Epidemiology of diabetic ketoacidosis in Arab patients with type 1 diabetes: a systematic review

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SUMMARY

Aims: Diabetic ketoacidosis (DKA) is an acute and risky complication of type 1 diabetes. The aim of this study is to build the overall rate of DKA in Arab patients with type 1 diabetes in the 22 Arab nations. This is expected to tailor the health-care approaches in Arab countries where attention is needed to save lives from the devastating consequences of DKA. Methods: The study here is a quantitative analysis of the articles indexed in four different scientific literature databases: Web of Science, PubMed, Science Direct and Scopus, from inception to June 2015. Arab patients with type 1 diabetes who presented with DKA have been captured. Key information was possible to extract for patients belong to only 12 Arab countries out of the 22 Arab patients. Results: Twenty-nine studies in 12 different Arab countries captured 4,688 type 1 diabetes patients with overall rates of 46.7% patients presented with DKA, ranging from a low of 17% in Egypt to a high of 100% in Morocco, Algeria and Tunisia. Conclusion: This is the first descriptive quantitative study to determine the overall DKA rate in 46 years of studies in the Arab world of patients with type 1 diabetes; DKA rates were found to range from 17% to 100% with overall rate of 46.7%.

Introduction

The Arab World is comprised of 22 Arab-speaking countries. According to the World Bank classification for 2015 (1), Arabs include high-income countries (HIC) such as: Bahrain, Kuwait, Oman, Saudi Arabia, Qatar and United Arab Emirates; middle-income countries (MIC) such as: Algeria, Egypt, Iraq, Jordan, Lebanon, Libya, Morocco, Palestine, Sudan, Syria and Tunisia; and low-income countries (LIC) such as: Comoros, Djibouti, Mauritania, Somalia and Yemen. They occupy a large area extended from the Atlantic Ocean in the west to the Arabian Sea in the east. The Arab population is approaching 0.5 billion, and this region has been extensively exposed to many successive invaders from Turkey, Rome, and Europe, as well as traders and immigrants contribute to mixing the ethnic demographic of the population.

Type 1 diabetes (T1D) is the most common chronic metabolic disease in children, which is responsible for 5–10% of the total cases in Diabetes worldwide (2), and is annually increasing by 3% (3). According to the Diabetes Atlas (4), more than 79,000 children developed T1D in 2013. The global annual incidence of T1D in the age group 0–14 years varies remarkably in different populations; for example, the three Scandinavian countries – Finland, Sweden, and Norway – feature the top three places in the list of countries with annual rates of 57.6, 43.1, and 32.8 per 100,000, respectively. By contrast, Venezuela has the lowest annual incidence rates (0.1/100,000) (4,5). In the Middle East and North Africa (MENA) region, mostly Arabs, it is estimated that there are around 64,000 cases of T1D in children less than 15 years old, with an annual incidence of 10,700 cases (4). Several studies reported large
variations in T1D incidence among Arab countries, ranging from a low of 2.54/100,000 in Oman (6) to a high of 29/100,000 in Saudi Arabia (7).

Type 1 diabetes is characterised by the complete deficiency of insulin, which makes patients prone to develop diabetic ketoacidosis (DKA). DKA is a metabolic imbalance which is characterised by the presence of ketosis, hyperglycaemia, metabolic acidosis and hyperketonemia, and occurs mainly in T1D patients; however, type 2 diabetes patients with metabolic decompensation could develop DKA (8).

Diabetic ketoacidosis occurs in any age of T1D patients, while it is more frequent in patients less than 19 years of age (9). According to the DIAMOND Project Group (2006) (3), 80% of T1D patients develop DKA. However, the prevalence of DKA varies widely in different countries (10). Although the mortality rates caused by DKA have been significantly decreased, DKA episodes are still the leading cause of mortality in children with T1D (11). The mortality rates range between 6% and 24% in developing countries (11,12), but it is less than 1% in developed countries (13). The objective of this study is to systematically review the frequency of DKA in Arab countries and quantitatively estimate the overall DKA prevalence among Arab patients with T1D. Moreover, other epidemiological parameters such as the incidence and prevalence of T1D, together with age, sex and consanguinity in Arab regions with different DKA prevalence, will be discussed.

Methods

Search strategy
A systematic review was conducted of all literatures published on Arab patients with T1D who presented with DKA. Four databases have been searched (PubMed, ScienceDirect, Web of Science and Scopus) from inception to June 2015 using different combinations of search terms, such as "Diabetic ketoacidosis" OR "DKA", together with the name of each Arab country, with or without the term "diabetes" or "type 1 diabetes". The search language was English; however, some information was extracted from French language article with an English abstract (n = 1). The relevant articles were screened for eligibility based on the title and abstract; eligible articles were fully screened to capture T1D patients with DKA complication.

Study selection
The study reported here have been selected according to the following criteria: (i) published as a primary research paper in a peer-reviewed journal, (ii) only the patients with T1D who manifested with DKA complication have been captured and (iii) only Arab patients residing in Arab countries were selected. Articles were excluded if: (i) study population is a mix of T1D and type 2 diabetes where it was not possible to determine the frequency of DKA in T1D, (ii) DKA frequency is solely because of type 2 diabetes or (iii) it is not clear which diabetes subtype is included in the study. As a result of the insufficient studies in Arabia, the study here captures all T1D patients without age limits; the citations were transferred to Endnote X7 and after removal of duplicates, 329 articles were assessed for inclusion or exclusions as explained above and shown in the flow diagram (Figure 1).

Data extraction and analysis
The data collected were reviewed three individual times to assure that the patients have been captured correctly and accurately. The eligible papers were fully screened and screening key words were used as follows: "type 1 diabetes" OR "IDDM" OR "Ketoacidosis" OR "T1D" OR "T1DM" OR "Keto" OR "age" OR "mean" OR "male" or "female" OR "mortality" OR "cons" or "relative" OR "family" OR "history" OR "First-cousin". The data collected here are analysed according to the relative contribution of each country to the overall prevalence of DKA in the 12 Arab countries. Other factors such as mortality, consanguinity, incidence of T1D, prevalence estimates of T1D, and male to female ratios have been also captured in all the studies reported here to make sense of the DKA prevalence rates in each Arab region (Tables 1 and 2).

Results
The search strategy identified 575 citations (Figure 1), of which 329 remained after duplicates removal, and 246 citations have been excluded because they are unrelated; the identified 329 citations are screened for inclusion eligibility as detailed in the Methods section. Of these, 38 were determined as eligible, which were fully screened, except one where information was extracted from the abstract because it was not possible to obtain the full article (14), and another article is in French language with an English abstract (15); these two articles were included in the 29 articles used for the analysis in this systematic review. The patients reviewed here are a mix of different ages: children 0–15 years old (n = 10); mix of children and young adults up to 26 years of age (n = 6); young adults and old patients up to 69 years old (n = 2); some studies include only the mean age ranging from 5.87 to 39
(n = 10), and in one study there was no age specification (n = 1) (Tables 1 and 2).

Quantitative analysis was obtained for the 29 articles as summarised in Tables 1 and 2. This search strategy used here did not find data related to the prevalence of DKA in two HIC (Bahrain and Qatar), five LIC (Comoros, Djibouti, Somalia, Mauritania and Yemen), and three MIC (Jordan, Syria and Lebanon). Additional search has been done through Google scholars and Google using the same search technique, and no relevant records have been retrieved for these countries.

In both the HIC and MIC (Tables 1 and 2), the study size is 4969 patients with T1D, of which 2469 developed DKA (49.7%); these patients were captured in 29 different individual studies surveying different areas across 12 different Arab countries (4 HIC and 8 MIC) for a period of 46 years between 1969 and 2015. In the studies reported here, the prevalence rates of DKA were estimated as a percentage of the T1D patients who presented with DKA; however, few studies (n = 4) started with screening the patients who already have DKA as a result of T1D as was reported in Libya (16,17), Saudi Arabia (18) and Sudan (19) to eliminate this bias; these four studies were excluded from calculating the overall percentage of DKA, and the final ratio now is 46.7%.

The frequency of DKA among Arabs ranges from a low of 17% in Egypt (20) to a high of 100% in Algeria (21), Morocco (22) and Tunisia (23). Saudi Arabia represents most of the T1D patients with 36.3% of the total number of patients (Figure 2) with DKA frequency ranging from 25% to 80%.
Table 1  Epidemiology of DKA among HIC patients with type 1 diabetes

| Country  | Con | Age (mean) | M:F | T1D PN | DKA PN | % DKAP | Study time  | Kind of study    | Reference          |
|----------|-----|------------|-----|--------|--------|--------|------------|-----------------|--------------------|
| Saudi Arabia | C   | (5.87)     | 0.9 | 110    | 74     | 67     | 1985–1989   | Follow-up         | Salman et al. (30) |
|           | C   | (9)        | 0.6:1.4 | 46    | 35     | 76     | 1986–1997   | Medical records   | Kulaylat et al. (29) |
|           | NC  | 0–14 (6.9) | 0.9:1.1 | 230   | 127    | 55     | 1992–2001   | Clinical          | Al-Magamsi et al. (27) |
|           | NC  | (6.7)      | 0.95:1.05 | 311   | 172    | 55     | 1992–2004   | Hospital records  | Habib (28)          |
|           | NR  | 0–14       | 0.8:1.2 | 438   | 175    | 40     | 1990–2007   | Observational     | Abduljabbar et al. (24) |
|           | C,FH| 0–14 (12.3)| 0.9/1.1 | 349   | 88     | 25     | 1993–2005   | Retrospective     | Al Rashed (25)      |
|           | C   | 0–12 (6.8) | 1.1:0.9 | 99    | 79     | 80     | 2011–2013   | Prospective       | Alanani et al. (26) |
|           | NC  | 13–18 (15.2)| 1.3:0.7 | 103   | 103    | 100*   | 2013–2014   | Cross sectional   | Al-Hayek et al. (18) |
|           | FH  | (4.75)     | 1.05:0.95 | 119  | 89     | 74     | 1980–2009   | Retrospective     | Cherian (14)       |
| Oman     | FH  | > 15       | NR   | 60    | 25     | 42     | 1990–1993   | Cohort            | Soliman et al. (38) |
| Kuwait   | FH  | 0.8–14 (6.7)| 1.1:0.9 | 135   | 42     | 31     | 2006–2013   | Retrospective     | Al-Yaarubi et al. (37) |
| UAE      | NR  | 0.8–14 (6.7)| 1.1:0.9 | 203   | 101    | 50     | 1992–1995   | Registry          | Al Khawari et al. (36) |
|          | FH  | 0–12       | 0.9:1.1 | 677   | 255    | 38     | 2000–2006   | Hospital records  | Abdul-Rasoul et al. (35) |
|          | FH  | 0–18       | 1:1   | 35    | 16     | 46     | 1990–1998   | Retrospective     | Punnose et al. (39) |

Con, consanguinity; M:F, male/female; T1D, type 1 diabetes; PN, patients’ number; DKAP, DKA patients; C, consanguineous relationship reported; NC, non-consanguineous relationship reported; NR, not reported; FH, family history. *Patients were hospitalised for DKA as a consequence of T1D.
Table 2  Epidemiology of DKA among MIC patients with type 1 diabetes

| Country  | Con    | Age (mean) | M:F  | T1D PN | DKA PN | % of DKAP | Year of study | Kind of study     | Reference          |
|----------|--------|------------|------|--------|--------|-----------|---------------|------------------|--------------------|
| Egypt    | C,FH   | 0 to > 11  | 1.05:0.95 | 416    | 252    | 61        | 2006–2007     | Retrospective     | Ismail et al. (32) |
|          | NR     | 12–18 (15.93) | 1:1  | 60     | 7      | 12        | 2006–2008     | Cross-sectional   | Salem et al. (33)  |
|          | C      | 4–20       | 0.8/1.2 | 22     | 12     | 55        | 2011–2012     | Immunogenetics    | Elaziz et al. (31) |
|          | FH     | (11.74)    | 0.8/1.2 | 40     | 18     | 45        | NR            | Clinical          | Shehata and Eltayeb (34) |
|          | FH     | (13.3)     | 0.7:1.3 | 576    | 100    | 17        | 2010–2013     | Hospital registry | Samahy et al. (20) |
| Libya    | C      | 0–19       | 1:1  | 220    | 65     | 30        | 1969–1985     | Hospital registry | Kadiki et al. (41) |
|          | NC     | 15–69 (26.5) | 0.4/1.6 | 90     | 90     | 100*      | 2008–2006     | Hospital records  | Elmehdawi and Elmagerhei (17) |
|          | NC     | (30.6)     | 1:1  | 73     | 73     | 100*      | 1995          | Follow-up clinical | Lakhdar and Elhabroush (16) |
| Tunisia  | C      | (7)        | 0.8/1 | 86     | 70*    | 81        | 1979–1989     | Hospital records  | Mongalgi et al. (15) |
|          | NFH    | (16.4)     | 1:1  | 88     | 88     | 100       | NR            | Immunogenetic     | Stayoussief et al. (23) |
| Algeria  | NFH    | 16–40      | 1.6/0.4 | 73     | 73     | 100       | NR            | Immunogenetic     | Raache et al. (21) |
| Morocco  | NFH    | < 15 to > 30 (13.1) | 125 | 125    | 100     | NR        | NR            | Immunogenetic     | Izaabel et al. (22) |
| Syria    | NR     | 11–26      | 0.8:1.2 | 69     | 18     | 26        | 2006–2012     | Medical records   | Alourfi and Homsii (42) |
| Sudan    | FH     | 0–15 (9.9) | 0.9:1 | 101    | 82     | 81        | 1977–1986     | Hospital registry | Elamin et al. (40) |
|          | NR     | (39)       | 1:1  | 15     | 15     | 100*      | NR            | Clinical          | Ahmed et al. (19) |

Con, consanguinity; M:F, male/female; T1D, type 1 diabetes; PN, patients’ number; DKAP, DKA patients; C, consanguineous relationship reported; NC, non-consanguineous relationship reported; NR, not reported; FH, family history; NFH, no family history. *Initially, the entire pool are DKA patients divided as either T1D or T2D. It is mentioned in the paper that most of patients developed DKA without specific numbers of patients, therefore at least 70 patients were captured.
Table 1) (14,24–30), followed by Egypt 23.8% of T1D patients (Figure 3), with DKA frequency ranging from 17% to 61% (Table 2) (20,31–34). The HIC represent 59.85% of T1D and 58.33% of the cumulative DKA rate among Arab countries, mostly shared by Saudi Arabia, followed by Kuwait (35,36), and little contribution of Oman (37,38) and UAE (39) (Table 1 and Figure 2). MIC countries represent 40.15% of T1D, and DKA frequency of 41.67% mostly shared by Egypt (20,31–34), followed by Tunisia (15,23), Morocco (22), Sudan (40), Algeria (21), Libya (41) and Syria (42) (Table 2 and Figure 3). Collectively for all Arab countries, excluding 281 patients from Libya, Sudan and Saudi Arabia who were surveyed initially as DKA patients as a result of having T1D (Tables 1 and 2) (16–19), the descriptive quantitative overall rate of the DKA is 46.7% among Arab patients with T1D.

Discussion

Principal findings

This systematic review provides the first comprehensive descriptive quantitative estimation of the prevalence of DKA using 25 different studies covering 12 Arab nations in a period of 46 years, starting from 1969 to 2015. DKA rates in the 12 Arab countries (4 HIC and 8 MIC) ranges from 17% to 100%, with overall DKA frequency of 46.7%. The frequency of DKA among Arabs ranges from a low of 17% in Egypt (20) to a high of 100% in Algeria (21), Morocco (22) and Tunisia (23). Saudi Arabia represents most of the T1D patients with 36.3% of the total number of patients with DKA frequency ranging from 25% to 80% (Table 1) (14,24–30), followed by Egypt with 23.8% of T1D patients and DKA frequency of 17–61% (Table 2) (20,31–34). The HIC

Figure 2 The prevalence/1000 person, the incidence/100,000 person, type 1 diabetes (T1D) patients’ ratio and the DKA patients’ ratio among Arab patients of HIC. No available data for Bahrain and Qatar for DKA rates among T1D patients.

Figure 3 The prevalence/1000 person, the incidence/100,000 person, type 1 diabetes (T1D) patients’ ratios and the DKA patients’ ratios among Arab patients of MIC. No available data for Iraq, Jordan, Palestine, Lebanon for DKA rates among T1D patients.
represent 59.85% of T1D and 58.33% of the cumulative DKA rate among Arab countries, mostly shared by Saudi Arabia, followed by Kuwait (35,36), and little contribution of Oman (37,38) and UAE (39) (Table 1 and Figure 2). MIC countries represent 40.15% of T1D, and DKA frequency of 41.67%, with the highest rate reported in Egypt and the lowest in Syria (Table 2 and Figure 3). Collectively for all Arab countries, the descriptive quantitative rate of the DKA is 46.7% among 4688 Arab patients with T1D. Saudi Arabia and Egypt contributed the most with 60.1% of T1D patients. Interestingly, Saudi Arabia and Egypt contribute to more than half of the new cases of T1D in MENA region (5).

Incidence and prevalence of T1D among Arabs

It has been reported that there are significant variations in the incidence of T1D among Arab countries. It ranges from a low in Oman (2.54/10^5/year) (38) to a high in Saudi Arabia (29/10^5/year) (7). Kuwait and Saudi Arabia are featured in the top 10 list of countries with the highest incidence rates in the world (4). The incidence of T1D is believed to be rising in the Arab world, but unfortunately there is no enough studies to understand the rising trend of diabetes; however, some extrapolation studies (43) show that here is a steady year over year rise of T1D among Arab children. These studies are based on the data derived from IDF Atlas. Although the IDF incidence estimates among Arab countries are more reliable in comparison studies, this is mainly because of the disagreement between studied population groups and applied methodologies, still might be inconsistent with individual country studies in some cases.

Although T1D is a prevalent disease in the Arab world, there is a lack of epidemiological studies to determine the actual prevalence in the 22 Arab countries, and it is challenging to separate the prevalence of the two subtypes of diabetes. However, few reports provided an estimate of the prevalence/1000 person in discrete regions of the Arab world, including Saudi Arabia (1.1) (44), Algeria (0.27) (45), Sudan (0.95) (46), Egypt (0.27) (47) and Kuwait (2.7) (48).

DKA prevalence in Arab countries

The percentage of T1D or DKA patients of each Arab country was obtained, after excluding the studies (n = 4) that start with DKA patients as a consequence of T1D (16–19), by dividing the number of patients with either T1D or T1D with DKA in each country by the total number of patients of all Arab countries for either T1D or DKA patients, respectively. Both the T1D and DKA rates were plotted against the incidence rates and prevalence estimates for the HIC (Figure 2) and MIC (Figure 3). Both the incidence and prevalence estimates of T1D are obtained from the IDF Atlas (4) and Patterson et al. (5), except for Morocco, Syria and United Arab Emirates are not published in the IDF Atlas (4), and were obtained through personal communication ID office in Brussels, Belgium (H. Zayed, unpublished manuscript).

It is not possible to statistically correlate the DKA rates with the timely and regional estimates of the prevalence and incidence of T1D in each Arab region in the studies quantified here, as the measured incidence and prevalence were estimated either in different times, regions or population groups, than the measured DKA rate populations. Therefore, the IDF estimates for the incidence and prevalence have been used, again, not to significantly correlate incidence rates and prevalence estimates with DKA rates but rather to have an idea whether the areas of high DKA rates have also higher prevalence estimates or incidence of T1D or not, to spot regions in Arabia which might need more attention for DKA screening and intervention with treatment.

The overall rates of DKA have been measured in 11 different research centres (12) and the overall rate was found to be 42%, which ranges from 26% to 67%, and showed a significant inverse correlation with the background incidence of T1D for these centres. Though it is not statistically correlated, in general, the Arab countries show higher incidence and prevalence estimates in areas where DKA rates are high (Figures 2 and 3). A study in Finland estimated the frequency of DKA, over a period of 19 years (1982–2001), found that the overall DKA incidence at diagnosis was 18.1% (49).

Among Arabs, there are dearth of studies related to the prevalence and incidence of T1D and subsequently the rates of DKA; however, the data presented here are enough to indicate not only there are geographical variations of DKA but also regional variations within each Arab country, which is more pronounced in Egypt and Saudi Arabia where more studies have been reported (Tables 1 and 2).

In the 29 studies quantified here, the mortality of T1D patients who presented with DKA was only reported in few studies (n = 4), including Kuwait (0.21%) (35), Libya, which ranges from 2% (16) to 6.6% (17), and the highest reported was in Sudan (12.9%) (40).

Age, sex and consanguinity

Most of the patients reported here are children (Tables 1 and 2), which indicate that T1D has a tendency to present with DKA in younger ages in Arab populations. This is consistent with several
studies across the globe (50–52). In most of the studies reported here, it was not possible to report the male/female ratio for patients presented with DKA; therefore, the ratios represented in Tables 1 and 2 are for T1D patients, and since the DIAMOND Project Group reported that ~80% of T1D present with DKA (3), the trend of the ratio is expected to be the same for DKA patients in the studies reported here. A male/female ratio of close to 1 has been generally assigned for T1D patients; however, there is female excess of Arab patients with T1D (Tables 1 and 2).

Consanguineous marriage is a common cultural practice in the Arab world, with extreme prevalence to the first-cousin marriage (53), which is responsible for the spread of genetic diseases in Arabia (54). In the patients’ population reported here (Tables 1 and 2), consanguineous marriage ranges from 27.3% to 67.8% (n = 9), consanguinity observed without mentioning rates (n = 2), with first-cousin marriage (n = 3), and family history was reported without mentioning consanguinity (n = 8), other studies with no consanguinity (n = 3), and consanguinity not reported (n = 5). Interestingly, a Kuwaiti study (35) demonstrated that the frequency of DKA is less among T1D patients who are first degree relatives, compared with patients with no family history, similar to what have been observed among Finish patients with T1D who presented with DKA (49). Remarkably, the DKA children with parents with higher education are 12-fold less likely to present with DKA even they live in high incidence areas (10,55).

**Limitation**

The limitation of this study include: (i) the dearth of studies related to patients with T1D and in particular the complications of T1D, (ii) the language of search was English, though one study published in French language (with English language abstract) is included in this analysis, there are several not able to be included as the abstracts were not enough to capture sufficient information, (iii) the variations of studies among different countries, make it difficult to follow a general trend of the prevalence of DKA among Arab countries, (iv) most of the DKA patients captured were mainly from medical records, which are subject to recording bias, (v) the large number of ‘guest workers’ from different Arab countries and Asia in the Gulf region and Libya, and (vi) most of the patients reported here are mainly from hospital records with no controls, therefore it was not possible to conduct meta-analysis.

**Looking forward**

Diabetic ketoacidosis is an emergency health condition that can be lethal if not treated appropriately, which frequently happens in patients with T1D. Treatment of DKA is a significant financial burden on families and governments (56); however, if it is detected in the right time it can be efficiently treated. DKA may show significant variations because of variable socioeconomic status, demographic variables, and educational level and income of the patients’ families (57), and its rates are significantly less when there is a greater awareness about DKA (58). In this regard, developing awareness programmes within the healthcare sectors in Arab governments, which aim to spread awareness related to T1D and its complications, is crucial in recognising the DKA early in childhood, which will enable the appropriate intervention strategies to determine the right therapeutic window for treatment of DKA patients, in order to avoid loss of lives. This is expecting to save lives and significantly impact on healthcare costs and resource planning.

**Conclusion**

Diabetic ketoacidosis is a prevalent acute complication of T1D in the Arab world; it is more common among Arab children with noticeable excess in females than in males. Areas where incidence and prevalence of T1D in Arab countries have increased rates of DKA. Consanguinity and family history of DKA is prevalent among Arab patients with T1D presenting with DKA. The finding of this study suggests more screening programmes among Arab patients with diabetes to provide secondary care of diabetic patients with DKA and alerts healthcare providers and clinicians for the spread of DKA among children with T1D.

Although the T1D and its complications are responsible for many lives in Arabia, there is no Arab centralised database which is in charge with registering family history of patients, including clinical, genetics and disease-associated complications. Therefore, the idea of building a nation-wide Arab registry for patients with diabetes, which able to separate the regional frequency of both subtypes of diabetes (T1D and type 2 diabetes), will enrich the epidemiological efforts for more studies to customise the healthcare and awareness programs to target the areas in need. This is expected to save lives worldwide now and in the future.
The rising incidence of type 1 diabetes mellitus and type 1 diabetes mellitus.

The role of environmental factors in the pathogenesis of type 1 diabetes mellitus.

The clinical presentation of type 1 diabetes mellitus:

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