Maternal and neonatal risk factors associated with Type 1 Diabetes Mellitus among Children in Zawia province

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Abstract

Objectives:

It is becoming increasingly well-recognized that the intrauterine and neonatal environment are influential in determining future patterns of disease , and evidence is accruing in relation to childhood diabetes.

A case-control study was carried out to determine the potential maternal, neonatal and early childhood risk factors for type 1 diabetes mellitus among children in Zawia province.

Methods:

This case control study was carried out in pediatric department, Zawia teaching hospital over the period from the 1st January 2003 to the end of December 2009. Data of 96 cases with type 1 diabetes mellitus who have been admitted to the department, aged 1-15 years were matched with 299 non –diabetic children with the same age range.

Results:

Maternal habits and illnesses during pregnancy, is a risk factor for type 1 diabetes mellitus in their offspring, ($p<0.05$). In addition, maternal pre-eclampsia and infections were found to be significant risk factor for type 1 diabetes mellitus, ($p<0.001$). Neonatal infections, eczema and rhinitis during infancy were also significantly associated with development of type 1 diabetes mellitus. Moreover, the results revealed that duration of <6 months breast feeding is an important trigger of type 1 diabetes mellitus.

Conclusion:

Exposure to environmental risk factors during pregnancy (drugs, coffee soft drinks, pre-eclampsia, and infectious diseases), neonatal period (respiratory distress, jaundice, cow milk feeding and infections) and early infancy are thought to play an important role in triggering the immune process leading to B-cell destruction and the development of type 1 diabetes mellitus.

Keywords:

Type 1 Diabetes Mellitus (T1DM); Children; Risk factors; Maternal ; Neonate.

Introduction:

Type 1 diabetes is perceived as a chronic immune-mediated disease with a subclinical prodromal period characterized by selective loss of insulin-producing β-cells in the pancreatic islets in genetically susceptible subjects, the major genetic contribution coming from loci within the HLA complex, in particular HLA class II.[1]

A series of evidence supports a critical role of exogenous factors in the development of type 1 diabetes, such as 1) the fact that <10% of individuals with HLA-conferred diabetes susceptibility do progress to clinical disease, 2) a pair wise concordance of type 1 diabetes of <40% among monozygotic twins, 3) a more than 10-fold difference in the disease incidence among Caucasians living in Europe, 4) a several-fold increase in the incidence over the last 50 years, and 5) migration studies indicating that the disease incidence has increased in population groups who have moved from a low-incidence to a high-incidence region.

The etiology of type 1 diabetes is uncertain,[2] environmental triggers such as certain dietary factors and viruses are thought to initiate the autoimmune process, leading to the destruction of pancreatic B-cell and consequent T1DM. A genetic predisposition is another pre-requisite, allowing the autoimmune process to progress.[3]

Environmental factors playing a role in the pathogenesis of T1DM may differ substantially from population to population. More specifically, disease incidence in one geographical area may differ from another because

of different exposures to a given risk factor or because of difference between population genetic susceptibilities to that risk factor.[4]

Many investigators have focused on the relationship between maternal and neonatal factors and the subsequent risk of type 1 diabetes. However, the evidence on the role of many maternal and neonatal factors in the development of childhood type 1 diabetes is inconclusive. Several studies have reported a significant increased risk of type 1 diabetes with increasing maternal age[5-7], while others have reported no association [8-9].

A recently published meta-analysis demonstrated an increase in the risk of childhood type 1 diabetes after Caesarean section delivery [10].

Disproportionate maternal influences on the risk of T1DM suggests that critical disease-inducing environmental events operate very early, even in the utero. A number of maternal-related events are associated with an increased disease risk in children but not in adults.[11]

The aim of this case- control study was to investigate the relationship between several maternal and neonatal factors and the risk of type 1 diabetes in children under 15 years in Zawia province .

Methods:

A case-control study carried out on children with T1DM and non-diabetic children over the period from the 1st January 2003to the end of December 2009.

Children with T1DM who have been admitted to pediatric ward at Zawia Teaching Hospital were recruited for this study. A total of 96 diabetic patients, (age range: 1 - 15 years) were included in the study. Sample size was determined by the availability of patients and time span of the study.

The control group included 299 non-diabetic children and adolescents who were randomly selected from children consulting the pediatric outpatient department of Zawia Teaching Hospital for minor illnesses or accompanying their parents during the visit were included in the study, their age ranged from 1 - 15 years. The cases and controls were all Libyans.

A special questionnaire was designed for the purpose of the study. The following information were taken; name, age, sex, age at diagnosis (for diabetic patients only), family history of DM: T1DM or type 2 diabetes (T2DM), family history of other autoimmune diseases (celiac disease, thyroid disease, vitiligo) in the first and second degree relatives. Maternal factors included; maternal habits (coffee, soft drinks) , while maternal diseases included pre-eclampsia, gestational diabetes , autoimmune diseases, and infectious diseases (e.g., fever, diarrhea, skin rash, etc). In addition, history of drug ingestion during pregnancy was assessed, including the use of antibiotics, analgesics, antihypertensive, anti-emetic, steroidal and non-steroidal anti-inflammatory drugs, anti-epileptic drugs, and insulin for diabetes. Soft drink quantification was done on 2 stages; a) whether they drink cola, merinda, 7up or Pepsi or not, and b) if they drink it, how many cans/day roughly.

Potential neonatal risk factors included, mode of delivery (vaginal delivery, assisted or cesarean section), birth weight and gestational age at birth (pre-term or full term). In addition, diseases during neonatal period were recorded including; respiratory distress syndrome, jaundice, and infections.

History of infectious diseases during early childhood; rubella, measles, varicella, pertussis, mumps, autoimmune diseases like celiac

disease, in addition to history of rhinitis and asthma were also recorded. Data regarding possible risk factors in early infancy were also assessed, such as conjunctivitis and eczema for all children recruited in the study.

The questionnaire also included the type of feeding in first 6 months of life (breast feeding, formula milk feeding) and its duration and introduction of weaning food .

Informed consent was obtained from one or both parents and/older children and adolescents, for recruitment in the study.

Statistical analysis was done using SPSS program, data were expressed and comparisons of proportions was performed using chi square, $p<0.05$ was considered as statistically significant.

Results:

Table A total of 96 children were diagnosed with type 1 diabetes between the 1st January 2003 to the end of December 2009 in Zawia and 299 non-diabetic children were included in this study. Among the 96 patients, 63 (65.6%) were female and 33 (34.4 %) males. There were 10 children diagnosed with type 1 diabetes under 5 years of age (early onset) and 86 diagnosed between 6 and 18 years of age (later onset). There is no statistically significant difference concerning the age and sex distribution between diabetic patients and control group ($p>0.05$). (Table 1)

Table 1—Age and sex distribution of cases and control included in the analysis

Age range (years)	cases **No. (%)**	control **No. (%)**
1-5	10 (10.4)	31(10.3)
6-9	39 (40.7)	108 (35.4)
10-15	47 (48.9)	160(40.4)

Sex		
Male	33 (34.4)	99 (33.2)
Female	63 (65.6)	200 (66.8)
Total	**96**	**299**

When considering potential risk factors during pregnancy, a significantly higher number of mothers in the control group had no particular dietary habits, no specific maternal diseases or medications intake during pregnancy. Drinking coffee and soft drink was reported in a significantly higher number of mothers of diabetic children compared to mothers in the control group. The mothers of 11 cases (11.5) had gestational diabetes compared to only 5 (1.7) of control (Table 2)

Table 2.Potential risk factors during pregnancy of the index child

Risk factor	Cases No. (%)	Control No. (%)	**p value**
Maternal habits			
No	10 (10.4)	105 (35.2)	
Coffee	2 (2.1)	7 (2.3)	<0.001
Soft drinks	84 (87.5)	187 (62.5)	
Maternal diseases			
No	54 (56.2)	256 (85.3)	
Pre-eclampsia	17 (17.7)	20 (7.0)	
Gest. Diabetes	11 (11.5)	5 (1.7)	<0.001
Infectious diseases	14 (14.6)	18 (6.0)	

Maternal drugs			
No	48 (50.0)	208 (69.6)	<0.01
Antibiotics	9 (9.4)	20 (6.7)	
Analgesics	5 (5.2)	13 (4.3)	
Antihypertensive	13 (13.5)	4 (1.3)	
Anti-emetic	18 (18.8)	49 (16.4)	
Anti-epileptic	0 0	2 (0.7)	
Insulin	3 (3.1)	3 (1.0)	

Potential neonatal risk factors that were assessed included mode and place of delivery (Normal vaginal delivery, assisted delivery, cesarean section) and neonatal diseases including (respiratory distress, jaundice and infection), as shown in Table 3.

A significantly higher number of cases were delivered by cesarean section ($p<0.01$). For neonatal diseases, a significantly higher number of children in the control group (66.6%) had no history of neonatal diseases, compared with diabetic children who had a statistically significant association of respiratory distress, jaundice and infectious diseases, ($p<0.01$).

There was no statistically significant difference regarding gestational age and birth weight at birth between the patients and the control group.

Table 3: Neonatal risk factors

Risk factor	**Cases** **No. (%)**	**Control** **No. (%)**	**p value**
Place and mode of delivery NVD	64 (66.7)	170 (56.9)	<0.01

Assisted	17 (17.7)	116 (38.8)	
C/S	15 (15.6)	13 (4.3)	
Neonatal diseases			
Negative	34 (35.4)	199 (66.6)	<0.01
Respiratory	22 (22.9)	18 (6.0)	
diseases	29 (30.2)	80 (26.8)	
Jaundice	11 (11.5)	2 (0.7)	
Infection			

NVD: Normal Vaginal Delivery

C/S: cesarean section

Potential environmental factors that have occurred during early life including infectious diseases and other diseases were also assessed, (Table 4).

This table demonstrates that a significantly higher number of children in the control group (86.3%) have no history of infectious diseases in comparison with diabetic patients. Measles, varicella, pertussis and mumps were reported in a significantly higher number of diabetic patients compared to control group. None of children in both groups gave a history suggestive of rubella. Two patients presented with celiac disease in first year of life and diabetes before 5 years of age.

Table 4: Environmental factors during early life among patients and controls

Risk factor	**Cases** **No. (%)**	**Control** **No. (%)**	**p value**
Infections			
Negative	53 (55.21)	258 (86.3)	<0.01
Measles	18 (18.75)	14 (4.7)	
Varicella	13 (13.54)	21 (7)	
Pertussis	10 (10.41)	2 (0.7)	

Mumps	2 (2.1)	4 (1.3)	
Diseases Negative Celiac disease Rhinitis Conjunctivitis Asthma Eczema	 48 (50) 2 (2.1) 25 (26) 6 (6.3) 7 (7.3) 8 (8.3)	 244 (81.7) 1 (0.3) 26 (8.7) 9 (3) 9 (3) 10 (3.3)	 <0.01

Most of the children in the control group (91.3%) were exclusively breast fed for more than 6 months compared to the diabetic children (57.3%), the difference was statistically significant, ($p<0.01$). Introduction of weaning foods before the age of 6 months was significantly higher among diabetic patients compared to the control group, ($p<0.01$). (Table 5)

Table 5: Nutritional risk factors among cases and controls

Feeding pattern	**Cases** **No. (%)**	**Control** **No. (%)**	**p value**
Duration of Breast feeding <6 months >6 months	 41(42.7) 55 (57.3)	 2 6(8.7) 273 (91.3)	 <0.01
Time of introduction of weaning foods	61 (63.5)	120 (40.2)	<0.01

<6 months >6 months	35 (36.5)	179 (59.8)	
Total	**96 (100)**	**299 (100)**	

All children included in the study were assessed in terms of family history of T1DM, T2DM and family history of other autoimmune diseases like celiac disease, thyroid disease, and vitiligo, the results are presented in Table 6. It was found that diabetic patients have a statistically significant positive family history of T1DM, or both T1DM and T2DM. However, a positive family history of T2DM was reported in a significantly higher number of children in the control group.

Table 6 Family history of autoimmune diseases among patients and controls

Family history of autoimmune diseases	**Cases** **No. (%)**	**Control** **No. (%)**	**p value**
Family history of DM Negative T1DM T2DM T1DM + T2DM	 40 (41.7) 26 (27.1) 20 (20.8) 10 (10.4)	 189 (63.2) 3 (1.0) 107 (35.8) 0 0	 <0.01
Family history of other autoimmune diseases Negative Celiac disease Thyroid disease Vitiligo	 71 (74.0) 9 (9.4) 15 (15.6) 1 (1.0)	 273 (91.2) 5(1.7) 10 (3.4) 11 (3.7)	 <0.01

Total	96	**299**	

Discussion:

This case-control study is the first study describing the risk factors for T1DM among children in Zawia.

Maternal habits (drinking coffee and soft drink) during pregnancy was significantly associated with T1DM, a similar result was reported by Visalli et al. in Italy.[4] Among maternal diseases, this study showed a significant correlation of T1DM with maternal pre-eclampsia, and infections among mothers of diabetic patients, similar results were found by Dahlquist et al. in a study which included 7 centers in Europe,[13] and Stene et al. in Denver.[14] Algert et al. reported that pre-eclampsia was significantly associated with childhood diabetes, but only among children diagnosed before 5 years of age.[15] Complications during pregnancy have been related to affect the fetal immune system, although the mechanisms are not known. Maternal diabetes either pre-gestational or gestational, is associated with an increased risk of a number of pregnancy related complications.[14] In contrast, studies in Norway and Scotland have concluded that maternal pre-eclampsia, perinatal infections and cesarean section were not significantly associated with the incidence of T1DM in children.[16,22]

Maternal infection during pregnancy are among the important environmental triggers of T1DM, a similar result was reported by Dahlquist et al. in Sweden**.**[17]

Certain enteroviruses or rotavirus during fetal life or infancy may be associated with B-cell autoimmunity and the development of clinical T1DM.[17,18]

Potential neonatal risk factors have confirmed a significant association between infections, respiratory distress and jaundice in neonates and T1DM. Similar results were obtained by Dahlquist et al. in Europe,[13] and by Mc Kinney et al. in the UK,[19] who reported that neonatal respiratory diseases, infections and jaundice are risk factors for T1DM. The most impressive increase in jaundice as a risk factor for T1DM was that found for blood group incompatibility, specifically ABO incompatibility, hence the mechanism is unknown.[13] Dahlquist et al. in Sweden,[20]have also reported that jaundice at birth or soon after birth has shown to be associated with increased risk of T1DM and it has been suggested that this association is due to phototherapy that these children have received. Neonatal infections were significantly associated with T1DM in this study, this result is consistent with that reported by Svensson et al. in Denmark.[21] No association was found between birth weight and risk of type 1 diabetes, which is in agreement with some case-control studies [39] However, a recent meta-analysis concluded that children who are heavier at birth have a significant and consistent, but relatively small increase in risk of type 1 diabetes.

A more recent study in Scotland did not reveal a significant association between type 1 diabetes and maternal pre-eclampsia, mode of delivery, jaundice, phototherapy, or breast feeding.[22] Early childhood infections were reported in a significantly higher percent of diabetic children compared to the control group. History of measles and varicella attend significant association with T1DM, similar results were reported by

Bengt et al. in Sweden.[23] Data from experimental animals as well as in vitro studies indicate that various viruses are clearly able to modulate the development of T1DM via different mechanisms including direct B-cell lysis, by activation of auto-reactive T-cell, loss of regulatory T-cell and molecular mimicry [24], however, Cardwell et al. reported a significant reduction in the risk of diabetes in children who lived with more siblings compared with one or none, and in children who moved house more often compared with never. The reduced risk of type 1 diabetes in children living with siblings, sharing a bedroom and moving house more often could reflect the protection afforded by exposure to infections in early life and consequently may provide support for the hygiene hypothesis.[25]

The hygiene hypothesis postulates that early environmental stimulation by infections is necessary for mature and balanced immune responses. The protective mechanisms induced by infection are thought to be related to the production of regulatory T-cells. Complex interactions between various components of the immune system control the production of Th1 cells, which are associated with autoimmune disease, and Th2 cells, which are associated with allergic disease. Such interactions could explain an inverse relationship between autoimmune and allergic disease such that the hygiene hypothesis is consistent with an inverse association between atopic diseases and type 1 diabetes.[26]

Eczema and rhinitis in early life were significantly associated with T1DM in this study, similar results were obtained by Visalli et al. in Italy,[4]and Sipetic et al. in Yugoslavia.[27]

Atopic eczema (AE) is one of the most frequent chronic inflammatory skin diseases due to complex interactions of deficient innate and adaptive immune responses based on a strong genetic predisposition

and triggered by environmental factors. AE patients exhibit a higher tissue eosinophilia, enhanced lesional cytokine expression, and higher surface expression of the high-affinity receptor for IgE (FcεRI) on epidermal dendritic cells compared to non-atopic eczema patients.[28]

In contrast to the Norwegian Children Diabetic Study Group by Stene et al. which showed that atopic eczema was associated with lower risk of T1DM, suggesting that it may confer partial protection against T1DM.[29] A weak inverse association between diabetes and each atopic exposure was also concluded from the meta-analysis of published literature, although none attained statistical significance.[19] The observed inverse association between childhood eczema and type 1 diabetes is not likely to be explained by the established diabetes susceptibility genes HLA-DQ, CTLA4, or PTPN22.[30]

Feeding pattern in early life (breast, cow milk or weaning food) and its duration were assessed in this study and showed that breast feeding less than 6 months is an important factor among diabetic children. Similar results were reported by Visalli et al. in Italy,[4] and by Holmberg et al. in Sweden who concluded that breast feeding modifies the risk of beta cells autoimmunity even years after finishing breast feeding.[31] However, Micheal et al. in Germany,[32] and Couper et al. in Australia,[33] did not confirm the role of the duration of the breast feeding or the introduction of cow's milk feeding as a risk factor for T1DM.

Accumulated evidence supports a critical role of environmental factors in its development. Prospective birth cohort studies show that the first signs of beta cell autoimmunity may be initiated during the first year of life. This implies that risk factors for beta cell autoimmunity and type 1 diabetes must be operative in infancy. Early nutrition provides essential

exogenous exposures in that period. Most studies suggest that the early introduction of complex foreign proteins may be a risk factor for beta cell autoimmunity.[34]

In this study, the risk of T1DM was significantly associated with the occurrence of T1DM (either alone or in addition to family history of T2DM) in first and second degree relatives. This finding is similar to that reported by Sipetic et al. in Yugoslavia,[27] Wahlberg and Moussa et al. in Kuwait.[35] In contrast, a family history of T2DM did not influence the risk, this result is consistent to that reported by Eltobelli et al. in Italy.[36]

T1DM and T2DM frequently co-occur in the same family, suggesting common genetic susceptibility. Such mixed family history is associated with intermediate phenotype of diabetes; insulin resistance and cardiovascular complications in T1DM, lower BMI and less cardiovascular complications in T2DM.[37]

Concerning family history of other autoimmune diseases, the study showed that there was a statistically significant association of occurrence of thyroid and celiac disease among relatives of diabetic patients compared to non-diabetic children, similar results was reported by Moussa et al. in Kuwait.[35] T1DM, autoimmune thyroid disease and celiac disease are the most common autoimmune endocrine disorders. A common genetic factor was suggested because of similar pathogenesis and tendency to occur together. HLA-DR3 was the major HLA allele contributing to the genetic susceptibility to TIDM and autoimmune thyroid disease.[38]

The study, however, has several limitations. The size of the study could mean we had limited power to detect the small effects currently being described in meta-analyses of perinatal risk factor

Conclusion:

From this study it can be concluded that early neonatal illness and the first years of life are positively associated with increasing risk of T1DM developing during childhood . Exclusive breast feeding for the first six months is protective.

Maternal habits (intake of coffee and soft drinks and drug exposure during pregnancy), maternal diseases (pre-eclampsia, gestational diabetes, autoimmune diseases and infectious diseases during pregnancy) also important determinants of risk.

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