

The Incidence Trend of Type 1 Diabetes among Children and Adolescents 0-14 Years of Age in the West, South, and Tripoli Regions of Libya (2009-2018)

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What is already known on this topic?

- The incidence of type 1 diabetes (T1D) is increasing in Arab countries in the Middle East and North Africa region of the world.
- A study from the Benghazi region of Libya in the period 1991-2000, reported an intermediate incidence of T1D.

What this study adds?

- The age-standardized incidence rate (IR) was 31.7 per 100,000 for the period 2014-2018, indicating more than a trebling of the IR of T1D since 1991-2000.
- There was a higher IR in the 0-4 and 5-9 years age groups compared to the 10-14 years age group.

Abstract

Objective: To estimate the incidence rates (IR) and analyse the trend in type 1 diabetes (T1D) among children aged 0-14 years in the West, South, and Tripoli regions of Libya.

Methods: A retrospective study was conducted on Libyan children aged 0-14 years with a new diagnosis of T1D who were admitted and/or had their follow-up at Tripoli Children's Hospital during the period 2004 to 2018. The data were used to estimate the IR and the age-standardized IR per 100,000 population in the studied region for the years 2009-2018. The IRs by sex and age group (0-4, 5-9, 10-14 years) for every calendar year were assessed.

Results: A total of 1,213 children were diagnosed during the study period (2004-2018), 49.1% were males with a male-to-female ratio of 1:1.03. The mean age (\pm standard deviation) at diagnosis was 6.3 ± 3.8 years. The distribution of incident cases according to age group 0-4, 5-9, and 10-14 years was 38.2%, 37.8%, and 24.1%, respectively. Poisson regression modelling in the period 2009-2018 revealed an overall trend of a 2.1% increase per annum. In the period 2014-2018, the overall age-adjusted IR was 31.7 (95% confidence interval: 29.2-34.2) per 100,000 population, the IRs of age groups 0-4, 5-9, and 10-14 years were 36.0, 37.4, and 21.6 per 100,000, respectively.

Conclusion: The incidence of T1D in Libyan children in the West, South, and Tripoli regions appears to be rising, with a higher rate in the 0-4 and 5-9 year age groups.

Keywords: Type 1 diabetes, epidemiology, incidence, children, adolescents, registry, Libya, Arabs

Introduction

Diabetes is a common non-communicable disease that has a major impact on the lives of individuals and communities (1). In most countries, the majority of children and

adolescents with diabetes have type 1 diabetes (T1D) (2). T1D is caused by an absolute insulin deficiency as a result of the autoimmune destruction of beta cells of the pancreas (3).



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There is wide variation in the incidence of T1D in the world, being very low in most Asian populations and high in European countries (4,5). However, the incidence increased by an estimated 2.8% per year worldwide during the 1990s (6). Furthermore, a recent report estimated the overall annual increase in the incidence rate (IR) of T1D in Europe to be 3.4% (7). Moreover, 42% of all incident cases were estimated to occur in children younger than 15 years of age (8).

Libya is one of the 18 Arab countries in the Middle East and North Africa (MENA) region of the world (9), with an estimated population of 6.69 million in 2018, of which 2.076 million (30.8%) are 0-14 years of age (10). Arabs have one of the highest prevalence of diabetes worldwide (11). Furthermore, three Arab countries (Algeria, Saudi Arabia and Morocco) are in the top ten countries for the estimated number of new cases of T1D in children and adolescents (0-19 years old) per year (11).

Information on recent trends in the incidence and prevalence of childhood T1D in Libya is lacking. This is the result of the absence of a national paediatric diabetes registry and a lack of organization and networking between different diabetes centres/clinics in Libya.

The most recent review of published rates of childhood T1D incidence by the International Diabetes Federation

(IDF) (11) relied on a report of rates in Libya in the 1990s (12). Since neighbouring Arab countries that are likely to have similar genetic characteristics to the population in Libya have a high incidence of childhood T1D, this earlier reported incidence in Libya is likely an underestimate of the true IR in the country.

This study aimed to estimate the IR of T1D in children 0-14 years of age in the West, South, and Tripoli regions of Libya from the number of cases seen in a single tertiary referral paediatric diabetes centre, Tripoli Children's Hospital, in the Tripoli health region.

Methods

Health Services in Libya

Public healthcare facilities are present in the six health regions of Libya, with each health region having several health districts. This organization is based on access and referral to the nearest tertiary care facilities. Tertiary healthcare facilities, which are located in the Tripoli health region, also cover the West and South health regions (Figure 1). Tripoli Children's Hospital and Tripoli University Hospital (formerly known as Tripoli Medical Centre until 2018) are tertiary healthcare facilities located in the Tripoli

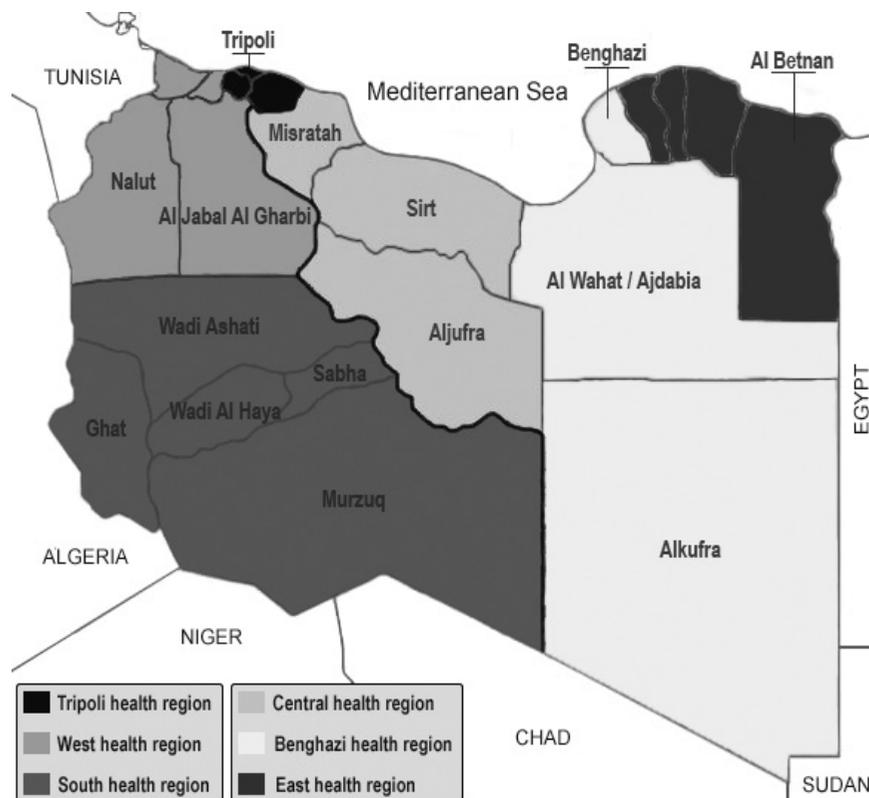


Figure 1. Location of health regions in Libya, modified from (13)

Table 1. Number of new cases of diabetes in children and adolescents seen at TCH and Tripoli University Hospital (2009-2018)

Diagnosis per period	Total number of new cases of diabetes A = (B + C)	Tripoli University Hospital	TCH			
		Number of new cases of diabetes per period (B)	Number of new cases of diabetes per period (C)	Percentage of cases at TCH D = (C ÷ A)* 100	Number of other forms of diabetes (E)	Percentage of other forms of diabetes F = (E ÷ C)* 100
Period 2 (2009-2013)	1,763	1,281	482	27.3 %	34	7.0 %
Period 3 (2014-2018)	2,089	1,412	677	32.4 %	38	5.6 %

With permission from the Head of the Paediatric Endocrinology and Diabetes Department at Tripoli University Hospital.
 TCH: Tripoli Children's Hospital

health region (13). The Departments located in these two hospitals cover these three health regions. In the studied geographical area, there are several other cities, however, during the study period, a consultant paediatric endocrinologist or a paediatric consultant/specialist with an interest in diabetes was available at Tripoli Children's Hospital and Tripoli University Hospital, and parents preferred that their children attend follow-up for management and initial diabetes education at these two hospitals.

In the Libyan health care system, all children aged 0-14 years with a suspected diagnosis of diabetes are referred to paediatric hospitals for admission and paediatric diabetes clinics for their follow-up.

Local Background

The Tripoli Children's Hospital Paediatric Diabetes Clinic provides services to over 1000 children and adolescents with diabetes, and the follow-up clinics are run five days a week. There has been an electronic paediatric diabetes registry in use since 2015. The researcher M.S.S. was involved in creating the electronic paediatric diabetes registry and oversees the data entry and running of the registry. Before and after 2015, new patients' details were entered in a handwritten register when opening a clinic file. Data from files of patients already followed up at the clinic were entered into the registry retrospectively in the year 2015. Data from all new cases seen at the clinic have been included in the registry prospectively since then.

At the Tripoli Children's Hospital Paediatric Diabetes Clinic, the majority of children and adolescents younger than 19 years of age have T1D. Other forms of diabetes represent an average of 5.6 % of new cases per year (Table 1).

To obtain the proportion of cases of diabetes diagnosed at Tripoli Children's Hospital in the studied geographical area, we compared the list of children with diabetes obtained for the study from Tripoli Children's Hospital with the handwritten paediatric diabetes register from Tripoli University Hospital and removed the duplicate cases that

were seen in each hospital. It was noted that 27.3 % of cases during the period 2009-2013, and 32.4% of cases during the period 2014-2018 were diagnosed at Tripoli Children's Hospital (Table 1).

Study Population

This retrospective study was conducted to ascertain all cases of T1D in children aged 0-14 years, who were diagnosed during the period between January 1, 2004, to December 31, 2018, in a single paediatric diabetes centre in Tripoli, Libya. The study is based on the number of incident cases of T1D admitted and/or had their follow-up at Tripoli Children's Hospital during the study period. Cases included were Libyan children and adolescents 0-14 years of age at the time of diagnosis, who had been diagnosed with T1D and resided in the West, South, and Tripoli regions of Libya during the study period.

Ethical Approval

The study proposal was approved by the Bioethics Committee at the Biotechnology Research Centre (ref no: BEC-BTRC 17-2019, date: 09.08.2020), which is under the auspices of the Ministry of Higher Education and Scientific Research (14).

Patient Selection

Data were extracted from notes using a specifically designed and adapted form (15,16,17,18). Data collected included full name, date of birth, sex, date of diagnosis, symptoms at presentation, mode of presentation, type of diabetes, treatment at presentation, place of diagnosis, address, nationality, and treatment at the last clinic visit.

The primary data source consisted of cases who were diagnosed as having diabetes by the treating paediatrician and had been identified from admission records with ICD E10 and E11 codes (hospital records from 2011 to 2018 only), hospital discharge letters in Paediatric Diabetes Clinic files (all available clinic files since the year 1999), paediatric diabetes

handwritten clinic files of patients attending the clinic (all notes for patients attending the clinic up to December 31, 2018), the electronic paediatric diabetes registry, and the Paediatric Diabetes Clinic archived handwritten notes (for patients no longer attending the clinic, for example having transitioned to adult services, changed follow-up to another paediatric clinic, or lost to follow-up). Cases that were registered in the handwritten register during the study period (2004-2018), but whose files were not found or were incomplete were excluded from the study (79 cases).

The data collected were reviewed by the researchers (M.S.S. and R.M.K.) to ascertain the completeness of the information. The diagnosis was reviewed by the researchers (M.S.S. and R.M.K.) according to the International Society for Pediatric and Adolescents Diabetes definition of diabetes (19) and was assigned as T1D according to the T1D Exchange criteria (20). In this study, 99.1% of cases (0-14 years of age) met the criteria for definite T1D, which is similar to the T1D Exchange study (100% and 99% for age groups 0-5 and 6-12 years respectively) (20). The date of diagnosis was defined as the date of opening the file with a diagnosis of diabetes (admission/presentation with symptoms and high blood glucose/high glycated haemoglobin) (21).

The data were entered in a Statistical Package for the Social Sciences (SPSS) file by the researcher R.M.K. Duplicate patients were removed using combinations of name, date of birth, date of diagnosis, sex, and address.

We collected data on 1,580 children with diabetes (1999-2018). We compared Tripoli Children's Hospital data with Tripoli University Hospital data and removed duplicate cases from Tripoli Children's Hospital data (143 cases), leaving 1,437 cases eligible to be included in the study.

Exclusion criteria (Figure 2) were age less than six months or 15 years or older at the time of diagnosis, non-Libyan nationality, residency outside the studied region of Libya, and a diagnosis of other forms of diabetes, such as type 2 diabetes, monogenic diabetes, or drug-induced diabetes. In incident cases that had other forms of diabetes, the diagnosis was reviewed by the researchers (M.S.S. and R.M.K.) before exclusion from the study. These exclusions left 1,213 children with T1D to be included in this study.

Since we are investigating incidence trends, we divided the study years into three 5-year periods, period one 2004-2008, period two 2009-2013, and period three 2014-2018.

Ascertainment

We calculated the completeness of case identification for each of the three periods from the primary source only. Completeness of ascertainment was 95% for the whole

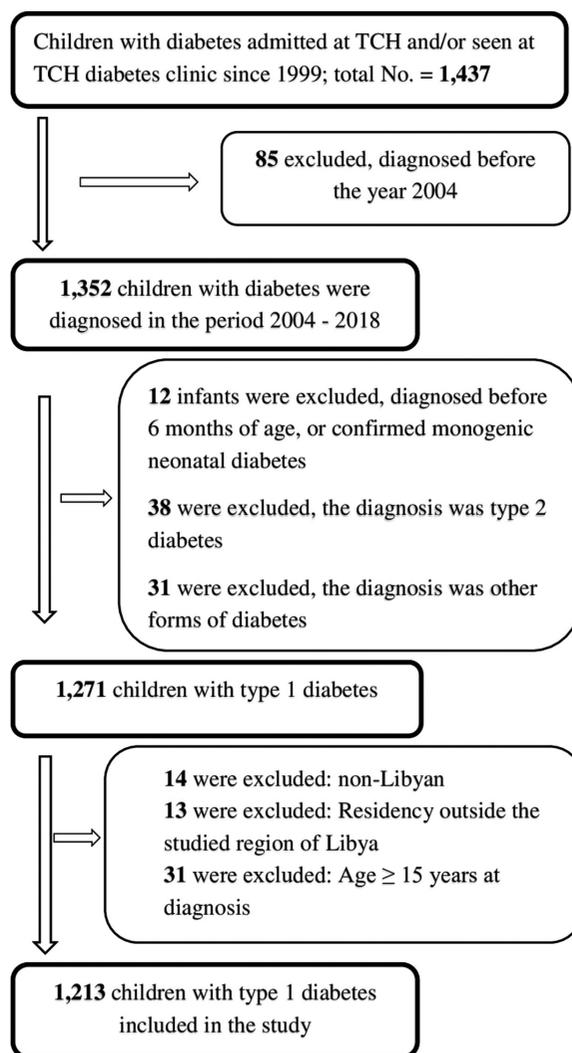


Figure 2. Flow chart of inclusion of cases diagnosed at TCH
TCH: Tripoli Children's Hospital

period (percentage of children with available and complete files to the total number of children registered in the handwritten clinic register). However, ascertainment was very high in periods two and three (95.6% and 99.2%, respectively) compared to the first period (79.3%).

In Libya, there were no secondary sources to verify the completeness of ascertainment, so our estimates can provide only an imperfect estimate of completeness. However, since all children 0-14 years of age with a diagnosis of diabetes are referred to paediatric hospitals for management, and individuals with T1D are offered treatment free of charge subsidized by the government after being registered in one of the public diabetes services, it is reasonable to assume that data from hospital files and paediatric diabetes clinic records will identify the majority of patients diagnosed in the study period.

Incidence Calculation

We excluded cases diagnosed in period one from the calculation of the IR because of low ascertainment. The incident cases from periods two (2009-2013) and three (2014-2018) were divided into male and female groups as well as three age groups, 0-4, 5-9, and 10-14 years. We used the incident cases seen as a numerator.

The data were used to calculate the crude IR of T1D in children 0-14 years of age in the West, South, and Tripoli regions of Libya. Since the number of incident cases in Tripoli Children’s Hospital represents approximately 27.3% and 32.4% of cases seen in the studied geographical region of Libya during periods two and three, respectively (Table 1), we assumed that the proportion of the population of the studied geographical area covered by the Tripoli Children’s Hospital Paediatric Diabetes Department is 27.3% and 32.4% in periods two and three respectively.

Age group population data (0-4, 5-9, and 10-14 years) of the West, South, and Tripoli regions of Libya from the last census in the year 2006, were obtained from the Bureau of Statistics and Census Libya (10). We used the projected population growth rate to estimate the population in the years before and after 2006. We used the population percentage covered by Tripoli Children’s Hospital (27.3% and 32.4% for periods two and three respectively) to obtain the population numbers for children 0-14 years of age and the six groups (according to age and sex), and these numbers were used as denominators. The estimated IR of T1D was calculated by dividing the number of children with T1D diagnosed (numerator) by the corresponding population (denominator).

The IRs were expressed as new cases per 100,000 population (both sexes) per year for age groups 0-4, 5-9, and

10-14 years as well as for male and female groups. The age-standardized IR was calculated using the direct method (22) and using the World Health Organization (WHO) standard population (23,24).

Statistical Analysis

The data of incident cases included in the study are presented as mean (\pm standard deviation), or frequency (%). Estimated IRs with 95% confidence intervals (CIs) were calculated assuming a Poisson distribution using MedCalc® Statistical Software version 20.106 (MedCalc Software Ltd., Ostend, Belgium).

Edward’s test was used to analyse a sinusoidal (sine/wave) pattern in seasonality.

Poisson regression was used to analyse the rate of increase in IR in the period 2009-2018 and incorporated adjustments for age and sex distribution.

Statistical analysis was done using SPSS for Windows, version 25 (IBM Corp, Armonk, NY, USA), Stata release 14 (Stata Corp, College Station, TX, USA), and the R-4.1.2 programming language.

A $p < 0.05$ was considered significant. P values are not adjusted for multiple tests and should be interpreted exploratorily only.

Results

Demographic Characteristics of Patients and Seasonality

During the period 2004-2018, a total of 1,213 children with T1D were diagnosed at Tripoli Children’s Hospital (Table 2). Of these, 595 (49.1%) were males and 618 (50.9%) were females, giving a male-to-female ratio of 1:1.03. The distribution of incident cases according to the age

Table 2. Number of children with type 1 diabetes diagnosed at TCH during the period 2004-2018 and included in the study

Patient’s characteristics		Study period (2004-2018)	Period 1 (2004-2008)	Period 2 (2009-2013)	Period 3 (2014-2018)
Total number of cases		1,213	169	434	610
Total group: by sex Number (%)	Male	595 (49.1%)	77 (45.6%)	212 (48.8%)	306 (50.2%)
	Female	618 (50.9%)	92 (54.4%)	222 (51.2%)	304 (49.8%)
Mean age at diagnosis (mean \pm SD, years)	Total group	6.3 \pm 3.8	6.6 \pm 3.8	6.4 \pm 3.9	6.2 \pm 3.8
	Male	6.1 \pm 3.9	5.7 \pm 3.6	6.4 \pm 4.0	5.9 \pm 3.8
	Female	6.5 \pm 3.8	7.3 \pm 3.7	6.4 \pm 3.8	6.4 \pm 3.8
	p* (M: F) [†]	0.03	0.007	0.99	0.11
Total group: by age group Number (%)	0-4 years	463 (38.2%)	56 (33.1%)	162 (37.3%)	245 (40.2%)
	5-9 years	458 (37.8%)	70 (41.4%)	160 (36.9%)	228 (37.4%)
	10-14 years	292 (24.1%)	43 (25.4%)	112 (25.8%)	137 (22.5%)

*Student’s t-test for independent samples, [†]Male-to-female. SD: standard deviation, TCH: Tripoli Children’s Hospital

Table 3. Periods two and three analysis; period IR, and annual increase in the IR of type 1 diabetes by Poisson regression analysis

		Period 2 (2009-2013)	Period 3 (2014-2018)	Periods 2 and 3 (2009-2018)	Percentage annual increase in IR [§] (CI)
		IR (CI, 95%)	IR (CI, 95%)	IR (CI, 95%)	
Total (0-14 years)		29.3 (26.6-32.2)	31.7 (29.2-34.3)	30.7 (28.8-32.6)	2.1% (-0.1-4.2)
Total: by sex (0-14 years)	Male	28.1 (24.5-32.2)	31.0 (27.7-34.7)	29.8 (27.3-32.5)	2.7% (-0.4-5.9)
	Female	30.6 (26.7-34.9)	32.4 (28.9-36.3)	31.6 (29.0-34.4)	1.5% (-1.5-4.6)
Total: by age group	0-4 years	31.1 (26.5-63.3)	36.0 (31.7-40.8)	33.9 (30.7-37.4)	3.4% (-0.1-7.0)
	5-9 years	34.0 (28.9-39.7)	37.4 (32.7-42.6)	35.9 (32.4-39.7)	2.6% (-0.9-6.3)
	10-14 years	22.9 (18.9-27.6)	21.6 (18.1-25.5)	22.2 (19.5-25.1)	-0.7% (-4.9-3.7)

[§]Using Poisson regression analysis.
IR: incidence rate, CI: confidence interval

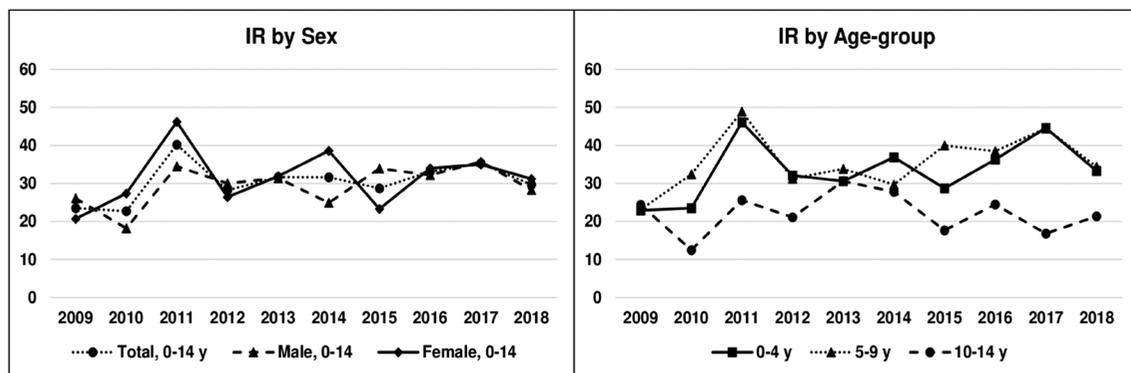


Figure 3. Annual IR of T1D in children aged 0-14 years in the West, South, and Tripoli regions of Libya (periods 2 and 3)
IR: incidence rate, T1D: type 1 diabetes

groups 0-4, 5-9, and 10-14 years was 38.2%, 37.8%, and 24.1%, respectively. The mean age at diagnosis for the total group was 6.3 ± 3.8 years. The mean age at diagnosis was significantly lower in males compared to females over the whole study period. However, on comparing the three periods, this difference was only significant in the first period.

More cases of T1D were diagnosed in autumn and winter (52.0%) than in spring and summer (48.0%). Edward's test was performed on 1044 cases in periods two and three and the analysis showed significant seasonal variation in the total cohort ($p=0.01$), for males ($p<0.001$), and the age group 5-9 years ($p<0.001$), with a fitted peak incidence in January.

Incidence and Trend

The IRs of T1D in the West, South, and Tripoli regions of Libya in periods two and three are shown in Table 3 and Figure 3. Age standardization made minimal difference to the IRs, as the numbers in the three age groups are roughly equal in both the Libyan and the WHO standard populations.

The highest IR was noted in the year 2011 in the total cohort, as well as in the female group, while the highest IR in males was in the year 2017. Furthermore, the highest IR in each age group was in the years 2011, 2011, and 2013 for the 0-4, 5-9, and 10-14 years age groups respectively (Figure 3).

Poisson regression modelling of periods two and three together (2009-2018) revealed that the overall trend, adjusted for age group and sex, was an increase of 2.1% per annum. The rates of increase in males were 2.7% and in females 1.5%. The rates of increase in the age groups 0-4, 5-9, and 10-14 years were 3.4%, 2.6%, and -0.7%, respectively.

Period three best represents the recent IR of T1D in the West, South, and Tripoli regions of Libya. The overall IR in this period was 31.7 (CI: 29.2-34.3) per 100,000, and the age-standardized rate was 31.7 (CI: 29.2-34.2). The sex-specific IRs among the male and female populations were 31.0 and 32.4 per 100,000, respectively. The age groups 0-4, 5-9, and 10-14 years had an IR of 36.0, 37.4, and 21.6 per 100,000, respectively (Table 3).

Discussion

This study on the IR of T1D in children aged 0-14 years is the first of its kind in the West, South, and Tripoli regions of Libya. The age-standardized IR for the 2014-2018 period was 31.7 per 100,000. This age-standardized IR for the West, South, and Tripoli regions, if extrapolated to the whole country, places Libya in the top ten countries with the highest age-standardized rates of T1D in this age group in the world, which already includes four other countries from the MENA region of the world, according to the tenth edition of the IDF Diabetes Atlas (11). Furthermore, it is similar to the rates reported recently from Tlemcen city in Algeria [IR: 38.5 (2015-2018)] (25), Oran city in Algeria [IR: 31.1 (2013-2017)] (26), and Qatar [IR: 28.4 (2012-2016)] (27).

The only previous data on the IR of T1D in Libya was produced by Kadiki and Roaeid (12) in children aged 0-14 years from the Benghazi region (1991-2000) who reported an age-standardized rate of 8.3 per 100,000, which is nearly equal to the age-standardized IR (8.6 per 100,000) from Oran city in Algeria (1990-1999) (6), suggesting that the increase in the IR in the two countries has followed a similar trend.

A comparison of the age-standardized IR in Libya from Kadiki and Roaeid (12) with the findings in the present study suggests a more than trebling of the IR of T1D since 1991-2000. Furthermore, in the present study, around 76% of cases (period 2009-2018) were diagnosed before the age of 10 years compared to 44% in the earlier study (12). The higher IRs in 0-4 and 5-9 years age groups in the third period of our study, also indicate an increase in the number of younger children diagnosed with T1D.

This high rate of increase was also seen in Oran city in Algeria (period 2013-2017, nearly double the rate compared to period 2003-2007), (26) in Kuwait (doubled from 1992 to 2013) (28), and in Qatar (nearly doubled from 2006 to 2016) (27,29). The annual rate of increase in the present study was 2.1%, which is lower than the estimated rate of increase worldwide (2.4-3.2%) (6), and in Kuwait (4.1% per annum) (28).

The mean age at diagnosis in our cohort was 6.3 ± 3.9 years, which is younger than the mean age in Tlemcen (7.51 ± 4.12 years) (25), and Kuwait (male 8.7 ± 3.4 , female 7.9 ± 3.1 years) (28). This is consistent with the higher IR in the age groups 0-4 and 5-9 years in our study. This contrasts with the reports from the MENA region of the world, which showed a higher IR in 5-9 and 10-14 years compared to the IR in the younger age group [Tlemcen, (25) Oran, (26) and Kuwait (28)]. Our study showed a high IR of T1D in children under 10 years of age.

The high IRs of T1D noted in the year 2011 could be because the year 2011 was the year of a military conflict that resulted in regime change in Libya. This armed conflict might have led to the collapse or disruption of health services in cities around Tripoli, and resulted in the internal displacement of people, thus increasing the number of children diagnosed in the studied geographical area (30).

The seasonality test (periods two and three) demonstrated significant seasonal variation with peaks in January, in the 0-14- and 5-9-years age groups and males. This finding is only partially consistent with the pattern seen in Europe (31).

Study Limitations

This study has certain limitations, it was based on incident cases from a single centre in the West, South, and Tripoli regions of Libya, and an assumption was made that the Tripoli Children's Hospital covers 27.3% and 32.4% of the population of the studied geographical area in periods two and three respectively. However, because of the organization of healthcare facilities in Libya, we are confident that the estimated IR of T1D is reflective of the actual IR in the West, South, and Tripoli regions of Libya. This study was partly retrospective, case ascertainment was from a primary source only, furthermore, some patients from cities near the west border of Libya might be seen in clinics in neighbouring countries (Tunisia and Algeria). Furthermore, some patients might be seen in an adult diabetes clinic in the small cities located in the West and South regions or the adjacent Central region of Libya. As a result, the reported IR in this study could underestimate the true IRs.

Despite its limitations, the strengths of this study should be highlighted. It is based on the population of a well-defined region of Libya, it includes cases diagnosed over 10 years, and is based partly on an electronic paediatric diabetes registry. Furthermore, the diagnosis of T1D was reviewed according to the well-defined criteria of the T1D exchange clinic registry, thus minimizing misdiagnosis, however, if there were adolescents with type 2 diabetes who were not obese and were treated with insulin, they would be considered as having T1D.

Conclusion

In conclusion, the incidence of T1D in Libyan children in the West, South, and Tripoli regions of Libya appears to be rising, with a higher IR in the 0-4 and 5-9 years age groups. We have demonstrated a more than tripling of the IR over 18 years in children aged 0-14 years compared to a previous study from the Benghazi region of Libya. We need to ensure

appropriate planning of services and that resources are in place to meet the needs of increasing numbers of children with T1D.

We hope that this study will stimulate further studies to determine the true incidence of T1D in Libya and encourage healthcare professionals looking after children with diabetes to collaborate in establishing a national paediatric diabetes registry.

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Ethics

Ethics Committee Approval: The study proposal was approved by the Bioethics Committee at the Biotechnology Research Centre (ref no: BEC-BTRC 17-2019, date: 09.08.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Rowida M. Khashebi, Mostafa S. Shebani, Design: Rowida M. Khashebi, Christopher C. Patterson, Mostafa S. Shebani, Data Collection or Processing: Rowida M. Khashebi, Mostafa S. Shebani, Analysis or Interpretation: Rowida M. Khashebi, Christopher C. Patterson, Mostafa S. Shebani, Literature Search: Rowida M. Khashebi, Mostafa S. Shebani, Writing: Rowida M. Khashebi, Christopher C. Patterson, Mostafa S. Shebani.

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