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Incidence of type 1 diabetes has doubled in Kuwaiti children 0-14 years over the last 20 years

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ABSTRACT

AIMS: This study had 2 aims: to report data on the incidence of childhood-onset type 1 diabetes in Kuwaiti children aged 0-14 years during 2011 to 2013 and to compare the recent data with those collected during 1992 to 1997.

METHODS: All newly diagnosed patients were registered through the Childhood-Onset Diabetes eRegistry (CODeR) in 2011-2013, based on the DiaMond protocol used in 1992-1997.

RESULTS: A total of 515 Kuwaiti children (247 boys and 268 girls) aged 0-14 years newly diagnosed with type 1 diabetes were registered from 1 January 2011 to 31 December 2013. Data ascertainment were 96.7%. The mean age ` SD at diagnosis was 8.7 ` 3.4 years in boys and 7.9 ` 3.1 years in girls. The crude incidence rate (95% CI) was 40.9 (37.4-44.6) and the age standardized rate 41.7 (95% 38.1-45.4) per 100,000 per year, 39.3 (34.6-44.4) among boys and 44.1 (39.0-49.7) among girls. A statistically significant increasing trend in incidence was observed as the overall crude incidence rose from 17.7 in 1992-1994 to 40.9 per 100,000 per year in 2011-2013. The Poisson regression model depicting the trend in incidence revealed that, the incidence rates adjusted for age and sex in 2011 to 2013 was 2.3 (95% CI 1.9-2.7) times higher than 1992-1997.

CONCLUSIONS: The incidence of type 1 diabetes in Kuwaiti children 0-14 years has doubled in the last 2 decades. The reasons for this increase requires further investigation.

KEYWORDS

childhood diabetes, type 1 diabetes, epidemiology, incidence, time trend

INTRODUCTION

The incidence of type 1 diabetes (T1D) in children younger than 14 years is increasing globally.[1] However, the contributing factors to this increase are poorly understood.[1–3] Large-scale studies such as the World Health Organization's (WHO) DiaMond study[4] and the EURODIAB ACE study[5] have collected standardized incidence data for T1D among children under 15 years of age in different populations and showed large regional differences. The highest incidence of T1D was found in northern Europe and the lowest in China.[6] Of particular concern is the doubling in incidence of T1D over the last generation in Europe and the shift to diagnosis at a younger age.[7,8]

The importance of good quality data, based on well established diabetes registries, is critical to monitor trends in the incidence of T1D in children globally. Unfortunately, the cost of maintaining such registries is often prohibitive. For example, in Kuwait a registry, as part of the DiaMond project was used during 1992-1997 to collect data on childhood onset T1D in children. On the basis of these data, the age standardized rate in Kuwaiti children was reported to be 20.9 per 100,000 per year.[9] The Kuwait registry was discontinued untill data collection was re-established by the introduction of the Childhood Onset Diabetes eRegistry (CODeR) in 2011. The introduction of CODeR was spearheaded by the investigators leading the previous DiaMond study[9,10] and used a similar approach to collect and analyze information on newly diagnosed T1D in children. CODeR was part of a larger initiative representing a partnership between Dasman Diabetes Institute, the Kuwait Ministry of Health, NHS Tayside, University of Dundee, and Aridhia Informatics Ltd, referred to as the Kuwait- Scotland eHealth Innovation Network (KSeHIN) established to contribute to improved diabetes care in Kuwait.[11]

The aims of this study were to evaluate the incidence of T1D in Kuwaiti children aged 0-14 years during 2011-2013 and to compare with data collected in 1992-1997.

RESEARCH DESIGN AND METHODS

Study population and data collection

Data were collected in Kuwait, a small country in the Arabian Peninsula. In 2013, the total population was 3,965,144 of whom 1,242,990 were Kuwaitis. The metropolitan area is concentrated within 200 km^2 and is home to approximately 97% of the population. The country is divided into 6 governorates and each Health Region Office supervises and manages general hospitals and nearly 100 primary health care centers and specialized diabetes clinics. In Kuwait, it is mandatory that at diagnosis of T1D, children are admitted to specialized pediatric diabetes and endocrine units in general hospitals for stabilization, management, and education by a multidisciplinary team.[12]

All children aged 0-14 years who were discharged from hospital after diagnosis of newly onset T1D based on IDF/ISPAD guidelines[13] and who met the following criteria were eligible for inclusion in the registry: (i) diagnosed with T1D; (ii) resident of Kuwait; (iii) treated with insulin from the time of diagnosis of diabetes which is not secondary to other conditions.[9] The date of onset was defined as the date of the first insulin injection.[14] Children discharged from hospital constituted the primary source to estimate the degree of ascertainment.[6]

This study included only Kuwaiti children and analysis was restricted to those aged 0-14 years for comparison with other historical studies.

Data capture and governance

Data used in this study were collected using CODeR, a national disease registry online application https://coder.health.org.kw:444/ index.php. Clinicians in government hospitals throughout Kuwait can manually input patient details at the time of diagnosis into a software application (via personal computer or iPad) which is securely stored; the repository is Dasman Diabetes Institute. It is accessed through a secure virtual private network (VPN). Data capture of linked laboratory data is partially automated and drawn from multiple sources and includes data validation, links to clinical coding information and laboratory range alerts. Data linkage is possible through the existence of a unique civil identifier for all residents of Kuwait. Notification of new T1D diagnosis from nearly 100 primary care centers and the Kuwait Diabetes Society was done through a surveillance system based on monthly report cards of newly diagnosed

cases collected by a trained site officer. This information was used as the secondary source for ascertainment rate estimation.

The study protocol was reviewed and approved by the Ethical Review Committee at Dasman Diabetes Institute. Governance and data quality assurance was provided by the CODeR Steering Group and access to data was restricted to its members.

The information collected in CODeR included type of diabetes, demographic, anthropometric and laboratory data. Children (n = 76) with family history of type 2 diabetes (T2D) in first degree relatives, skin manifestations of insulin resistance, negative pancreatic autoantibodies, high insulin, and high C-peptide values were excluded from further data treatment.[12] The protocol included a systematic review of the patients' records, similar to the DiaMond standard protocol[6] to allow a detailed study of relevant records using the WHO International Classification of Disease (ICD) standards[15] using ICD-10.

Information on the total number of Kuwaiti children in the different age groups was obtained from the official statistics provided by the Public Authority of Civil Information for 2011 to 2013.

Ascertainment: capture-recapture

The registry used the capture-recapture method to estimate the degree of ascertainment as recommended by the WHO DiaMond Project.[6] Ascertainment probability (percentage) described previously[16] was calculated using the equation $N = (a + b + c)/(a + c)(b + a)$ where a is the number of cases found by either source, b is the number found by the secondary source only and c is the number found by the primary source only.

Statistical analysis

Age adjustment was done in 5 year intervals (0-4, 5-9, and 10-14 years) using the direct method with a standard population consisting of equal numbers of children in each of 3 subgroups.[6] Age-specific incidence rates were calculated for the different age groups for each year of the study. Poisson regression was used to derive ratios between the incidence rates during 1992-1994 versus 1995-1997 and also between the incidence rates during 1992-1994 versus 2011-2013. Annual rate of increase in incidence rates was calculated based on the incidence of T1D in

children 0-14 years from 1992-1997[9] to 2011-2013 using Poisson regression. Data analysis was performed using the computing environment of R.[17]
Data from CODeR were coded to ensure patient confidentiality and validated prior to analysis on the Aridhia AnalytiXagility platform (http://www.aridhia.com)

RESULTS

The total number of children aged 0-14 years diagnosed with T1D in Kuwait was 721 during 2011-2013. The hospital records identified 258 cases, 40 were reported from the secondary source and 423 were identified by both sources and the ascertainment rate was 96.7%. Kuwaiti children accounted for 71.4% (n = 515) of the cases.

Non-Kuwaiti children (n = 206; 28.6%) were excluded from analysis. Out of 515 Kuwaiti children, 247 were boys and 268 were girls; the male to female ratio was 0.9. The mean age ` SD at diagnosis was 8.7 ` 3.4 years for boys and 7.9 ` 3.1 years for girls. When patients were classified into age groups, 103 (20.0%), 225 (43.7%), and 187 (36.3%) of the children were in the age groups 0-4, 5-9, and 10-14 years respectively. Two infants aged 9 and 11 months are included in the data set as the youngest children diagnosed with T1D. The crude incidence rate (95% CI) in 2011-2013 was 40.9 (37.4-44.6) and the age standardized rate was 41.7 (95% CI. 38.1- 45.4) per 100,000 per year. The gender-specific incidence rate among boys was 38.4 (95% CI 33.7-43.4) and girls 43.5 (95% CI 38.5-49.1). per 100,000 per year (Table 1). The youngest age group (0-4 years) had significantly lower incidence rate as compared with the 2 older age groups ($P < .001$). The difference in the incidence rate between children 5-9 and 10-14 years was only statistically significantly different in 2013 ($P < .05$).

Comparison with previous registry Results were compared to data collected from 1992 to 1997. In these datasets, the degree of case ascertainment varied between 90% and 96% with an average of 92.5%.[9] In the previous dataset, the age standardized rate was 20.9 (95% CI 18.8-23.0) and in 2011-2013 it was 41.7 (95% CI 38.1-45.4), indicating a doubling of the incidence rate of T1D during the last 2 decades (1992 to 2013). The age specific incidence (Table 2)

increased significantly from 17.7 (during 1992-1994) to 40.9 per 100,000 per year in 2011-2013. Incidence rates in the 3 time periods (1992-1994, 1995-1997, and 2011-2013) show a steadily increasing trend for all the 3 age groups of 0-4, 5-9, and 10-14 years, with a steeper increase noted between 1995-1997 and 2011-2013 (Fig. 1)

The Poisson regression model depicting the trend in incidence rates adjusted for age and sex revealed that compared with data collected during 1992-1994, the incidence rates have increased by 1.3 (95% CI 1.1-1.6) and 2.3 (95% CI 1.9-2.7) fold in 1995-1997 and 2011-2013, respectively. Incidence of T1D among children in the age groups 0-4, 5-9, and 10-14 years increased from 13.2, 17.7, and 23.8 to 22.7, 54.3 and 47.8 per 100,000 per year, respectively during the period per year in 2011-2013, and the average annual increase in incidence was 4.1% for all age groups, and 3.2%, 4.9% ,and 3.3% for the age groups 0-4, 5-9, and 10-14 years respectively (Table 2). No statistically significant difference in incidence of T1D was found between boys and girls in any dataset.

DISCUSSION

Kuwait was previously reported to have the fourth highest incidence of T1D in the world.[7] Based on the recent nationwide registry, implemented according to the DiaMond protocol, a twofold increase in incidence rate is seen during the last 20 years in Kuwaiti native children, as the incidence of T1D increased from 17.7 per 100,000 per year (1992 to 1994) to 40.9 per 100,000 per year (2011 to 2013). Our data thus support the observation of a North to South gradient in T1D incidence, with the exception of 2 'hot spots', that is, Sardinia and Kuwait,[4] where T1D incidence is approaching the situation in Finland in the nineties.[18] However, Kuwait does not represent an isolated case of increasing incidence in the Gulf region, as high incidence rates of T1D have been reported from neighboring countries.[19,20] In particular, data from the Eastern province of Saudi Arabia has shown an increased incidence of T1D from 18.1 per 100,000 to 36.9 per 100,000 per year between 1990 and 2007.[19]

A doubling of T1D incidence over a period of about 20 years, represents an undesirable but

apparently well-established and well-documented trend in Western countries such as Finland, Sweden, Germany, and Colorado (USA).[21] For example, data from Sweden collected over 20 years showed a doubling of the incidence from 20 per 100,000 per year to 40 per 100,000 per year[7], showing a trend similar to that observed in Kuwait. Clearly, our data contribute to the overall conclusion that the global trend of incidence of T1D is still on the rise across the world[22–24] with a few exceptions such as a recent study from the Biscay region of Spain.[25] Among Kuwaiti children, we found an overall annual increase in T1D incidence of 4.1%, over the last 2 decades. These results are well in agreement with international data, as an average relative increase of 3-4% per calendar year has been reported worldwide.[7]

Although we did not find any statistically significant differences between boys and girls, the annual increase was slightly higher in girls aged 5-9 years (5.4%). In contrast to the previously reported observation that T1D incidence is increasing in younger children[26] our data show that the youngest age group (0-4 years) had statistically significant lower incidence rates as compared with older children ($P < .001$). This observation is in agreement with pooled data from the DiaMond study, showing that 5 to 9-year-old children had a 1.62 times higher risk of developing T1D compared with 0 to 4-year-old children.[4] In addition, only minor differences were found between children aged 5-9 and 10- 14 years as the incidence rates were only statistically different in 1 year (2013) between these age groups. We did not observe any significant gender differences, although, in general, high incidence countries tend to have a slight male excess, while the opposite is seen in low incidence countries[4] with a few exceptions.[19,20,27]

The reasons for the increasing incidence of T1D globally are largely unknown in spite of numerous large-scale studies implemented to evaluate the contributing factors to its etiology. T1D is a chronic autoimmune disease involving an interplay between genetic and environmental factors and the HLA region remains the most important genetic determinant as

more than 90% of children with T1D carry the HLA class II haplotypes DRB1*03-DQB1 *2:01(DR3- DQ2) and/or DRB1*04-DQB1*03:02(DR4-DQ8).[28] Analysis of HLA- DQBI/DQA1 haplotypes in Kuwaiti children confirmed that DQA1*0301/DQB1*0201, a high-risk haplotype, was present in 63% of children with T1D as compared with 14% of controls.[29] Moreover, HLA DQB1 non-aspartate 57 alleles (non-Asp 57) were found in 87% of children with T1D compared with 44% of controls in accordance with results reported from Sardinian and Norwegian populations.[30] These data indicate the importance of further investigations into the genetic susceptibility to T1D among Kuwaiti children as a priority area for research.

The etiology of T1D is clearly complex and the influence of rapidly changing life style and environmental effects are important factors to be considered.[2] A range of potential triggers for immunologically mediated destruction of the beta cells have been suggested, including viruses,[31] exposure to cow's milk in infancy,[32] composition of the microbiome,[33] and nutrition.[34] Further studies to elucidate the importance of various factors contributing to the etiology of T1D are clearly needed.

In addition, although there is long-term experience in the diagnosis of diabetes globally, it is important to stress that accurate diagnosis of different types of diabetes remains difficult and controversial.[35] It has been suggested that a scheme of islet autoantibody testing, with the aid of HLA-DR, DQ genotyping, and fasting C-peptide measurement in autoantibody-negative subjects may be necessary for correct diagnosis of diabetes.[7,35] Currently, diagnosis of diabetes does not include such elaborate testing and, for example, in our dataset it cannot be ruled out that some children with T2D have been misdiagnosed as T1D. However, based on the strict inclusion/exclusion criteria used for the registry, we are confident that the misclassification of children was kept to a minimum. For any comparison with previous data, such as in our study, the influence of changes to medical practice and/or procedures (for example the coding systems) cannot be ruled out but is assumed to not influence the data significantly.

A further limitation to our study is that the duration of the registry was relatively short. It would be important to expand the registry to continue monitoring incidence of T1D and evaluate trends in a high incidence country such as Kuwait. The need for long-term health care of children diagnosed with T1D cannot be underestimated and with increasing numbers of children diagnosed, additional resources must be made available to provide state-of-the-art care.

Our data clearly indicate the importance of well established electronic registries to monitor trends in incidence of T1D in the pediatric population. In Kuwait, the use of a unique identification number facilitated the quality control of data. Furthermore, close collaboration of researchers and clinicians working in a small country made the implementation of a nationwide registry feasible but also highlighted the importance of securing adequate resources to continue data collection.

CONCLUSION

We have demonstrated a doubling of incidence of T1D over the last 20 years in Kuwaiti children aged 0-14 years. Adequate healthcare resources must be made available to meet the needs of children diagnosed with T1D.

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Author contributions

A.S., T.A.T., L.D., D.W., D.O., and D.A. are responsible for the scientific content of the manuscript. A.M.C. and S.M. are responsible for statistical analysis. H.A.K., M.A., are responsible for data collection and validation, N.C. and J.T. for critical review of the manuscript. Conflict of interest The authors declare that there is no conflict of interest associated with this manuscript.

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Appendix

The Steering Group for the Study of Childhood Diabetes in Kuwait: E. Haroon, Y. Almeheymi (Dasman Diabetes Institute), M. AlKhawari, M. Qabazard, H. AlSane, Fahed Al Jasser (Amiri Hospital); A. Al Tararwa (Farwaniya Hospital); M. Al Mahdi, N. Alzanati (Adan Hospital); F. Mandani, N. Al Terkait, A. Al Adsani, E. Maarafi (Sabah Hospital); E. Albasiri (Mubarak Hospital); F. Hussein, M. Al-Oteibi, Z. AL Shemmari, Huda Ghareeb, A. Michael, W. Saba M. Al-Oteiby, S. Al Jassar (Ministry of Health); A. Al Anezi, H Mahmoud (Al Jahra Hospital); H. Sorrour (Kuwait Oil Company Hospital).

FIGURES and TABLES

Table 1. Mean annual age- and sex- specific incidence of childhood type 1 diabetes in Kuwait between 2011 and 2013

	Number of patients	Person-years at risk	Mean annual IR (95% CI)	Standardized IR (95% CI)
Boys				
0-4 yr	47	232613	20.21 (14.9-26.9)	
5-9 yr	100	210459	47.52 (38.7-57.8)	
10-14 y	100	200906	49.78 (40.5-60.5)	
Total	247	643978	38.36 (33.7-43.4)	39.3 (95% CI 34.6- 44.4)
Girls				
0-4 yr	56	221752	25.25 (19.1-32.8)	
5-9 yr	125	203573	61.40 (51.1-73.2)	
10-14 y	87	190273	45.72 (36.6-56.4)	

Total	268	615598	43.53 (38.5-49.1)	44.1 (95% CI 39.0- 49.7)
Boys and girls				
0-4 yr	103	454365	22.67 (18.5-27.5)	
5-9 yr	225	414032	54.34 (47.5-61.9)	
10-14 yr	187	391179	47.80 (41.2-55.2)	
Total	515	1259576	40.89 (37.4-44.6)	41.7 (95% CI 38.2- 45.4)

Table 2. Annual increase in incidence rates of type 1 diabetes in age group 0-4, 5-9 and 10-14 years in 3 time periods

		1992-1994		**1995-1997**		**2011-2013**	**Annual increase**
	n	**Incidence Rate (95% CI)**	**n**	**Incidence Rate (95% CI)**	**N**	**Incidence Rate (95% CI)**	
0 – 4 years	43	13.2 ; (9.6 - 17.8)	37	10.2; (7.2 - 14.1)	103	22.7; (18.5- 27.5)	4.2 (2.6%)
5 – 9 years	52	17.7 ; (13.2- 23.3)	90	28.4; (22.8 - 34.9)	225	54.3; (47.5- 61.9)	7.2 (5.5%)
10- 14 years	58	23.8 ; (18.1 - 30.8)	84	31.0; (24.7 - 38.3)	187	47.8; (41.2- 55.2)	5.7 (3.4%)
0 – 14 years	153	17.7; (15.0- 20.8)	211	22.1; (19.2- 25.3)	515	40.9; (37.9-44.6)	5.9 (4.1%)

Figure 1: Comparison of annual age-specific incidence rates between 1992-1994, 1995-1997, and 2011-2013

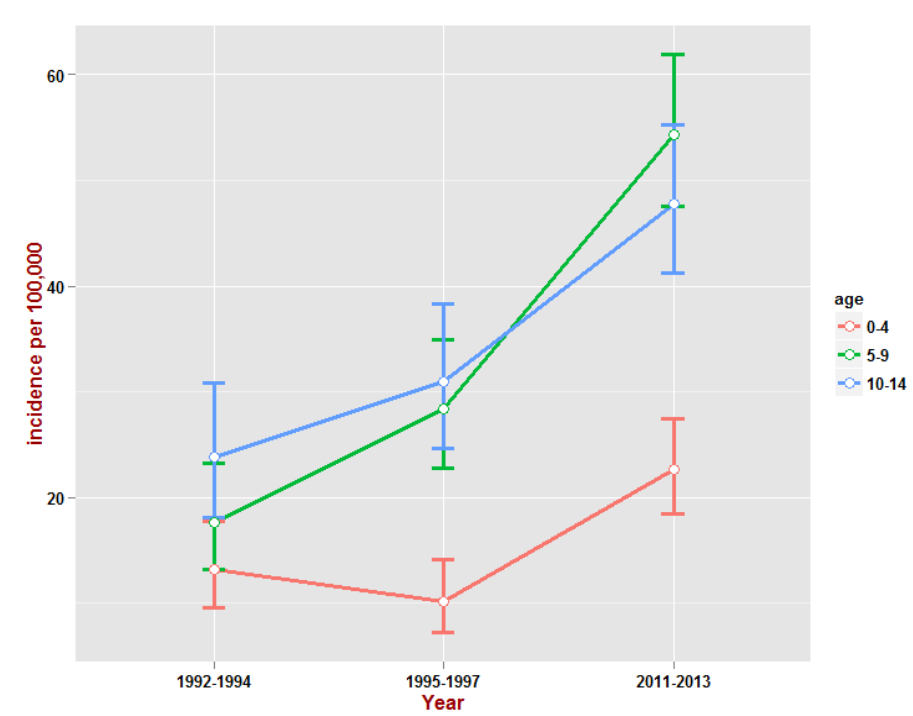

Figure 1: Comparison of annual age-specific incidence rates between 1992-1994, 1995-1997, and 2011-2013

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