Epidemiology of type I diabetes mellitus among Arab children

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ABSTRACT

In this article, the epidemiology of type 1 diabetes mellitus among Arab children (<15 years) living in Arab and non-Arab countries is reviewed. These data include the incidence, prevalence and etiopathogenic factors including genetics, environmental factors as well as autoimmune disease markers aside from clinical presentation at onset. The review is based on the information from publications in the international literature identified by searching Medline, other websites as well as personal experience and some communications. The obtained data suggest that the incidence of type 1 diabetes in these countries is increasing similar to the experience in other parts of the world. High incidence has been reported among Arab children who immigrated to some Western countries. The highest incidence is in Qatar and Kuwait and the lowest is in Oman and Jordan. There is considerable variation among countries, which could not be explained on genetic or climatic variations alone. Other environmental factors particularly nutritional ones including high intake of dairy products and vitamin D deficiency are possibly operating. Further, nationwide research from different countries covering the rural as well as urban areas and different ethnic intermixes are needed. To overcome financial and facility problems that hinder research; some cooperation between these countries as well as international bodies are needed.

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The World Health Organization (WHO) defines diabetes mellitus (DM) as a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both.[1] It is now one of the most common non-communicable diseases globally. It is the fourth or fifth leading cause of death in most developed countries.[1,2] Complications from diabetes such as coronary artery and peripheral vascular disease, stroke, nephropathy, neuropathy, amputations and blindness are resulting in increasing disability, reduced life expectancy and enormous health cost for most societies.[2] Current studies have shown a definite global increase on incidence and prevalence of diabetes with WHO projecting to have almost 221 million cases in the year 2010 and up to 285 million cases in the year 2025.[2] Though this increase is mainly expected to be in type 2 diabetes, a parallel increase in childhood diabetes including type 1 and 2 have been reported.[3] The WHO Diabetes Mondial (WHO DIAMOND) reported data on type 1 diabetes have shown a worldwide increase incidence and variation (over 400-fold) with the highest occurring in Finland (over 45 per 100,000 under the age of 15 years) and the lowest in parts of China and Fiji,[4] North-South as well as racial and population variations were reported. It is said to be more common in Caucasians than Asian and Negroid races.[4] Therefore, both genetic and environmental factors, were incriminated to explain these variations.[4,5] The epidemiology of type 1 diabetes in Arabs was only reviewed in 1990.[6] In that review, the author, could only cite 3 articles,[7-9] addressing this problem. Thereafter, many papers

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were published. In this article, I am trying to review and update the epidemiology of type 1 diabetes among Arab children living in Arab and non-Arab countries.

Arab countries. Arab countries are those 22 countries that belong to the Arab league including Algeria, Bahrain, Comoro Islands, Djibouti, Egypt, Iraq, Jordan, Kuwait, Lebanon, Libya, Mauritania, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, United Arab Emirates and Yemen. These countries stretch some 5000 miles from the Atlantic coast of North Africa in the west to the Arabian sea and Indian ocean in the east and from the borders of Turkey in the north to Equational Africa in the south covering an area of 5.25 million square miles.[6]

In these countries, the climate, varies markedly (desert, tropical, subtropical and Mediterranean), both from one country to another and in different areas of the same country; for example, Sudan where the temperature can vary from 45-26^{0}C in summer and can go down to 0^{0}C in the Northern Sudan in winter. North African countries have the typical Mediterranean climate whereas in Gulf countries the temperature can vary from over 50^{0}C in summer to below zero in cool winter.[6] The population of Arab nations was approximately 253 million in 1994 and is expected to have reached more than 280 million in 2000. Most of the Arab population live in coastal areas and major river valleys, in cities or villages for example in Egypt and others are scattered in the desert (the nomadic tribes). Therefore, Arabs live under different climatic conditions. Arabs are semitic people who originated in the Arabian Peninsula. After the rise of Islam in 622 AD, Arabs moved into different parts of the world and mainly settled in what are now called the Arab countries. In these places, they got mixed up with other races; such as Barbers and Negroid races in Africa and Kurds, Turks, Armenians, Persians, and Indians in Asia. Currently the term Arabs is mostly used for population of the Arab countries whose main language is Arabic and have been mostly affected by Arab culture and Islamic religion and to less extent Christianity and atheism.

The Arab countries vary in their socioeconomic states; for example, very rich countries in the Gulf and poor ones in Africa. The annual per capita l income ranges from 100-29,000 US dollars. This is associated with change in lifestyle and eating habits. The lifestyle also varies considerably in Arab countries from nomadic, semi-nomadic to urban. All these facts are of importance in studying and understanding the interaction between environmental and genetic factors that predispose to type 1 diabetes in these countries.

Incidence data. The current incidence rates and grades as per WHO DIAMOND study classification[4] are shown in **Table 1**. All incidences rates are reported as per 100,000 population of children <15 years old.

Saudi Arabia. In a hospital-based study, between 1980-1982, from Aramco Oil Company Community in Eastern Saudi Arabia the incidence in children <15 years was reported to be 7.[8] In the same community, this figure increased to a mean of 12.3 in the period between 86-97 with a peak age of 10-14 years, male to female ratio of 1:1.5 and no seasonal variation was observed.[10] However, it is the current impression of the local pediatricians that the incidence is perhaps higher as reflected by increase in numbers of patients in the clinics. Over 6 years period, from 1983-1989, approximately 80 patients registered in one clinic at the University Hospital compared to a figure of 500 patients from 1990 up-to-date at the Security Forces Hospital, Riyadh. Moreover, there are some worrying unpublished data from Aramco Hospital to suggest that the incidence might be over 30 (personal communication with Dr. M. A. Jabar). I hope a definite answer will come soon when the data of the National Diabetes Registry are published.

Sultanate of Oman. In a whole country, population-based-prospective study, between 1993 to 1994, covering 0-14 year-old-age group, the incidence was found to be 2.45-2.62, with peak among the 10-14-year age group, male to female ratio of 1.5:1 and most cases were reported during winter season.[11] This figure is one of the lowest reported from the Arab countries.

Kuwait. The first publication from Kuwait showed that the mean incidence among the 0-14 years aged group was 3-96 in 1981-1982.[7] Ten years later, the incidence increased to 15.4 with 4-fold increase among <5 years.[12] Recently, a figure of 20.9 was reported in a nationwide prospective study.[13] It was slightly higher in males, some peak was noticed in the 5-9 years age group with more cases in the cooler months (September to March).[13] Therefore, a significant rise in incidence in Kuwait giving one of the highest figures published from the Arab countries so far.

Jordan. In study conducted by the Jordanian National Center for Diabetes, Endocrine and Genetics diseases among the 0-14 year age group, between 1992-1996, the incidence rates for these years were 2.8, 2.9, 3.2, 3.6, and 3.6.[14] The male to female ratio was 1:1.03, maximum cases were reported in winter months and in the 10-14 year age group. This figure is one of the lowest in the region and is rather similar to the neighboring Arabs who live in Israel.[15]

Egypt. In a review article, the incidence in children <15 years was reported as 8.3 and 7.6 in the urban and rural areas.[16] The most common age of onset was between 12 and 14 years.[16]

Libya. In a prospective study from Benghazi city, the mean annual incidence between 1981-1990, was 7 (6-8.2) in the 0-14 years old with no significant difference between males and females or between seasons of onset.[17] This figure increased to 8.3 between 1999-2000 with females being higher than males and more cases had an onset in cooler months.[18] This figure was said to be similar to those reported from most of the non-Arab Mediterranean countries.[18]

Tunisia. As part of the WHO DIAMOND project conducted in Tunisia between 1990-1995, the incidence rates, were 6.76 and 6.95 in the 0-14 and 0-19 year age groups. Two peaks were seen at 0-14 and 10-14 year age groups, with no gender difference and 62% had an onset in winter.[19] These figures were said to be close to those observed in most Mediterranean countries.[19]

Algeria. In a retrospective study carried out in children <15 years in Oran area, between 1979 and 1988, the mean incidence rate was 4.4 with an increased from 1.6 in 1981 to 8.1 in 1988.[20] Therefore, there was a regular increase over years.

Sudan. In a prospective hospital-based registry in Khartoum City between 1987 and 1990, the incidence of type 1 diabetes in Sudanese children <15 years increased from 5.9 in 1987 to 10.1 in 1990[21] with a mean annual incidence rate of 7.9. Girls were slightly but not significantly more affected than boys, 2 peaks of age of onset at 7 and 12-14 years were noted with more cases having onset in cooler months. The figure from Khartoum is higher than a figure of 5 that was reported in 1990 from Medina (Gezera region), 200 kilometers South of Khartoum.[4] Later, in another study from Khartoum between 1991 and 1995, the mean annual incidence rate, increased to 10.1. The peak age of onset was 10-14 years and 3.5% of the cases were <5 years.[22]

Other countries. According to International Diabetes Federation (IDF) atlas,[23] the reported incidence rates from Bahrain was 5, Lebanon 5, Morocco 7, Qatar 5 and Syria 5. However, current incidence data are possibly higher and in a recent presentation at the Pan Arab conference in Riyadh, the incidence in Qatar was said to have increased in 2003 to 22.2/100,000.[24] Therefore, there is no doubt that similar or higher figures will soon be reported from Bahrain and many other rich Gulf countries.

Prevalence. Studies on prevalence from Arab countries are scanty and are summarized in **Table 2**. Estimated prevalence as published by IDF[23] are shown in **Table 3**. There are estimated to be approximately 173.7 thousands patients with type 1 diabetes. If we assume that almost 12% of these would be under 15 as suggested by Green[25] for Middle East countries, then currently there are approximately 22,500 children <15 years with type 1 diabetes in Arab countries and this figure is

Table 1 - Incidence of type 1 diabetes in Arab countries as per DIAMOND study classification.

Incidence*	Arab countries
Very low (<1)	-
Low (1-4.99)	Oman, Jordan, Palestine
Intermediate (5-9.99)	Egypt, Libya, Tunisia, Morocco, Algeria, Bahrain, Lebanon,Syria
High (10-19.99)	Saudi Arabia, Sudan
Very high (≥20)	Kuwait, Qatar
No data from Somalia, Djibouti, Comoros, Mauritania, Iraq, Yemen, United Arab Emirates	

Table 2 - Studies on prevalence of type 1 diabetes in children <15 years.

Country	Reference	Year	N of type 1 diabetes x 1000
Algeria	20	1988	0.27
Sudan	9	1989	0.95
Saudi Arabia	6	1980-1982	0.2
Egypt	15	1988	0.01-0.14
Libya (Benghazi)	17	1981-1990	0.24
Libya (Benghazi)	18	1991-2000	0.37

Table 3 - Estimated prevalence of type 1 diabetes mellitus in Arab countries (in thousands).

Countries	1995	2000	2010
Saudi Arabia	6.8	10.9	18.2
Yemen	0.7	2	4.1
Oman	0.9	1.5	2.7
United Arab Emirates	1.2	1.5	1.8
Qatar	0.3	0.4	0.5
Bahrain	0.4	0.5	0.7
Kuwait	8.5	9.2	9.7
Egypt	21.5	36.4	53.5
Libya	3.4	9.1	18.9
Tunisia	6.7	9.5	12.6
Algeria	18.9	27.3	38.6
Morocco	8.9	15.2	21.2
Mauritania	-	-	no data
Sudan	2.2	5.1	9.3
Somalia	0.1	0.1	0.2
Gaza strip	0.8	1.3	2.3
Jordan	4.8	8.8	15.3
Lebanon	2.2	2.3	2.3
Syria	12.9	18.4	26.9
Iraq	7.8	14.2	24.7
Total	**109**	**173.7**	**263.4**

expected to increase to 34000 in the year 2010. Based on total population numbers, most of these cases will be in the non-rich Arab countries particularly those in Africa, though the incidence data are higher in the richer ones.

Childhood diabetes among Arabs living in non-Arab countries. Earlier reports from France showed that the incidence of the disease in the Maghrebi population was high (10.2 per 100,000 per year) compared to a figure of 7.8 in the local population.[26] In Netherlands, the incidence for Moroccan children was 20 compared to figures of Dutch (13.2), Turkish (4.5) and Polynesian children (2); namely 1.5, 4.5 and 10 times higher than these populations.[27] This high incidence among migrant Arabs compared to their original homes is similar to the experience among other migrant ethnic groups.[28] In Israel, the incidence of type 1 diabetes among Arabs was initially reported as 1.2/100,000 and this low figure was thought to be due to missing of high proportion of Arab patients who seek treatment at Arab hospitals in Israel and in neighboring countries.[29] However, in further prospective studies, Arab children maintained comparatively lower incidence of diabetes ranging from 2.3-3.6 whereas Ashkenazi Jews had incidence of 6.3 in 1980-1984 to 10 in 1990-1993 but the highest incidence was seen among the Yemenite Jews which increased from 9.1 in 1980 to 18.5 between 1990-1993.[30,31] It is interesting that the incidence among Arabs living in Israel is similar to the neighboring Jordanians.[14] This low figure among Arabs who live in the same climatic environment could be related to genetic or other environmental factors.[30,31] It is also interesting to see that Arabs living in the same latitude in Kuwait are having the highest incidence, and those living in Jordan and Israel are having the lowest incidence in the Arab world. This, in my opinion, further supports the role of non-temperature related environmental factors as similar to the observation among the Sardinians who have a high incidence compared to the neighboring areas.[4]

Etiopathogenesis. The exact etiology of type 1 diabetes is unknown. However, it is suggested that it develops in individuals who are genetically susceptible, who come in contact with certain environmental factors, which trigger immune mediated destruction of the ß-cell mass. The interplay between genetics, environmental triggers and immunological response involve a balance between susceptibility and protective factors in each category.[32,33]

How do these facts apply to Arab countries. Genetic studies. Some of the genetic studies published before 1990 were reviewed elsewhere.[6] At that time it was felt that the prevalence of human leukocyte (HLA) (DRB8 and DRB15) antigens that were associated with type 1 diabetes in Arab countries appeared to be heterogeneous and different from that of European populations.[6] Thereafter, some papers, mostly with a limited number of cases, were published from Algeria,[34-36] Tunisia,[37] Sudan,[38] Morocco,[39] Kuwait,[40,41] Egypt;[42] and Saudi Arabia.[43] Most of these studies have shown that the predominant genotypes are the DQA1 (Arg 52+) and DQB1 (Asp 57-) ones as reported from other parts of the world.[32,33] However, variable predisposing and protective haplotypes[34-43] were reported from different countries and this could be attributed to different racial mix-ups that happened to Arabs in different part of the world for example in Algerian Arab and Berber mix-up community the haplotypes were thought to be as a mixture of those reported from sub-Saharan Africa and South Europe.[34-36] Certainly, further work with larger numbers of cases is needed from the Arab countries, taking into consideration the different ethnic mix-up communities.

Immune markers among Arab children. In most children with diabetes, the classification of the type of diabetes is based on clinical grounds.[1,2] Almost 95% of cases of type 1 diabetes are immune mediated, but in 5% of cases no antibodies are detected and thus called idiopathic.[1] The later form is said to be more common among the black community in the United States.[2] It would have been very interesting to see how common is this variant among Arabs. Perhaps due to its limitations of facilities, there are very few publications on antibody studies from Arab countries. In Saudi Arabia, 56% of the newly diagnosed diabetic children were reported to be positive for islet cell antibodies.[44] However, in a recent work carried out by Dr. Awadallah from King Saud University, Riyadh (personal communication) 84% of the newly diagnosed children were positive for Glutamic Acid Decarboxylase (GAD) antibodies and almost 96% were positive for either of insulin auto-antibodies (IAA), protein tyrosine phosphatase antibodies (IA2) or GAD antibodies when carried out together. Prevalence of antibodies to GAD in newly diagnosed Syrian, and Jordanian cases were 88.8%.[45] These figures are said to be similar to data published from Finland and other countries.[46]

Environmental factors. The variability in incidence of type 1 diabetes in different countries as well as the rising incidence in many parts of the world, have raised questions about changes in environmental risk factors that may either initiate or accelerate the autoimmune process leading to pancreatic ß-cell destruction. This point was well reviewed elsewhere.[3,4] As discussed earlier currently published data from Arab countries have shown variation among countries with high incidence in countries such as Kuwait,[13] Saudi Arabia,[10] Qatar,[24] and low incidence in countries such as Oman[11] and Jordan.[14] This variation cannot solely be explained on genetic basis alone if we assume that Arabs have

the same genetic background. Practically most Gulf countries have the same temperature, yet there is an incidence variation. Kuwait, a country with a high incidence rate falls in the same latitude with Jordan and Palestine where the incidence is considered to be low.[14, 29-31] Therefore, this variation cannot be solely due to climatic reasons. The incidence of type 1 diabetes seems to be higher in Arab countries with high per capital income such as Kuwait and Saudi Arabia, and thus, change in dietary habits and lifestyle could be playing a role. This subject was recently well reviewed elsewhere.[47] Energy of animal source including meat and dairy products and that of vegetal origin were positively and negatively associated with incidence of type 1 diabetes.[47] In another study, markers of wealth and affluence, were significantly associated with high incidence of type 1 diabetes and acute lympho-blastic leukemia.[48] The possible association of type 1 diabetes and consumption of cow's milk were reviewed elsewhere.[5] The incidence of type 1 diabetes seems to be higher in Arab countries with low breast feeding rate such as Kuwait[49] and Libya compared to those with relatively higher breast feeding rate such as Oman.[50,51] Until a definite answer to this question is settled people, should continue promoting breast feeding in these countries.

Many studies have recently been published on the possible role of vitamin D deficiency in etiopatho-genesis of type 1 diabetes.[52-57] Vitamin D deficiency is a common problem in many Gulf countries both among children,[58] adolescents,[59] as well as pregnant women.[60] It has also been reported from non-Gulf countries such as Jordan.[61] We wonder if vitamin D deficiency is playing some role in the increase in incidence of type 1 diabetes in this area. Further research in this subject should be encouraged.

The issue of association of high nitrite intake and etiopathogenesis of type 1 diabetes has been discussed elsewhere.[5] As nitrites are mainly found in water, food and meat industry as well as in fertilizers and pesticides, we wonder if the high incidence in rich Arab countries could be related to the high consumption of preserved meat as well as of vegetables grown with the use of fertilizers rather than naturally grown products. The possible role of infections in etiopathogenesis of type 1 diabetes is reviewed elsewhere.[5,32,50] The issue of clustering of birth time of diabetic children was recently reviewed[62,63] supporting the hypothesis that viral infections possible play a role. No such data were published from the Arab countries. However in one study from Israel a significant different seasonal pattern was noticed between Arab (low incidence) and Jewish (high incidence) population living in the same country.[29,31] It was suggested that a possible protective (immune and/or genetic) mechanism might exist among Arabs.[29,31] Further research in this area from Arab countries is needed.

Aside from infections, many articles were recently published linking clustering of cases of type 1 diabetes with vaccination including measle-mumps-rubella, pertussis and influenza vaccines.[64] It is thus tempting to suggest that the increase in incidence in some Arab countries could be related to increase in vaccination coverage particularly in the rich ones. However, a recent work from Europe showed convincing evidence that there is no causal relationship between childhood vaccination and type 1 diabetes.[65]

Clinical presentation. The incidence of diabetic ketoacidosis at onset among children in Arab countries varies from 10-80%.[22,66-71] Figures reported from Western countries varied from 15-68%.[72] The high incidence in some Arab countries was attributed to the lack of awareness by families or misdiagnosis particularly in infants and young children where some cases are misdiagnosed as gastroenteritis due to the high prevalence of diarrheal diseases in some of these countries.[66] The best way to overcome this is through health education for both primary care physicians and families.

In conclusion, these data suggest that the incidence of type 1 diabetes in children in Arab countries is rising similar to other parts of the world. However, there is considerable variation among different countries which could not be explained on genetic basis or temperature variation alone. We suggest that in addition to infections, other environmental factors particularly change in nutritional habits, including high meat, consumption, vitamin D deficiency, low breast- feeding and high intake of nitrites might be playing a role as the highest incidence is mainly seen among rich countries. However, most of the data published so far were the hospital based and from major cities and urban areas in addition, many publications, were made a decade ago. Further, nationwide studies including from rural areas and from different ethnic groups in the same countries are needed. In many countries; however, lack of facilities and financial support tends to hinder research. To overcome this collaboration between well-to-do and poor countries as well as international bodies is needed.

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