United Kingdom	1989–2003	158.3
Canada	1990–1999	146.7
Denmark	1996–2005	141.2
Australia	1999–2008	137.8
United States	2002–2003	135.6
Germany	1989–2003	126.7
Netherlands	1996–1999	124.8
Czech Republic	1989–2003	117.5
New Zealand	1999–2000	115.9
Belgium	1989–2003	107.7
Ireland	1997	107.3
Austria	1989–2003	97.6
Portugal	1994–1998	95.5
Luxembourg	1989–2003	94.9
Slovak Republic	1989–2003	94.2
Iceland	1994–1998	91.1
Poland	1989–2003	85.7
France	1998–2004	84.5
Greece	1995–1999	80.2
Hungary	1989–2003	76.5
Spain	1989–2003	74.6
Switzerland	1991–1999	61.1
Italy	1990–1999	59.9
Turkey	1992–1996	19.8
Japan	1998–2001	15.7
Mexico	1990–1993	8.1
Korea	1990–1991	6.7

Table 3. The prevalence of type 1 diabetes in children younger than 15 years in different OECD countries. Data are based on estimations of the International Diabetes Federation (2009) and related to 100,000 children (0 to 14 years of age) of each country.

4.2. The age-related differences of type 1 diabetes mellitus prevalence

Regarding age dependents phenomena of type 1 diabetes incidence (see section 3.4) it becomes conclusive that 1) the prevalence of type 1 diabetes shows no sex-related differences and increases with age due to accumulation of individuals suffering from the disease and 2) the age-dependent increment of prevalence is not just linear but more likely exponential due to an age-dependent increment of type 1 diabetes incidence. These assumptions have been confirmed for example by the findings of the Australian Institute of Health and Welfare (see Table 4) that were based on the Australian National Diabetes Register.

Age (years)	Persons	Prevalence
0 to 4	405	28.8 (26.0 to 31.6)
5 to 9	1,731	128.0 (122.0 to 134.1)
10 to 14	3,597	256.3 (247.9 to 264.7)
total	5,733	137.8 (134.2 to 141.4)

Table 4. The estimated prevalence (per 100,000 inhabitants of the respective age group with 95% confidence interval) of type 1 diabetes among Australian children aged 0-14 years (Australian Institute of Health and Welfare 2011).

5. What the changing epidemiology implies for future research

The number of investigations concerning the epidemiology of type 1 diabetes is extensive. However, the published results are controversial or even contradictory. There is consensus about fundamental aspects, such as the increasing incidence and prevalence of type 1 diabetes. Thereby, it becomes clear that type 1 diabetes will become more and more of a burden. Although most investigations and publications have been of high methodological quality, they lack exact explanations of the described phenomena, and understanding the mechanisms and triggers of type 1 diabetes remains a mystery.

Future research should lead to improved methods of estimating the epidemiology of type 1 diabetes. Like this, more valid and thereby comparable data on type 1 diabetes epidemiology and risk factors have to be gained, but also more data on the epidemiology of type 1 diabetes over the whole lifespan are definitely needed (Knip 2012). Furthermore, future research may lead to a better understanding of the underlying pathogenesis of type 1 diabetes by complementing the results of descriptive epidemiology with those of 'aetiological' epidemiology (Knip 2012) including the assessment of suspected environmental triggers and risk factors as well as genetic background of the assessed individuals. Conclusively, future research on type 1 diabetes cannot exclusively be performed with population-based approaches. Individualized approaches, e.g. metabolic profiling in both the pre-autoimmune

period and the preclinical period (Oresic, Simell et al. 2008), may provide clues to environmental triggers, such as infections or dietary changes, which likely cause disturbances in the intestinal microbiota and the immune system and contribute to the onset of type 1 diabetes. Thereby, children/adolescents at a high risk may be identified and possibilities for prevention of type 1 diabetes may be detected.

In part promising therapeutic approaches to type 1 diabetes as immunotherapy, stem cell-, β -cell- or islet of Langerhans-transplantation have to be assessed in future studies to find causal therapeutic strategies (Chatenoud, Warncke et al. 2012; Li, Gu et al. 2012; McCall, James Shapiro et al. 2012). Additionally, further research is needed in the field of chronic type 1 diabetes and the detection and treatment of its complications. The role of genetics in susceptibility to nephropathy, retinopathy and other diabetic complications still largely remains to be explored (Borchers, Uibo et al. 2010).

6. What the changing epidemiology implies for future health care

Until now, the treatment of type 1 diabetic patients has been the duty of pediatricians, internal specialists, or diabetologists. The consultation prevalence of type 1 diabetic patients in the general practitioners' consultation hour was low (Frese, Sandholzer et al. 2008). However, if the present trends continue, a doubling of new cases of type 1 diabetes in European children younger than 5 years is predicted between 2005 and 2020, and prevalent cases younger than 15 years will rise by 70% (Patterson, Dahlquist et al. 2009). Adequate health-care resources to meet these children's needs should be made available (Patterson, Dahlquist et al. 2009). It is important to ensure appropriate planning of services and that resources are in place to provide high-quality care for the increased numbers of children who will be diagnosed with diabetes in future years (Patterson, Dahlquist et al. 2009).

In Germany, the costs of pediatric diabetes care exceeded €110 million in 2007. Compared with estimates from the year 2000, average costs per patient had increased by 20% and direct total costs for German pediatric diabetes care by 47% (Bachle, Holl et al. 2012). The treatment costs rose because of new therapeutic strategies and an increase in diabetes prevalence. This illustrates that type 1 diabetes will be an increasing challenge for future health care.

Regarding future health care, it should be kept in mind that elderly and old patients with type 1 diabetes represent a growing population that requires thorough diabetes care. Especially type 1 diabetic patients older than 60 years will suffer from a longer diabetes duration, a doubled risk for severe hypoglycemia, and a higher percentage of cardiovascular complications (Schutt, Fach et al. 2012). In order to provide an adequate health care service, treatment strategies for adults and elderly persons suffering from type 1 diabetes have to be implemented in practice and the knowledge of involved physicians, especially general practitioners, has to be enhanced.

7. Summary

Data on the epidemiology of type 1 diabetes are based on standardized registry data, such as the Diabetes Mondiale (DIAMOND) Project worldwide and The Epidemiology and Prevention of Diabetes (EURODIAB) study in Europe. Some countries provide national registers. Regional or loco-regional registers as well as (cross-sectional) studies have added further data to the current knowledge. Epidemiologic data from developing countries are scarce and may not be fully representative.

The incidence of type 1 diabetes varies up to 100-fold among different countries. The highest incidences are found in northern countries, especially Finland. The lowest incidence rates were recorded in South American and Asian countries. When discussing type 1 diabetes incidence, also strong variations within countries have to be regarded and care should be taken when generalizing results from a regional sample to a general population. The incidence of type 1 diabetes increases worldwide exponentially. The mean of increment is 3.0% per year. Some assume that the incidence of type 1 diabetes in 2020 will be twice that of the year 2000. Before the age of puberty type 1 diabetes there is no sex-related difference in the incidence of type 1-diabetes. However some early childhood risk factors show different odds for boys and girls and after puberty males are more frequently affected by new onset of type 1 diabetes than females. Type 1 diabetes incidence increases with the age of the children/adolescents, but the annually increase of incidence is higher in younger children and those with moderate genetic susceptibility. There is evidence for a circannual variation with a peak of type 1 diabetes incidence during the winter months. Possible effects of the season of birth have to be further investigated with attention to the genetic background of assessed individuals. Genetic susceptibility explains some of the variation of type 1 diabetes incidence and prevalence with the highest risk in individuals with Caucasian or Latino background. As supported by migration studies, the increasing incidence of type 1 diabetes illustrates the importance of environmental risk factors as triggers of the disease.

Future research should focus on identifying environmental and genetic risk factors of type 1 diabetes and its complications, preventive strategies and causal treatment options. The prevalence, which doubled worldwide over the last decades, will increase further and type 1 diabetes will shift more and more into the focus of general practitioners. It becomes conclusive that type 1 diabetes will be a burden for more and more patients and for the majority of health care systems.

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