Type 1 and Type 2 Diabetes among Youths in Jordan: Incidence and Trends for the period (2011-2016)

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Abstract
This study aimed at analyzing the incidence of Type 1 and Type 2 diabetes among youths in Jordan for the period (2011-2016), the researchers adopted the survey methodology for the period of five years from the records of the medical centers (public and private) in Jordan. Also investigated the differences between Type 1 and Type 2 diabetes in diagnosis and treatments. Results showed significant upward trend in the incidence of type 1 diabetes was observed overall with considerable variation across demographic subgroups of age, sex. And also showed among youths who were 10 to 19 years of age, unadjusted models revealed significant increases in the incidence of type 2 diabetes with increases observed across all age and sex.

1.1 Introduction

All forms of diabetes have very serious effects on health. In addition to the consequences of abnormal metabolism of glucose, there are a number of long-term complications associated with the disease. These include cardiovascular, peripheral vascular, ocular, neurologic and renal abnormalities, which are responsible for morbidity, disability and premature death in young adults. Furthermore, the disease is associated with reproductive complications causing problems for both mothers and their children. Although improved glycemic control may decrease the risk of developing these complications, diabetes remains a very significant cause of social, psychological and financial burdens in populations worldwide (Horenstein & Shuldiner, 2004).

Diabetes mellitus is a heterogeneous group of disorders characterized by persistent hyperglycemia. The two most common forms of diabetes are type 1 diabetes (T1D, previously known as insulin dependent diabetes or IDDM) and type 2 diabetes (T2D, previously known as non-insulin-dependent diabetes or NIDDM). Both are caused by a combination of genetic and environmental risk factors. However, there are other rare forms of diabetes that are directly inherited.

Diabetes is a long-term condition that can have a major impact on the life of a child or young person, as well as their family or careers. In addition to insulin therapy, diabetes management should include education, support and access to psychological services, as detailed in this guideline. Preparations should also be made for the transition from pediatric to adult services, which have a somewhat different model of care and evidence base (National Collaborating Centre for Women's and Children's Health, 2015).

Physicians face challenges when diagnosing diabetes among young adults. Type 1 diabetes (T1DM: see figure 1) can be diagnosed at any age, and type 2 diabetes (T2DM: see figure 1) is becoming more prevalent among the young. Moreover, diabetes first presenting itself in young adulthood may prove to be something in between T1DM and T2DM (Lammi, 2009).
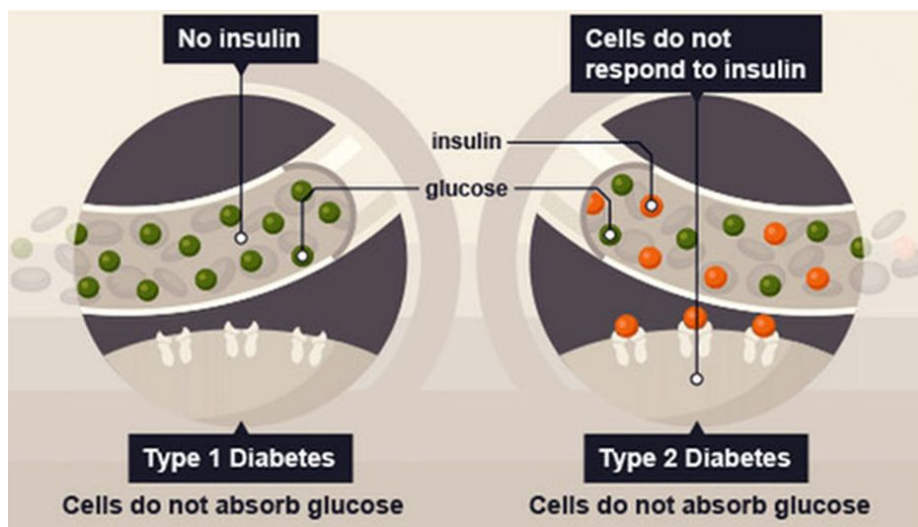
Figure (1): Type 1 and Type 2 Diabetes

Diagnoses of type 1 and type 2 diabetes in youths present a substantial clinical and public health burden owing to the challenges of disease management and the risks of acute and chronic complications. The search for diabetes in youth study previously showed increases in the prevalence's of both diseases in the 2011-2016 period. However, data on the trends in incidence are needed to understand the current and potential burden of diabetes more fully (Mayer-Davis, Lawrence, Dabelea, Divers, Isom, Dolan, & Pihoker, 2017).

Diabetes mellitus is amongst the most common chronic illnesses in the UK. Its prevalence is increasing and it has significant economic importance. As well as the direct costs of treating the illness and its associated complications, diabetes also has a number of indirect social and productivity costs, including those related to increased mortality and morbidity and the need for informal care. Diabetes UK reports that one in 10 people admitted to hospital have diabetes and approximately 15% of deaths per year are caused by diabetes.

The two primary forms of diabetes, which are more often than not implicitly grouped together, but the causes and costs of which are different. Type 1 diabetes is an autoimmune disease that affects 10–15% of those with diabetes. It is caused by an absence of insulin produced in the body, with onset mostly before the age of 30 years, the exact cause being unknown. Type 2 diabetes affects 85–90% (see figure 2) of those with diabetes and is caused by the body not effectively using the insulin it produces because its cells are resistant to the action of the insulin. It is often caused by obesity, age and genetic risk factors, with onset usually after the age of 40 years. These two main subtypes of diabetes mellitus are rarely distinguished in the media and even in some academic studies (Hex, Bartlett, Wright, Taylor & Varley, 2012).
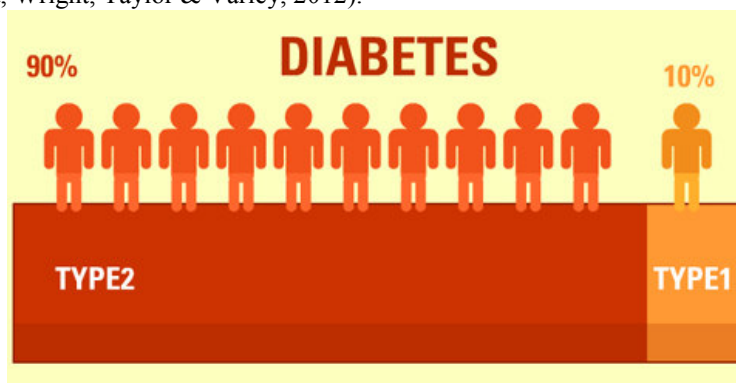

Figure (2): Type 1 vs Type 2 Diabetes percentages

The cause of type 1 diabetes remains unknown. There is clear evidence of a genetic predisposition and strong, but circumstantial, evidence for environmental factors triggering an autoimmune destruction of the beta cells leading to absolute dependence on insulin treatment. Living with type 1 diabetes remains a challenge for the child and the whole family even in countries with access to multiple daily injections or an insulin pump, glucose monitoring, diabetes education and expert medical care. Poor metabolic control may result in the acute complications of hypoglycaemia and ketoacidosis, poor growth and chronic microvascular and macrovascular complications. Children are more sensitive to a lack of insulin than adults and are at higher risk of a rapid and dramatic development of diabetic ketoacidosis. Episodes of severe hypoglycaemia or ketoacidosis, especially in young children, are risk factors for structural brain abnormalities and impaired cognitive function which may

cause schooling difficulties and limit future career choices. Even in developed countries there is still significant excess mortality among children and young adults with type 1 diabetes diagnosed in childhood (Patterson, Guariguata, Dahlquist, Soltész, Ogle & Silink, 2014).

1.2 Literature review

1.2.1 Definition of diabetes mellitus

Diabetes mellitus is defined as a group of metabolic disorders characterized by hyperglycemia. A diagnosis of diabetes is made by measuring the concentration of glucose from a venous plasma sample after 12 hours of fasting, or by an oral glucose tolerance test (OGTT, where 75 g of glucose dissolved in water is consumed after 12 hours of fasting, and the plasma glucose concentration is measured at 2 hours post load). The diagnostic criteria are met when the fasting plasma glucose concentration (FPG) is 7.0 mmol/l, or if the 2-h post load glucose is 11.1 mmol/l during an OGTT) (World Health Organization (WHO), 2006).

The glucose concentration can also be measured from a venous or capillary whole blood sample, in which case the diagnosis of diabetes is made at the glucose concentration of 6.1 mmol/l (fasting value). According to the ADA definition, a diagnosis of diabetes can also be made if any casual plasma glucose measurement is 11.1 mmol/l and the person presents classic symptoms of diabetes (15). In Finland, the current diagnostic guidelines follow these international criteria (fasting plasma glucose 7 mmol/l, or 2-h post load glucose >11 mmol/l) (Working group, 2007).

1.2.2 Classification of diabetes mellitus

The classification of diabetes mellitus has been under continuous revision. The previous classifications of diabetes were based either on age of onset (juvenile vs. adult-onset diabetes), or on the pharmacological treatment (insulin dependent diabetes mellitus vs. non-insulin-dependent diabetes mellitus) (National Diabetes Data Group, 1979).

The current ADA and WHO classifications of diabetes are based on the etiology and pathogenesis of diabetes mellitus, as this classification is found to be more appropriate for research purposes. Several etiopathogenetic subgroups can be identified among persons with diabetes mellitus.

1.2.2.1 Type 1 Diabetes Incidence in Jordan

There are approximately 500,000 children aged under 15 with type 1 diabetes in the world (Patterson et al. 2014); in 2013 alone, 79,000 more children developed type 1. Worldwide, the incidence of type 1 diabetes increased, on average, 3% per year between 1960 to 1996 in children under age 15 (Onkamo et al. 1999).

Between 1990 and 1999, incidence increased in most continents, with a rise of 5.3% in North America, 4% in Asia, and 3.2% in Europe. This trend is especially troubling in the youngest children; for every hundred thousand children under age 5, 4% more were diagnosed every year, on average, worldwide (De Beaufort, 2006).

In type 1 diabetes (T1DM), which accounts for 5-10% of those with diabetes, hyperglycemia results from an absolute deficiency of insulin caused by the destruction of insulin-secreting pancreatic β-cells. The insulinopenia may be evidenced by low or undetectable concentrations of C-peptide (connecting peptide released with insulin in equimolar amounts), and patients with T1DM are dependent on exogenous insulin for survival. T1DM is further subdivided into two entities: immune-mediated type 1A diabetes, where the destruction of β-cells is caused by an autoimmune process, and idiopathic type 1B diabetes (only the minority of cases) with marked insulinopenia, but no evidence of autoimmunity (American Diabetes Association, 2007).

In Jordan, the latest data show that the prevalence of type 1 diabetes increased by 18% in children between 2011 and 2016. More recent numbers show that overall, type 1 diabetes incidence in children increased by 1.7% per year between 2011 and 2016. Those numbers are from the search study. The Jordanian Ministry of Health collects nation-wide data on diabetes, but does not differentiate between type 1 and type 2 diabetes. A different study of a large population of Jordan patients with commercial health insurance found that type 1 (and type 2) prevalence increased between 2011-2016 in children. Researchers are figuring out ways to determine exactly how many children have type 1 (or type 2) diabetes in Jordan using electronic health records.

1.2.2.2 Type 2 Diabetes

Type 2 diabetes is a progressive condition in which the body becomes resistant to the normal effects of insulin and/or gradually loses the capacity to produce enough insulin in the pancreas. We do not know what causes type 2 diabetes. Type 2 diabetes is associated with modifiable lifestyle risk factors. Type 2 diabetes also has strong genetic and family related risk factors, and type 2 diabetes:

1. Is diagnosed when the pancreas does not produce enough insulin (reduced insulin production) and/or the insulin does not work effectively and/or the cells of the body do not respond to insulin effectively (known as insulin resistance).
2. Represents 85–90 per cent of all cases of diabetes.
3. Usually develops in adults over the age of 45 years but is increasingly occurring in younger age groups including children, adolescents and young adults.
4. Is more likely in people with a family history of type 2 diabetes or from particular ethnic backgrounds.

5. For some the first sign may be a complication of diabetes such as a heart attack, vision problems or a foot ulcer.
6. Is managed with a combination of regular physical activity, healthy eating and weight reduction. As type 2 diabetes is often progressive, most people will need oral medications and/or insulin injections in addition to lifestyle changes over time.

Diabetes runs in the family. If you have a family member with diabetes, you have a genetic disposition to the condition.

While people may have a strong genetic disposition towards type 2 diabetes, the risk is greatly increased if people display a number of modifiable lifestyle factors including high blood pressure, overweight or obesity, insufficient physical activity, poor diet and the classic 'apple shape' body where extra weight is carried around the waist.

People are at a higher risk of getting type 2 diabetes if they:
1. have a family history of diabetes
2. are older (over 55 years of age) - the risk increases as we age
3. are over 45 years of age and are overweight
4. are over 45 years of age and have high blood pressure
5. are a woman who has given birth to a child over 4.5 kgs (9 lbs), or had gestational diabetes when pregnant, or had a condition known as Polycystic Ovarian Syndrome.

1.3 Characteristics of diabetes in youth

In addition to the typical cases of T1DM and T2DM, the clinical manifestation of these types of diabetes can overlap substantially in young adults, thus making the classification intricate in this age group. Individuals with T1DM first diagnosed in young adulthood exhibit higher C-peptide values at diagnosis, slower disease progression, and less high-risk genotypes than children with a prepubertal diagnosis of T1DM. On the other hand, individuals with early-onset T2DM can have characteristics of T1DM, as a considerable number of individuals diagnosed to have T2DM in adolescence have been demonstrated to be positive for islet autoantibodies (30% GAD positive and 35% IAA positive). In Jordan Prospective Diabetes Study, the percentage of patients with T2DM presenting GAD autoantibodies was negatively correlated with age at onset (34% in 24-35-year-olds vs. 7% in 55-60-year-olds), and positive autoantibodies strongly predicted the need for insulin therapy during a 6-year follow-up period. A marked loss of β-cell function has also been associated with early-onset T2DM (Burns, Finucane, Hatunic, Gilman, Murphy & Gasparro, 2007).

1.3.1 Risk factors for diabetes mellitus

The confirmed and suggested risk factors for diabetes mellitus by clinical type are summarized in Table 1.

Table 1. Risk factors for T1DM and T2DM

Risk factors	T1DM	T2DM
Confirmed risk factors	Genetic predisposition Young age	Genetic predisposition Old age Obesity, overweight, and central obesity
Possible risk factors	Microbial infections Microbial toxins Vitamin D deficiency High intake of nitrosamine-rich food	High intake of saturated fat Low intake of dietary fiber Lack of exercise Cigarette smoking

1.3.2 Comparison chart between type 1 and type 2 diabetes

Table (2): Comparison differences between type 1 and type 2 diabetes

Category	Type 1 diabetes	Type 2 diabetes
Definition	Beta cells in pancreas are being attacked by body's own cells and therefore can't produce insulin to take sugar out of the blood stream. Insulin is not produced.	Diet related insulin release is so large and frequent that receptor cells have become less sensitive to the insulin. This insulin resistance results in less sugar being removed from the blood
Diagnosis	Genetic, environmental and auto-immune factors, idiopathic	Genetic, obesity (central adipose), physical inactivity, high/low birth weight, GDM, poor placental growth, metabolic syndrome
Commonly Afflicted Groups	Children/teens	Adults, elderly, certain ethnic groups
Bodily Effects	Believed to be triggered autoimmune destruction of the beta cells; autoimmune attack may occur following a viral infection such as mumps, rubells cytomegalovirus	Appears to be related to aging, sedentary life-style, genetic influence, but mostly obesity
Common physical attributes found	Mostly Normal or Thin	Mostly Overweight or Obese
Estimated percentage of occurrence	5% -10% of the people affected by diabetes in 2016	90% - 95%-of total cases.
Treatment	Insulin Injections, dietary plan, regular checkup of blood sugar levels, daily exercise Goals: optimal glucose, prevent/treat chronic complications, enhance health with food/PA, individual nutrition needs	Diet, exercise, weight loss, and in many cases medication. Insulin Injections may also be used, SMBG

1.4 Data Collection

The researchers analyzed data from the search study, a multicenter observational study that since 2011 has conducted population-based case ascertainment among youths who have received a diagnosis of non-gestational diabetes before the age of 20 years. Youths were identified at five clinical centers in Jordan. All the surveillance networks included participating endocrinologists. Additional cases were identified by other health care providers, hospitals, community health centers, clinical and administrative data systems, and diabetes registries. Case reports were validated on the basis of a physician's diagnosis of diabetes in the medical record. Eligibility was based on age (less than 20 years), nonmilitary status, noninstitutionalized status, and area of residence for the centers in Jordan at the time of diagnosis. After case validation and the deletion of duplicate cases, case patients were registered centrally. Diabetes type was noted as the physician-assigned diabetes type within 6 months after diagnosis. The case-ascertainment window was defined as 30 months after December 31 of each year in which the diagnosis was made (the incident year). All registered case patients were invited to complete a survey questions. For the incident years of 2011 through 2012 and 2013 and 2014 and 2015 and 2016, all youths with diabetes other than diabetes that was due to a secondary cause were invited to a research visit. Written informed consent and assent, when appropriate, were obtained from all the participants or from parents or legal guardians for participants who were too young to provide written consent. Blood samples were analyzed for three diabetes autoantibodies glutamic acid decarboxylase (GAD65); insulinoma-associated 2 molecule (IA-2), with the use of a standardized protocol; and zinc transporter 8 (ZnT8), with the use of a radio assay.

The study steering committee led and approved the study design, and data were collected under standardized protocols that were approved by the institutional review board at each center. The coordinating center was responsible for data quality control and analysis. All the investigators vouch for the completeness and accuracy of the data. Drafts of the manuscript were written by the first authors, with all the authors providing review and input. The study publications committee and steering committee approved the manuscript before it was submitted for publication.

1.5 Statistical Analysis

Patients with type 1 diabetes (including physician defined types 1, 1a, and 1b) who were younger than 20 years of age on December 31 of the incident year were included. For type 2 diabetes, we report the incidence rates among youths who were 10 to 19 years of age at diagnosis, because there were too few case patients who were

younger than 10 years of age at diagnosis to produce stable rates (137 cases in the 2011 to 2016 period). Persons with all other types of diabetes, including secondary forms (e.g., diabetes due to cystic fibrosis or glucocorticoid-induced diabetes) were excluded. Patent group were based on self-report when available from the participant survey (10,250 participants [81.6%]), from medical records (1988 [15.8%]), from geocoding, with missing data (267 [2.1%]).

The annual incidence rates according to physician-assigned diabetes type were calculated as the number of the valid, registered patients (with duplicate cases deleted), regardless of subsequent participation in study surveys or visits, divided by the number of persons in the surveillance networks over the same period across the five centers.

Trends in incidence were tested with the use of a generalized autoregressive moving average (GARMA) to account for serial correlation. Likelihood-ratio tests were performed to compare three possible formulations: a first-order autoregressive and first-order moving-average model (GARMA [1, 1]), a first-order autoregressive model (GARMA [1, 0]), and a first-order moving-average model (GARMA [0, 1]). Model selection suggested that the first-order moving-average model (GARMA [0, 1]) provided the best fit for the majority of models. Trends that were adjusted for age, sex, and unadjusted trends in incidence were estimated with the use of a negative binomial distribution with logarithm link.

1.6 Study results

1.6.1 Incidence Trends of Type 1 Diabetes

From unadjusted models, a significant upward trend in the incidence of type 1 diabetes was observed overall with considerable variation across demographic subgroups of age, sex. The incidence decreased in the subgroup of participants who were 0 to 4 years of age (P=0.04) and increased in the subgroups of participants who were 5 to 9 years of age (P=0.046) and those who were 15 to 19 years of age (P=0.02). There was no significant change in the subgroup of participants who were 10 to 14 years of age (P=0.16). The incidence increased among boys (P=0.003) but not among girls (P=0.40).

1.6.2 Incidence Trends of Type 2 Diabetes

Among youths who were 10 to 19 years of age, unadjusted models revealed significant increases in the incidence of type 2 diabetes with increases observed across all age, sex, and study-site subgroups for all comparisons. Some significant differences according to study center were observed. We estimated that approximately 3800 cases of type 2 diabetes were diagnosed annually in the 2011– 2012 period, and the number increased to 5300 annually in the 2015–2016 period. Overall, after adjustment for age, sex, the annual relative increase in the incidence of type 2 diabetes was 4.8% (95% CI, 3.2 to 6.4; (P<0.05).

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