An-Najah National University

Faculty of Graduate Studies

ENVIRONMENTAL AND GENETIC RISK FACTORS AMONG TYPE 1 DIABETES MELLITUS / CASE CONTROL STUDY IN NABLUS CITY

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This Thesis is Submitted in Partial Fulfillment of the Requirements for the Degree of Master of Public Health, Faculty of Graduate Studies, An-Najah National University, Nablus, Palestine.

2023

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Dedication

I dedicate my study to my lovely father and mother whose affection love and encouragement make me able to get such success….

My husband Abd-Alqadir the lifelong companion and supporter also my brothers Waseem, Baha', Rasem, Ahmad and Lewa'.

My children Qamar & Omar.... Qamar who was the reason for me to choose this study.

Acknowledgment

I pray thankfulness to Allah for providing me the well to complete this work.

I would like to thank my supervisor, Dr. Mariam Al-Tell, for her efforts, support and guidance throughout this project.

Many thanks are also extended to An-Najah National University instructors, particularly, department of public health.

Very special thanks to Palestine Diabetes Institute (PDI), for their welcoming, supporting and letting me communicate with their patients.

Also, thanks for Ministry of health at Nablus for their welcoming and supporting in collecting my data.

Declaration

I, the undersigned, declare that I submitted the thesis entitled:

ENVIRONMENTAL AND GENETIC RISK FACTORS AMONG TYPE 1 DIABETES MELLITUS / CASE CONTROL STUDY IN NABLUS CITY

I declare that the work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

Student's Name: براءة خليل غالب دواجبة

Signature: 

Date: 3/10/2023

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ENVIRONMENTAL AND GENETIC RISK FACTORS AMONG TYPE 1 DIABETES MELLITUS / CASE CONTROL STUDY IN NABLUS CITY

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Abstract

Type 1 diabetes is a result of an autoimmune reaction in which the body immune system attack himself the exact risk factors that enhance this mechanism are not as clear as for type 2. In this study, a questionnaire for risk factors (environmental and genetic factors) for type 1 diabetes mellitus at maternal and child level.

The study is aiming for identifying the risk factors (environmental & genetic) at maternal and patient level associated with type 1 diabetes mellitus in Nablus city West Bank, Palestine.

A case control study design was adopted to find the risk factors associated with type 1 diabetes occurrence 68 cases and 50 control filled a questionnaire that was developed by the researcher, then the data was analyzed by SPSS.

A total of 118 participants included in the study: 68 cases (57.6%), 50 controls (42.4%), mean age in cases 8.8703 ±5.2053, mean age of controls 8.5600±5.83938. 53.4% males and 46.6% females. The comparison between case and control groups showed significant association with multiple risk factors. BMI pre pregnancy (p 0.009), hypertension during pregnancy (p 0.077, OR 5.623, 95%CI 0.8294 – 1.4206), exposure to hair salon chemicals (p 0.033, OR 4.632, 95%CI 0.9269 – 1.3808), passive smoker (p 0.002, OR 3.458, 95%CI 1.1415 – 1.3868), consumption of soft drinks (p 0.051, OR 2.217, 95%CI 1.1516 – 1.4484), and family history of T1DM (p 0.000, OR 42.690, 95% CI1.4095 – 1.6109).

T1DM is associated with genetic and environmental risk factors. Recommendation for further studies about the result founded in this study, with more sample size, and more details

Keywords: Diabetes and risk factors**;** T1DM.

Chapter One

Introduction

1.1 Background

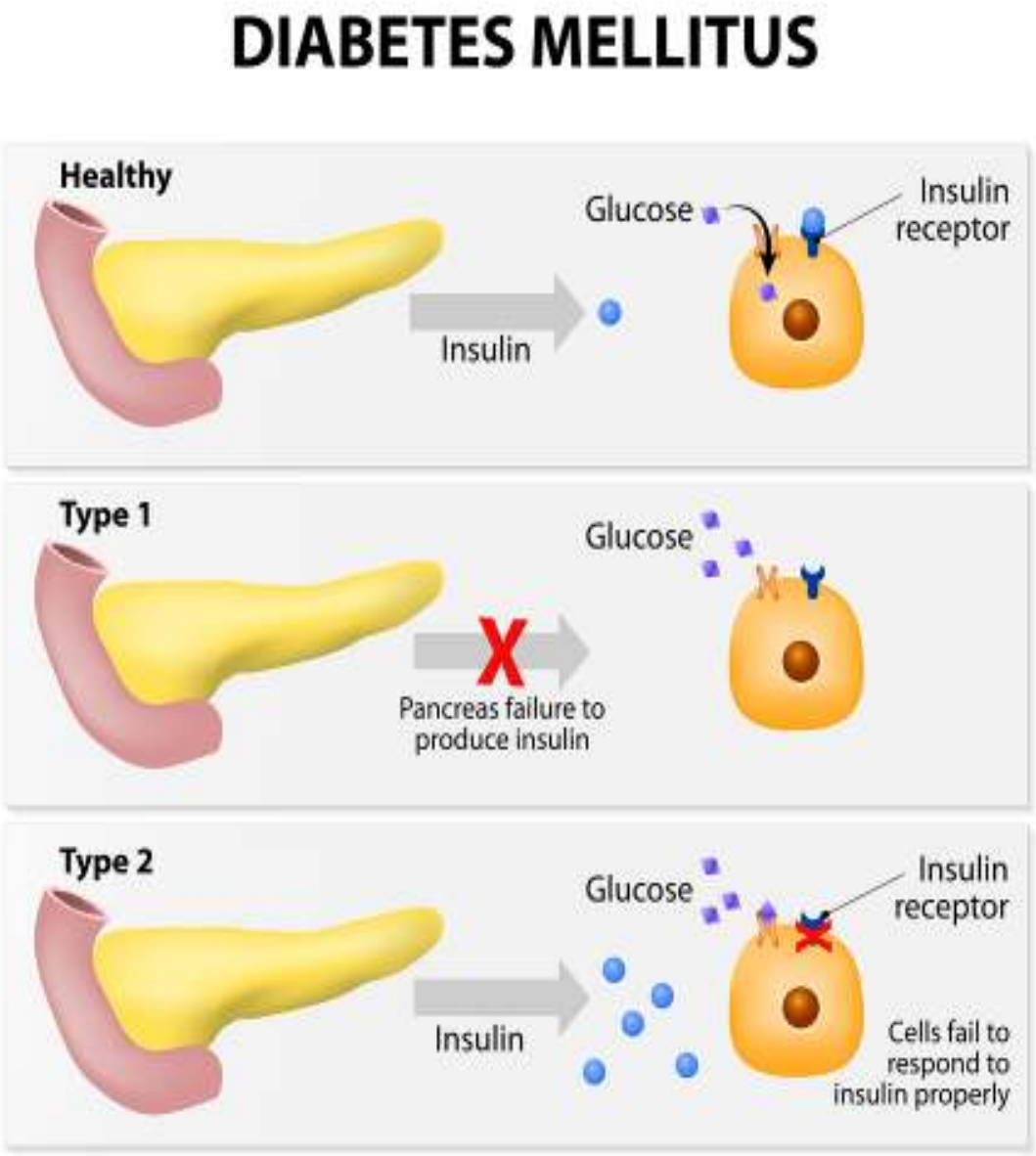
Diabetes is a chronic (long-lasting) health condition in which blood glucose is too high (hyperglycemia) the glucose is the main energy source for the body develops when there is insulin insufficiency or even no insulin is produced by the pancreas, or insulin resistance, leading to hyperglycemia, prolong hyperglycemia may cause serious health problems that such as: kidney failure, coronary heart disease, vision loss, and even dental problems (NIDDK/2022).

Diabetes mellitus is a major health problem worldwide, several risk factors play role in developing diabetes. Approximately 537 million adults aged 20-79 years are living with diabetes in the year 2021, 10% are T1DM (IDF Diabetes Atlas 10th Edition,n.d.). In 2022 almost 8.75 million people are living with T1DM and the incidence have increased during recent decades (IDF Diabetes Atlas 10th Edition, n.d.). In Palestine 2489 nowadays are living with T1DM (Type 1 Diabetes Index/2023), unfortunately in Palestine no previous studies were found on T1DM, so it's important to do such study for health researches, individual with diabetes and also to help in future prevention and delaying of T1DM developing.

There are several types of diabetes; Type 1 Diabetes Mellitus (T1DM), Type 2 Diabetes Mellitus (T2DM), gestational diabetes (develops in pregnant women who have never had diabetes and goes after delivery), maturity onset diabetes, and other specific types of diabetes: endocrinopathies, genetic defects of beta cell function or in insulin action, and drug or chemical induced diabetes (Diagnosis and Classification of Diabetes Mellitus, 2014).

Figure 1

Types of diabetes



Note: (Dwivedi et al., 2020)

T1DM occurs in children also called juvenile or childhood onset, which is an autoimmune disease attack beta cell in the pancreas that produce insulin so the insulin production will be affected (DiMeglio et al., 2018).

What is insulin?

Insulin is a polypeptide hormone that is produced normally from the pancreas as a response to increase in blood glucose. It has a vital role in regulating blood glucose level as it increase the glucose uptake in the liver, muscles and fat cells. In patients with

diabetes especially T1DM, there is a need to take insulin injection with every meal to survive. For people living with diabetes to achieve the balance in insulin level several types of synthetic insulin are provided nowadays categorized by:

- onset of action
- peak
- duration
- concentration
- route of delivery

Below is the list of insulin types that is provided nowadays for people living with diabetes:

- Rapid acting: onset starts within 15-20 minutes after injection and last up to 4-5 hours in the body, examples of rapid acting insulin Lispro and Aspart. There is inhaled rapid acting insulin.
- Intermediate acting: onset of action is around 1 to 2 hours and duration of activity 10 to 16 hours. Examples are LENTE from the Latin lentus. In this type of insulin zinc is added in the preparation to reduce the absorption rate of insulin in order to last in the body for long time.
- Short acting: onset starts within 0.5 to 1 hour onset of action and last up to 6-8 hours, examples Humulin.
- Long acting: have an onset of action around 2 hours and last in the body up to 36 hours. In this type of insulin an amino acid is added to the insulin chain to increase the isoelectric point then the PH of the insulin become near to the neutral so the absorption of insulin is prolonged, examples of this type is detemir (Ahmad, 2014).
- Ultra long acting: work within 6 hours and last up to 36 hours or longer in order to provide steady insulin for long period.
- Premixed: need 5 to 60 minutes to start working and last up to 16 hours, it contains combination of intermediate and short acting insulin.

The doctor decides for each patient which type of insulin is needed based on type of food, physical activity, age, how long the body takes to absorb the insulin and the ability of each patient to manage his glucose level. Usually the patients takes rapid

acting insulin with every meal which works after 15 minutes of injection and long acting insulin that works as background and work as long as 14 to 40 hours.

Type 1 patients are also susceptible to other autoimmune diseases, especially for the thyroid gland as well as celiac disease. According to WHO around 9 million people are living with type 1 diabetes in the year 2017, most of them are living in high income countries (WHO/2023).

T2DM occurs in adult but can in some cases occurs in children. The cause is combination of resistance to insulin action and inadequate insulin production so the cell doesn't respond to the insulin well and less glucose is being taken to the cells. The risk factors for type 2 diabetes are:

- Unhealthy life style
- Being overweight
- Fat in the abdomen
- Family history of the disease
- And age.

Unhealthy life style with consuming high carbs diet leads to increase in the load of work of the beta cells in the pancreas. This increase leads overtime to type 2 diabetes, so type 2 diabetes can be prevented by keeping a normal body weight exercising daily and having healthy diet. In this type of diabetes oral medication are the choice to decrease blood glucose level by increasing the sensitivity in the insulin receptors and decreasing hepatic glucose production and intestinal glucose absorption. Recent studies shows that an early loss of beta cell functions play a role in T2DM pathogenesis ((Unnikrishnan et al., 2017).

Symptoms of marked hyperglycemia include:

- Increase urination
- Feeling more thirsty
- Weight loss with excessive hunger
- Blurred vision.
- Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Acute, life-threatening consequences of uncontrolled

diabetes are diabetic ketoacidosis or the nonketotic hyperosmolar syndrome ("Diagnosis and Classification of Diabetes Mellitus," 2014)

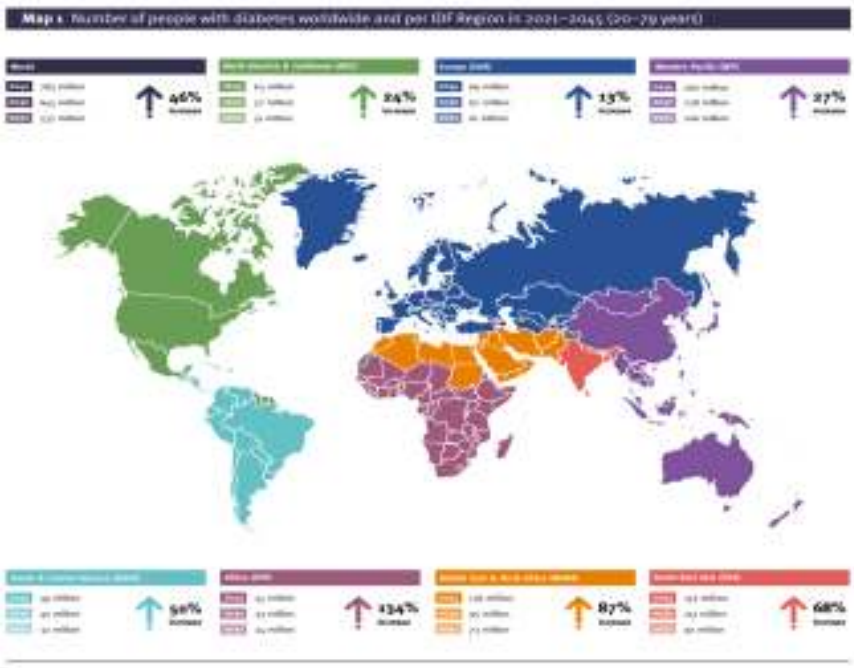
What is diabetic ketoacidosis?

Diabetic Ketoacidosis (DKA) is one of the consequences of diabetes that develop when there is no enough insulin to help the glucose to get in to the cells, so the body try to get fuel from other sources. The liver breaks the fat and proteins, this process produce acid called ketone bodies leading to high level of ketone in blood and urine, so the blood become acidic and the patient may develop coma and death if not treated quickly.

1.2 Prevalence of Diabetes

Figure 2

Prevalence of diabetes



According to International Diabetes Federation (IDF), approximately 537 million adults aged (20-79) years are living with diabetes in 2021 worldwide. In the Middle East & North Africa 73 million, around 10% are having T1DM, and almost 1.2 million aged (0-19) years having T1DM in 2021, while the number in 2022 increased to 1.52 million. The incidence over the time increased rapidly mostly due to environmental changes (*IDF Diabetes Atlas 10th Edition*, n.d.).

In Palestine, the new reported diabetes mellitus cases in West Bank was 4700 cases for all types of diabetes in 2021, with an incidence rate of 166.9 per 100,000 population (MOH Palestine/2021).

Of the total diabetic population in Palestine, 4.4% are diagnosed of type 1 diabetes and 95.3% are diagnosed with type 2 diabetes. The prevalence of diabetes mellitus in Palestine is 15.3% much higher than the world prevalence 6% (World Diabetes Foundation/2020).

Global estimate for type 1 diabetes in 2021 and 2022

Globally in 2021, around 8.4 million were living with type 1 diabetes mellitus, 5.4 million of them were at the age 20-59 years and 1.6 million were 60 years and older. an estimate of 35,000 person died due to type 1 diabetes 2021 within 12 month of symptomatic onset before being diagnosed, life expectancy for 10 years old diagnosed T1D patient is 13 years in low income countries, and 65 in high income countries. Half million new cases reported in 2021 with median age diagnosis of 29 years, and the missing prevalence cases around 3.7 million (Gregory et al., 2021).

According to IDF, around 8.75 million people are living with T1DM in 2022 around the world. Prevalence of type 1 diabetes cases (existing) age (0-19) years were 1,211,900 while the incidence (new cases) of T1DM per year was 149,500 knowing that global population of people aged (0-19) is 2.61 billion (*IDF Diabetes Atlas 10th Edition*, n.d.).

Type 1 Diabetes Index for Palestine reported that 2489 nowadays are living with type 1 diabetes mellitus with 45 healthy years of life are lost per person, almost 1810 person who should be alive now if they hadn't die early due to complications. If there was a good access to timely diagnosis of T1DM 3.2 healthy years can be restored, with the access to insulin and strips 22.5 healthy years can be restored, with access to pump and CGMs 5.5 healthy years can be restored, and finally with the access to prevention and cure full life can be restored with God's will (Type 1 Diabetes Index/2023).

In Iran a study was done to report the burden of T1DM by sex, age, year and province between 1990 and 2019 over 30 years, in both male and female there was increase in incidence and prevalence at all age numbers, the death rate decreased from 1.1 to 0.7

per 100,000, the prevalence rate of T1DM increased from 199.6 in 1990 to 388.9 per 100,000 in 2019 (Bandarian et al., 2023).

According to the report of WHO, Diabetes has entered the top 10 causes of death globally. It is also responsible for the largest rise in male deaths among the top 10 since 2000(WHO 2020). In Palestine diabetes mellitus is the 3rd causes of deaths in West Bank and the 10th causes of death responsible for 12.8% of total deaths in West Bank, while in Gaza responsible for 3.2% of total deaths in 2022(MOH Palestine 2022)

Coronavirus and type 1 diabetes

Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus called SARS-CoV-2, appeared in December 2019 and spread worldwide (News medical 2020).

WHO recorded that the cumulative cases for COVID-19 till May 15 2023 were 766,440,796, and deaths due to COVID-19 were 6,932,591(WHO/2023).

The virus spread when the infected person breathes out the droplets that contain the virus and other healthy individual breath them, signs and symptoms start to appear after 2-14 days of infection, the main symptoms include:

- Fever
- Cough
- Tiredness
- Sore throat
- Shortness in breath
- Loss of taste
- Headaches
- Chest pain
- Diarrhea

The list is not complete there is other non-familial symptoms. Not all the patient have the same symptoms. In some cases the infected person does not show any symptoms they called this asymptomatic state. Also the severity of the disease differs between

individuals, for example children may have mild illness while the older have more severe one(Victor Babu et al., n.d.).

To evaluate the risk of new diabetes diagnosis after infection with SARS-COV-2 >30 days of infection, CDC estimated diabetes incidence among patient aged less than 18 years and diagnosed with COVID-19 from retrospective cohort constructed in comparison with patients who didn't receive COVID-19 diagnosis, the incidence of T1DM was significantly higher among those with COVID-19 than without (Barrett et al., 2020).

SARS-COV-2 can enter beta cells in the pancreas through Angiotensin Converting Enzyme-2 receptors (ACE-2), this receptor is important for COVID-19 to invade the cells through. Any cells express this receptor the virus can invade them like lung and pancreatic cells, leading to reversible beta cell damage and hyperglycemia which lead to severe ketoacidosis. The exact mechanism of COVID-19 in triggering the diabetes occurrence need to be proven by follow up the children and adult who present with hyperglycemia during the pandemic of the disease (Boddu et al., 2020)

SARS-COV-2 is not only linked to T1DM, several studies support the link between autoimmune diseases and SARS-COV-2, a notable increase in autoimmune disease incidence in individual after COVID infection via several pathways also some similarities were noted between SARS-COVID-2 and autoimmune disease, both have the same organ damage which is immune mediated, and in COVID patients various auto antibodies was detected that is usually found in immune diseases for examples antinuclear antibodies (Sharma & Bayry, 2023).

Viral infections can induce beta cell damage through two mechanism:

- Direct beta cell lyses while the virus replicate in the cells
- Host inflammatory response that lead to autoimmunity

There are several pathways for beta destruction, one of them is molecular mimicry when the virus and the host cells share same component this lead to autoimmunity in which the body cannot discriminate between own cells and viral one, some studies mention that the molecular mimicry accelerate the autoimmune process rather than initiate it. Many viruses came to be associated with developing type 1 diabetes mellitus

(Enterovirus especially Coxsackie virus, Mumps and Rubella and recently SARS-COV2 the studies on going to prove the relation (Boddu et al., 2020)

Several theories support the link between environmental factors (virus, dietary factors, vitamin D deficiency, decrease in gut micro biota and stress) and genetic factors with type 1 diabetes mellitus, either by triggering the immune response or by driving beta cell autoimmunity and apoptosis (Butalia et al., 2016)

1.3 Aim and Objectives

The study aimed at exploring the factors that is associated with type 1 diabetes mellitus occurrence in Nablus city at Palestine.

Study Objectives

1. To identify risk factors associated with developing T1DM in cases group in comparison to control group in this study. In people whose age between 1-22 years, diagnosed after April 2020 to August 2022. In Nablus city.
2. To define the maternal related risk factors, that associated with developing T1DM. The maternal risk factors that the mother exposed to them during her pregnancy with the her son who developed T1DM included in this study are:

- BMI pre- pregnancy
- Extra weight gain
- Hypertension
- Preeclampsia
- Gestational diabetes
- Exposure to hair saloon chemicals
- Experience negative emotions
- Smoker, and passive smoker
- and consumption of soft drinks

3. To define patient related risk factors that associated with developing T1DM:

- Birth weight
- Exposure to COVID-19
- Other viral infections
- Breastfeeding

- Early induction to cow milk, gluten, and fruit
- Genetically (family history and genetic testing).

1.4 Study questions

For the mothers:

- Dose the mothers of T1DM patient has pre-pregnancy BMI more than the mothers of healthy group?
- Dose the mothers of T1DM patient has extra weight gain during their pregnancy more than the mothers of healthy group?
- Dose the mothers of T1DM patient has hypertension during pregnancy more than the mothers of healthy group?
- Dose the mothers of T1DM patient has preeclampsia more than the mothers of healthy group?
- Dose the mothers of T1DM patient has gestational diabetes more than the mothers of healthy group?
- Dose the mothers of T1DM patient has exposed to hair salon chemicals during pregnancy more than the mothers of healthy group?
- Dose the mothers of T1DM patient has experience negative emotion during pregnancy more than the mothers of healthy group?
- Is maternal smoking and being a passive smoker are associated with occurrence of T1DM?
- Is consumption of soft drinks during pregnancy associated with occurrence of T1DM?

For the patients:

- Is birth weight above or below normal range associated with occurrence of T1DM?
- Is exposure to COVID-19 or other viral infections associated with occurrence of T1DM?
- Is breastfeeding associated with T1DM occurrence?
- Is consumption of cow milk earlier than 1 year associated with T1DM occurrence?
- Is consumption of fruit earlier than 6 months associated with T1DM occurrence?
- Is consumption of gluten earlier than 3 months associated with T1DM occurrence?
- Dose the patients have family history of T1DM more than the control group?

1.5 Problem statement

The incidence of T1DM is increasing worldwide, with rate doubling every 20 years (Rewers et al., n.d.). Worldwide 8.75 million people are living with T1DM. In Palestine 2489 (Type 1 Diabetes Index/ 2023). The purpose of this study aimed at exploring the genetic and environmental risk factors associated with T1DM, and determined whether COVID-19 is one of those factors, also to detect if exposing to certain environmental risk factors at maternal and child level could associated with the disease developing. T1DM is a life threating condition, and can't be cured. Over the time the complication of T1DM can affect major organ in the body. Knowing the risk factors that is associated with T1DM can help in future prevention trial, by detecting all factors that may lead to T1DM (prenatal) and during childhood before having T1DM, then any child who's under the risk (high risk group) may need early intervention, preventive, evaluation, and long-term monitoring.

Chapter Two

Theoretical framework

2.1 T1DM risk factors

The exact cause of T1DM still unknown, but obviously the genetic and environmental factors play an important role in T1DM development, genetically the HLA locus is the most linked region to T1DM, environmentally many factors involved in developing the disease.

A structured questionnaire was used for collection of the data from the mothers of both cases and control. Demographic data, potential genetic and environmental factors identified though the literature review. Demographic data included gender, age, date of diagnoses, maternal and paternal education level, and economic status. Environmental factors include

- Double strand DNA viruses
- Early induction to fruit (earlier than 6 months)
- Early induction to bovine milk (earlier than 1 years)
- Early gluten induction (earlier than 3 months)
- Toxins
- Breastfeeding
- Decrease in gut microbiota
- Lack of vitamin D (Saberzadeh-Ardestani et al., 2018)
- COVID-19 infection
- Birth weight

Birth weight

The baby birth weight is linked directly to several health issues for the future health of baby. A systematic review and meta-analysis was done on twelve studies involve 2398150 persons, 4 studies suggested that high birth weight above 4 kg was associated with increased risk of T1DM OR = 1.17. The study conclude that high birth weight and early weight gain at first year of life could be associated with later developing of T1DM (Harder et al., 2009).

Maternal risk factors

According to Barker's developmental origins theory, maternal life style, environment and nutrition may affect directly embryonic development and some effect related to later life health events, so the adult disease may have fetal origin (Wadhwa et al., 2009). Based on this theory several questions were included in the study about maternal life style, if she was playing sport, if she smoking or if she was a passive smoker.

The maternal variables that were included in the study which may be associated with T1DM, those variables are:

- Maternal Body Mass Index (BMI): is a statistical index that use the body weight and high to generate an estimate of body fat for both male and female, the equation of calculation is {weight (in kg)/ height^2 (in m^2) }. (Weir et al., 2023).

The BMI was calculated for each participant based on BMI equation, before pregnancy and at the end of pregnancy, extra weight gain was calculated based on CDC recommendations see table (table 1), and the result of BMI was divided into 4 groups normal, overweight, obese and underweight, according to CDC around 48% of pregnant women are gaining weight above the recommended and 21% below the recommended, only 32% are gaining weight within the recommendation, also low birth weight babes may have difficulty in breastfeeding and may suffer from future illness (CDC, 2022).

A study was done between 2006 and 2015 to examine the effect of pre pregnancy BMI on neonatal weight outcome, consist of 3431 mothers and their twins infant it conclude that pre pregnancy maternal obesity is associated with high birth weight and high risk of preterm birth, and pre pregnancy underweight is associated with lower birth weight and high risk for small for gestational age, so mother who plane for future pregnancy should maintains a normal BMI (Qu et al., 2021). A systematic review and meta-analysis of 18 studies suggested that preterm birth was significantly associated with increased risk of T1DM (OR = 1.18). it's worth mentioning the BMI in this study to examine if it has effect on T1DM development.

- Extra weight gain during pregnancy based on BMI was another maternal variable that included in this study.

- Hypertension and preeclampsia: preeclampsia is a hypertensive disorder characterized by systolic blood pressure above 140 mm Hg or diastolic blood pressure of 90 mm Hg, after 20 weeks of gestation, preeclampsia have several complication for both mother and fetus, pulmonary edema, renal and retinal injury, for fetus a growth restriction may occurred and placental abruption, fetal and mother death (Karrar., et al, 2023).

A meta-analysis in 2011 of the association between preeclampsia and childhood T1DM. There was little evidence of an increase of the risk of T1DM in children born to mothers who had preeclampsia during pregnancy (OR=1.10, P=0.17) (Henry et al., 2011)

Children of old mothers and mothers with preeclampsia are at high risk of future developing T1DM (McKinney et al., 1999).

- Diabetes during pregnancy, either gestational diabetes or type1 and 2 diabetes. It was found that between birth and 22 years, the kids of mothers with gestational diabetes were twice more likely to develop Type 1 diabetes than of normal mothers (Medical News Today/2023).

According to a study was done in Quebec, Canada, randomly a singleton live birth of mothers with gestational diabetes were matched with singleton live birth without gestational diabetes (1990-2007). Follow up was to 2012, it conclude that gestational diabetes is associated with incident diabetes in offspring during childhood and adolescence. Future studies is needed to examine the long term outcome of gestational diabetes in patient of pediatric diabetes (Blotsky et al., 2019).

- Hair saloon chemicals: none of the previous studies about risk factors for T1DM studded the effect of hair saloon chemicals as a risk factor for T1DM. Some chemical compound and toxins in food or water may activate autoimmune mechanism in genetically susceptible individuals such as nitrate and nitrosamines (Rewers et al., n.d.).

- Negative emotions, if there was extreme shock or losing for someone dear. Physiological disturbance during pregnancy associated with low birth weight baby and preterm delivery (Satyanarayana et al., 2011). The researcher didn't found any preveous studies about negative emotions and risk of T1DM.

- Vitamin D deficiency: vitamin D deficiency in mothers during pregnancy can affect their fetal health. Autoimmune disease diabetes and cardiovascular disease thought to be linked for vitamin D deficiency in mothers, vitamin D is also conceder as protective factor from T1DM (Rewerts et al., 2016), a question about previous testing for vitamin D level and if the mother was committed for taking vitamins and minerals during pregnancy.

- Smoking and negative smoker: according to case control study was done to investigate the risk of T1DM in children exposed to tobacco smoking in utero taking HLA haplotype into account, the result conclude that maternal smoking in early pregnancy was associated with high risk of developing T1DM in early childhood (Mattsson et al., 2015).

- Consumption of soft drink during pregnancy: high amount carbohydrate diet is associated with high weight gain for both mother and child with various complication like gestational diabetes, preeclampsia and other complications, the glucose and fructose can pass the placenta reaching to the fetus leading to high birth weight (Goran et al., 2019)

Table below shows the weight gain recommendation for the pregnant women based on her BMI before pregnancy:

Table 1

Weight gain recommendation for pregnant women according to CDC

BMI before pregnancy	Weight gain during pregnancy(kg)
Underweight less than 18.5	12.7-18.1
Normal 18.5-24.9	11.3-15.8
Overweight 25.0-29.9	6.8-11.3
Obese greater than or equal 30.0	5-9

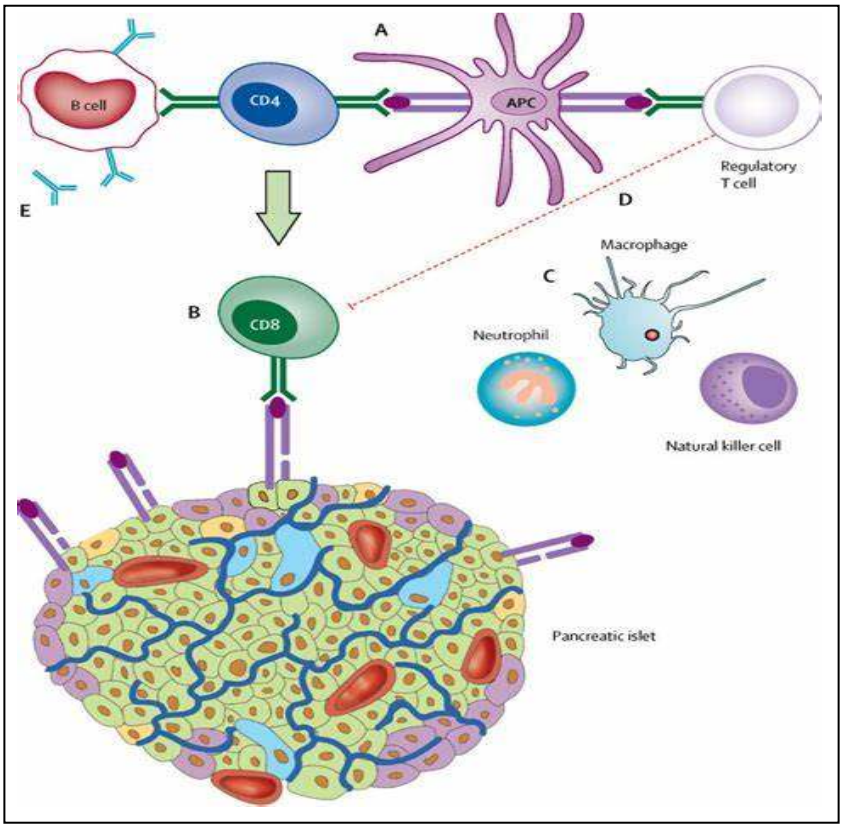
2.2 Pathophysiology of T1DM

Insulin hormone is produce at the beta cells in the pancreas, after response to elevated glucose level in the blood, in T1DM an autoimmune destruction targeted those cells, which lead to deficiency in insulin. The first emerged hypothesis that explained this process was by Eisenbarth in 1980 it is thought that infective or environmental stimuli stimulates the autoimmunity in genetically predisposed individuals (Pharmaceutical Journal/2013).

Destruction of beta cells require cooperation of dentric cells, macrophages, T, B, and Natural killer cells after antigen presenting cells present beta cell antigen to the immune system (Saberzadeh-Ardestani et al., 2018).

Figure 3

Pathophysiology of T1DM



Antigen presenting cell (APC) stimulate CD4+ T lymphocyte which in turn mediate the activation of CD8+ T cell, which return to beta cell in the pancreas that express (immunogenic self-antigen) and lyse the beta cells, another pathway for this destruction through (natural killer cells, macrophages and neutrophil) that all excrete pro inflammatory cytokines and reactive oxygen species, also T cells stimulate B

lymphocyte to produce autoantibodies against beta cells, regulatory T lymphocyte should suppress the autoimmunity but due to defect this suppression was eliminated and all process was amplified (DiMeglio et al., 2018)

2.3 Symptoms of T1DM

Symptoms for hyperglycemia are polyuria (increase urine output), polydipsia (increase fluid intake due to thirst), weight loss, some patient may complain from abdominal pain, blurred vision, decrease consciousness, tiredness, and susceptibility to certain infections ex. UTI, sometimes vomiting and deep breathing, those symptoms are associated with hyperglycemia, in case of hypoglycemia sweating, tingling lips, hunger, feeling confused and week are the most common symptoms ("Diagnosis and Classification of Diabetes Mellitus," 2014)

Specific symptoms in men & women:

- Men: in addition to regular diabetes symptoms men may have decries in sex derive, erectile dysfunction and decries in muscle strength.
- Women: urinary tract infections, yeast infection and dry itchy skin (Dwivedi et al., 2020)

The symptoms of T1DM developed very quickly, in young ages it took hours or days to appear, not like T2DM which usually takes years for symptoms to appear.

2.4 Diagnosis of T1DM

Diagnosis often after emergency admission, the patient may be unconscious due to diabetic ketoacidosis (high glucose level & high ketone level), several tests can be done to diagnose T1DM:

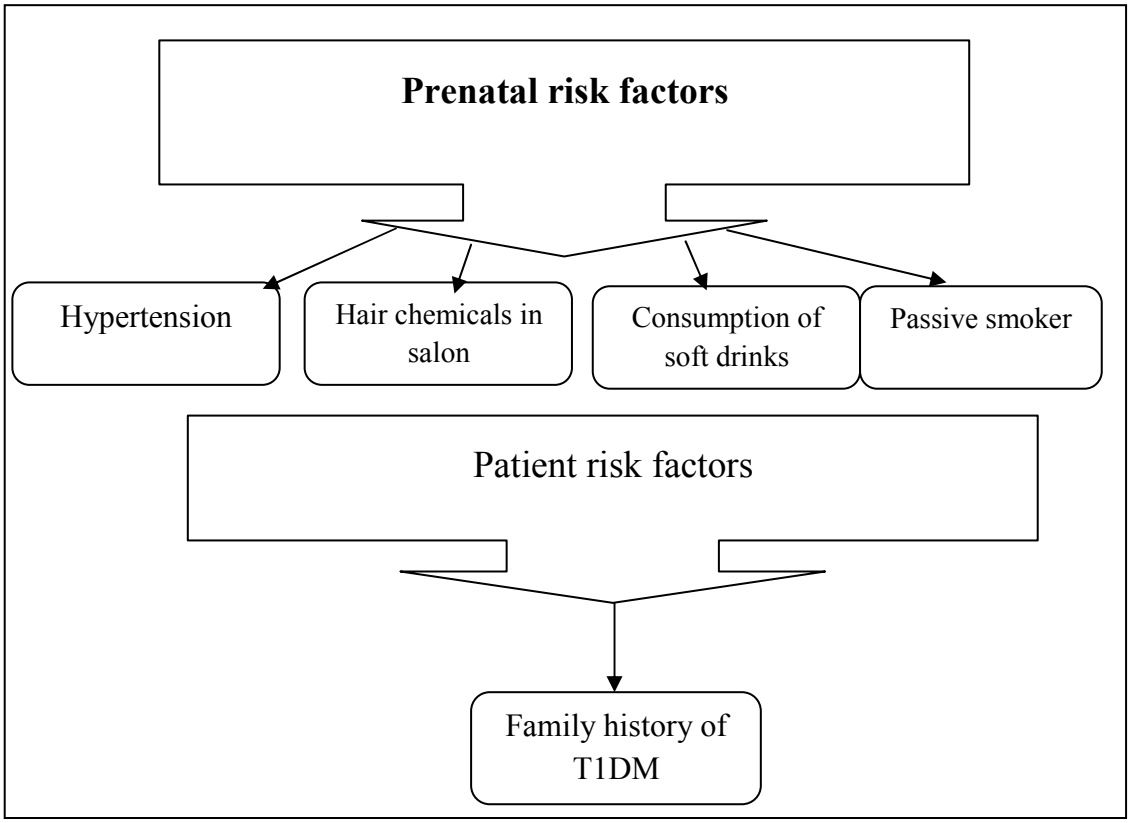
1. Plasma Glucose level, fasting more than 7 mmol/L (126mg/dl), randomly more than 11 mmol/L (198mg/dl).
   a. Hemoglobin A1c: it measure the amount of glucose attached to hemoglobin or glycated hemoglobin, normal range for A1C is less than 5.7%, any result above this number indicate problem in the glucose regulation, for type 1 patients the evaluation of a1c is recommended every 3 to 6 month to indicate how the glucose control was over the previous 3 month.

2. Diabetes autoantibodies: this test is used to distinguish between T1 & T2, the presence of one or more antibodies indicate T1DM (ICA, GAD-65, IAA and IA-2A)
3. C-peptide: also called connecting peptide which connect alpha and beta chain of pro-insulin in pancreas then in the blood it separated from the insulin with more half-life than the insulin so it conceder a good indicator for the pancreas indicating that the pancreas is functioning well.
4. Urine/ and or blood ketone: a building up of ketone can happen only if the insulin is absent, also if the blood glucose is more than 180mg/dl the kidney will filtrate the excess amount in the urine so in the blood test a positive glucose will be found.
5. Genetic testing: to determine any gene mutations (lab test online/2021)

2.5 The risk factors of T1DM based on the study results

Figure 4

Risk factors for T1DM based on study results



Based on the study results, this diagram represent the main significant risk factors associated with T1DM.

Chapter Three

Literature review

3.1 Introduction

Research on risk factors for T1D is an active area of research to identify genetic and environmental triggers that could potentially be targeted for intervention. The incidence of T1DM has increased 3-4% over the past 3 decades, many factors associated with this increase, one of them is environmental factors (Norris et al., 2020).

A complex interaction between many factors (environmental, genetics, micro-biome, metabolism and immune system) that vary between each individual case result of T1DM (DiMeglio et al., 2018).

According to the CDC Risk factors for type 1 diabetes are not as clear as for pre diabetes and type 2 diabetes, no way to prevent T1DM till now is known but knowing the family history is the most important, although some people may inherit the genes and doesn't develop T1DM, which support the fact that environmental factors play a role in triggering the disease (CDC 2021).

A prediction model was found to help in future prevention of T1DM by knowing people at risk and following them to prevent or revert the progression of T1DM, the model consist from 4 stages:

- Stage 1: autoimmunity to Beta cell with normal glucose level and still pre-symptomatic, with 2 or more pancreatic autoantibodies.
- Stage 2: Beta cell autoimmunity with multiple autoantibodies, dys-glycemia (fasting glucose 100-125 mg/dl) and still without diabetic symptoms, and HBA1C between 5.7% and 6.4%.
- Stage 3: Beta cell autoimmunity with symptoms and hyperglycemia random glucose test more than 200 mg/dl and fasting more than 125 mg/dl, HBA1C more than 6.5% (Primavera et al., 2020).
- Stage 4: long standing type 1 diabetes.

3.2 Autoimmune disease

Immune system normally defend against any forging bodies, diseases and infections through several organs (lymph node, tonsils and adenoid, bone marrow, spleen and appendix), in case of autoimmune disease the mechanism of defense is altered and the immune system by mistake attack own body.

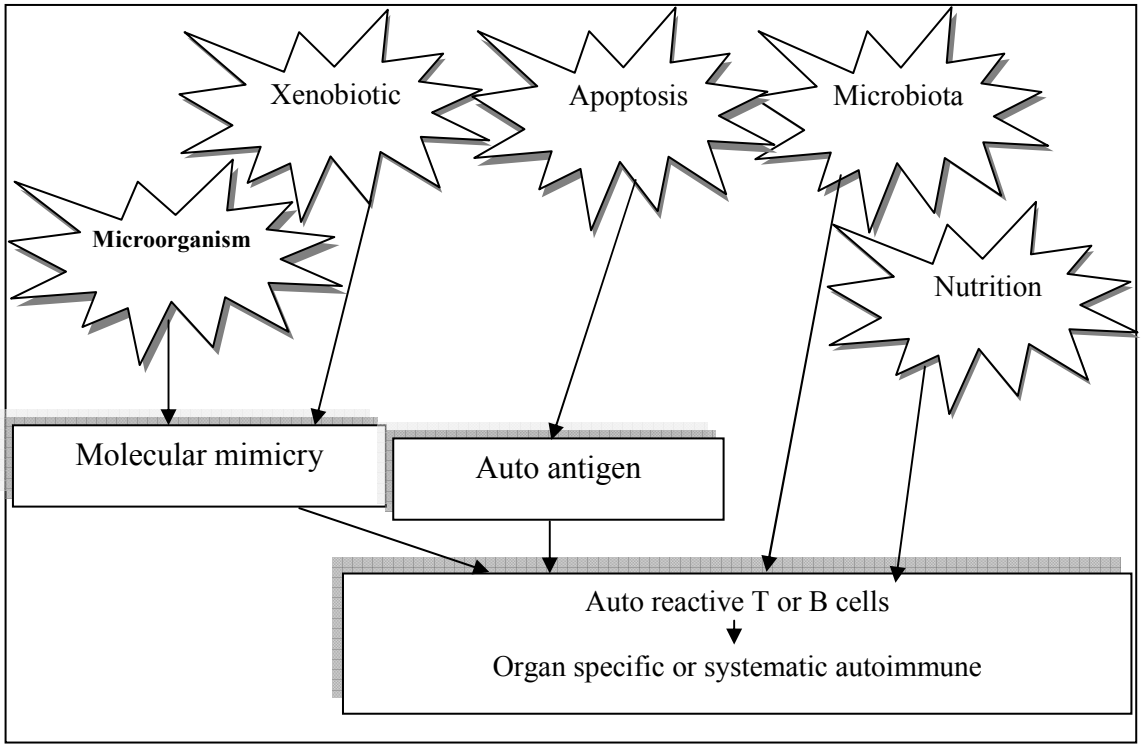
Autoimmune disease known as disease in which antibodies directed against bodies own tissues, the immune system depend on two factors in the immunity, the first is inactivation and rejection of foreign substances and the second is the differentiation between the foreign or own body material, the certain mechanism in autoimmunity is not known exactly, one of the possibilities that a certain body protein may be altered by viral infections, by combination with drug or chemicals that then recognized as foreign and directed by the autoimmunity (The free dictionary/2022)

Autoimmune disease are divided into 2 types: organ specific in which the T cells and antibodies react to certain antigen at specific tissue, examples T1DM and Graves' disease, the second type is non organ specific or systematic in which the antibodies directed against antigen spread at various tissue in the body, example: Systematic Lupus erythematous, the most common diseases affecting people are type 1 diabetes and thyroid autoimmune disease. Autoimmune diseases can be due to genetic factors (multiple genes with specific gene mutation) either in HLA or non HLA loci, or due to environmental factors:

- Nutrition
- Normal flora in intestine
- Infections specially viral infections
- Xenobiotic, example: tobacco smoking
- Pharmaceutical agent
- Hormones
- Vaccines
- Collagen and silicone implants (Wang et al., 2015)

Figure 5

Environmental factors in autoimmunity



Molecular mimicry is one of the mechanism that activate auto reactive T & B cells that generate (epitopes): the part of the antigen which the immune system recognizes, leading to the immune response, after T & B cell activation the adaptive and innate immunity, then all the factors along together led to (loss of tolerance): the body immune system cannot discriminate between own cells and foreign (Wang et al., 2015).

There are almost 100 identified autoimmune disease (SLE, RA, T1DM, and others) with several autoantibodies are produced by pathogenic B cells, the autoantibodies conceder as marker for autoimmunity for example in SLE anti Ro and anti dsDNA are produce. In T1DM the autoantibodies are GAD (Glutamic Acid Decarboxylase), IAA (Insulin Autoantibodies), IA-2A (Insulinoma Associated Autoantibodies), Islet Cell Cytoplasm Autoantibodies (ICA), and (Zinc Transporter-8 Autoantibodies) ZnT8A which all direct against pancreatic beta cells that lead to T1DM (Xiao et al., 2021).

GAD antibodies test is broadly used in Palestine for diagnosis of T1DM, in some cases if the diagnosis of T1DM was in early stages the test result may be negative in this case other antibodies test can be done, or the test can be repeated again after months.

Patient with type 1 diabetes are at high risk of developing other autoimmune disease, primarily thyroid autoimmune disease (Graves and Hashimoto), secondly coeliac disease (immune reaction to protein called gluten found in wheat and rice) which trigger the autoimmunity against the intestine and damage them, other autoimmune disease may developed in T1DM like rheumatoid arthritis and SLE but in rare cases, so patient with T1DM need to do regular testing for at least thyroid function test and coeliac disease (DiMeglio et al., 2018).

3.3 Genetic factors

Prior to stage one a genetic susceptibility for T1DM risk is explained by, Human Leukocyte Antigen (HLA) region on chromosome 6 account for 30%-50% of this risk, remaining genetic risk in non-HLA Loci found either in moderate or low effect. The reason why the effect is varied for these loci is that they need other environmental factors to work with (Rewers et al., n.d.).

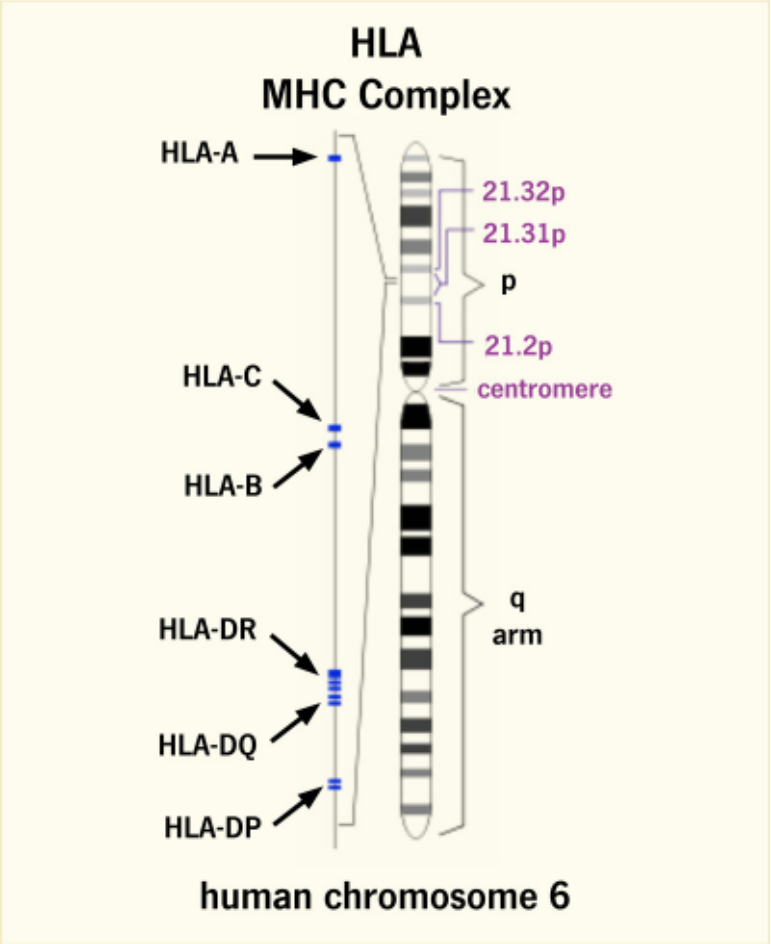
HLA- I and HLA –II account for about one half of the genetic risk for type 1 diabetes, with three amino acid located in HLA-2 define almost 90% of the variation in MHC (Major Histocompatibility Complex) that affect antigen binding, other non MHC loci related to type 1 diabetes affect more gene regulation rather than altering protein structure (Rich et al., 2018).

High risk for developing T1DM in people who has relative with the disease, for example in identical twins the risk is 25-50% while in sibling the risk is 6-7%, specific allele for HLA class II play an important role in T1DM, example if a combination between DR4 & DQ8 allele can increase the risk for T1DM (Primavera et al., 2020)

Chromosome 6p21.3 has a gene rich region that code for HLA class I and class II molecules this region called MHC, HLA which play a role in immune response either by differentiation between self and non self or by presenting the antigen to the immune system (Rich et al., 2012)

Figure 6

Human chromosome 6, genomic localization of MHC on chromosome 6p21.31 and position of HLA class I & II



Note: Rich et al., 2012.

Some patient with T1DM has HLA genetic variations which involved in presenting antigen to the immune cells and initiate the production of autoantibodies, but the actual reason for autoimmunity thought to be result of immune cell sensitized to component of islet tissue rather than autoantibodies (Britanica, 2023).

3.4 Environmental factors

The increase in T1DM incidence in the previous years cannot be explained by genetics factor only, the environmental and behavioral factors are the reason for this increase (DiMeglio et al., 2018). Two identical twins (monozygotic) with identical genes have different health fate, due to differences in exposure to environmental factors (Saberzadeh-Ardestani et al., 2018).

Host with genetic and immune factors along with environmental triggers together lead to T1DM by direct beta cell damage, abnormal autoimmune response and inflammation, (Butalia et al., 2016).

Seasonality of type 1 diabetes: A population based three years cohort study in Japan concludes that the incidence of type 1 diabetes being higher in spring (Nishioka et al., 2020), this relationship may be explained by the increase viral infection in winter, which enhance the destruction of beta cell and triggering autoimmunity mechanism in T1DM.

Viral infection: the first study about the relationship between T1DM and Entervirus infections was in 1969 in which high level of Coxsackie virus antibodies was found in newly diagnosed T1DM patient, a rectal swabs and blood venous samples were collected from genetically predisposed children for T1DM detect that Enterovirus infection increase the progression of T1DM (Stene et al., 2010). Positive Enterovirus RNA and serology can lead to T1DM development, some studies suggested that prenatal infections of Enterovirus can increase the risk of having T1DM, other studies found no significant relationships (Rewers et al., n.d.).

A study in Romanian children age (0-14) found a marked increase in T1DM incidence after the first year of COVID-19 pandemic, from 11.6 per 100,000 in 2019 to 13.3 per 100,000 in 2020, much more than the previous years, also the new reported cases of T1DM in the second half of 2020 was much higher than in the second half of the previous year, which suggest the role of COVID-19 in triggering pancreatic autoimmunity (Vlad et al., 2021).

In viral infection the body immune system within hours start the response by attacking any forging bodies, by mistake some body tissue attacked by immune cells and destroyed, as the disease is more vigorous more confusion is occurs, so more cell is destroyed and more antibodies is released, another explanation for the autoimmunity mechanism is that some viruses replicate in specific body cell and as a result the virus contain some of human phospholipid so the immune system cannot discriminate between own and foreign cell, some protein associated with viruses and bacteria are closely resemble the body own protein so the immune system target not only the virus but also the self-tissue (Virus Mechanism in Autoimmunity, n.d.).

Recent report support that COVID -19 may increase the incidence of type 1 diabetes and the incidence of diabetic ketoacidosis, the number of new onset of diabetes has increased in 2020.

Breastfeeding and early induction to Bovine milk: breastfeeding is very important for the health of the baby as it contain very essential nutrients for baby growth, it has been hypnotized that breastfeeding can reduce allergic reaction and autoimmunity diseases such as type 1 diabetes (Butalia et al., 2016), a review of 21 articles conclude that lack of breastfeeding can be a risk factor for T1& T2 diabetes (Pereira et al., 2014).

In 2012 a pooled analysis was conducted of 43 retrospective studies concluded that there was a small reduction in the risk of T1DM associated with breastfeeding for more than 3 months (exclusive breastfeeding), other studies found a protective relationship between breastfeeding and developing T1DM (Rewers et al., n.d.).

Bovine milk contain a hormone known as insulin like growth factor1 (ILGF1), this hormone promote the production of androgen hormone like testosterone leading to the hormone imbalance rather than the huge amount of antibiotics and external hormone that is being pumped to the cows, all that can make the cow's milk a good area to research about its effect on children**.** Early induction to bovine milk can increase the risk of having T1DM, due to cross-reactivity between the human insulin and the milk which increase the risk of autoimmunity against beta cells (Saberzadeh-Ardestani et al., 2018). In number of studies it was found in newly diagnosed type 1 diabetes children antibodies against cow's milk protein. The hypothesis that cow milk can lead to type 1 diabetes and the possibility of avoiding T1D by preventing cow milk consumption was almost killed in 2018 by a study was published after 6 years of following up for two groups of children more than 2000 participants with first degree relevant of T1DM were included in randomized double blind placebo, to investigate the effects of cow's milk in T1DM, for both groups there were no differences either they consume hydrolyzed cow milk or untreated cows' milk, so it conclude that there is no relationship between cow's milk and T1DM. Other studies found similarities between the amino acid sequences of cows' milk protein and parts of human leukocyte antigen chain which increase the risk of type 1 diabetes development (Ludvigsson, 2019).

Vitamin D deficiency: Several studies support the role of vitamin D in autoimmune disease examples Sjogren syndrome, intestinal bowel disease, Autoimmune thyroid disease, Multiple sclerosis and type 1 diabetes mellitus, all immune cells express vitamin D receptors like dendritic cell, macrophages, and B and T cells, so it has a role as immunoregulatory, in T1DM Calcitriol supplementation (the active form of vitamin D) can reduce the level of autoantibodies and delay beta cell destruction at early stage of the disease, other studies mentioned vitamin D as protective factor from type 1 diabetes (Illescas-Montes et al., 2019).

Vitamin D level in both mother and child should be take into account while studding T1DM risk factors, as low level of serum vitamin D in pregnancy is associated with several health problems like preeclampsia.

Other environmental risk factors can lead to T1DM

The infant exposed to several antigens in the first year of life that enhance the immune system and oral tolerance leading to later developing of T1DM, examples of those factors: early induction to fruit, toxins, gluten, gut microbiota reduction, exposing to chemicals and possibility using of antibiotic (Saberzadeh-Ardestani et al., 2018)**,** several studies support the fact that early induction to gluten less than 6 month can increase the risk of T1DM and delaying exposure to gluten containing food was protective factor for T1DM developing (Rewers et al., n.d.).

Gut microbiota

Several studies support the role of gut microbiota in promoting or protecting from T1DM development as it modulates the immune system, gut microbiota can be affected by several factors for examples:

- Using of antibiotic
- Mode of delivery
- Diet in early life

All those factor affect the intestinal and gut microbiota, using of antibiotics can affect intestinal microbiota, but to date there's no direct evidence that antibiotics use can associated with T1DM, in this study two questions was included about microbiota the

first one if there was excess using of antibiotic in early childhood and the second if the child have too much diarrhea before having diabetes.

Mode of birth, incidence of T1D increased in babies who were delivered by cesareans sections, the bacteria strains that first colonized in the baby intestine can be either from his mother skin in case of caesarian section or from their mother's birth canal (Gülden et al., 2015).

The intestinal barrier separate the luminal antigens from the interior body, in case of disruption in this membrane an autoimmune disorder will happened like inflammatory bowel disease and celiac disease, increase in the permeability of intestine precede the clinical onset of type1 diabetes mellitus (Gülden et al., 2015).

Intestinal flora is essential in developing the immune system and tolerance for later disease of intestine, a study was done on rats, using the bio breeding rats (the animal model for type 1 diabetes) a rats that spontaneously develop type 1 diabetes but not all of the bio breeding rats develop the disease and this support the fact that not only the genetic factors affect type 1 diabetes but other environmental factors are associated with, in the rat study an analyze for the intestinal flora was done before the onset of diabetes also one group was receiving antibiotic treatment in order to evaluate the effect of antibiotic treatment in the amount of different bacteria, the result shows that the amount of bacteria was reduced in the rats that were receiving antibiotic from 10^10/g feces to 10^8/g feces, the study conclude that the faecal flora for each group is differ(group who develop and doesn't develop the disease), using of antibiotic delayed and lowered the diabetes incidence as it reduce the antibodies load leading to reduction in diabetes incidence and reduce stimulating of lymphocyte (Brugman et al., 2006).

BMI before pregnancy

Maternal BMI is linked directly to baby birth weight, several studies support the fact that obese mother are more likely to have baby with high birth weight (Qu et al., 2021), (Rewers et al., n.d.). The birth weight is also one of the risk factors that is associated with T1DM as previously mentioned (Harder et al., 2009).

The risk of developing gestational diabetes in the obese pregnant women is high and much higher in severely obese pregnant women, this obesity is linked directly to

macrosomia, and other study shows that maternal obesity is associated with large for gestational age infant (Kc et al., 2015).

The researcher hypotheses is that maternal BMI and later weight gain during pregnancy could be one of the risk factors for T1DM.

Birth weight

Cross sectional study was conducted between 2017 and 2019 in china to conduct the effect of birth weight and preterm birth and the risk of T1DM, high birth weight affect only girls with OR 3.15, for both genders the OR was 1.71 also preterm birth can increase the risk of T1DM (Huang et al., 2021).

T1D children have lower birth weight and lower BMI compared to with healthy children with no gender differences either according to study was done in Caucasian children (García Cuartero et al., 2009).

Result of case control studies have been inconsistence regarded the birth weight and T1DM.

Chemicals in salons (hair dye and straightening) during pregnancy

Pregnancy and early life is very critical phase in susceptibility, also preconception conceder as critical phase in future health of the baby, the life nowadays changed and the consuming of hair chemical has increased also the type of chemical used in salon is modified so more research is needed to find any reproductive risk will be associated with this chemicals, the most frequently cited chemicals names in related to salon are Nitrosamines, Toluene, and Formaldehyde ("Occupational Chemical Exposures Among Cosmetologists: Risk of Reproductive Disorders," 2013).

Below the table show the chemicals and their possible mechanism of action in reproductive outcome:

Table 2

Chemicals in salon and their effect in reproductive outcome

Occupational Exposure	Chemical	Reproductive Outcome	Possible Mechanism of Action
Hair dye	Nitrosamines	Undetermined	Undetermined
Nail polish	Toluene	Spontaneous abortion	Undetermined
Hair dye and nail polish	Formaldehyde	Alterations to female reproductive and endocrine systems	Genotoxicity, oxidative stress, disruption of the activity of proteins, enzymes, and hormones important for the maturation of the male reproductive system, apoptosis, and DNA methylation

Some studies and experimental on animals suggested that exposing to chemicals compounds in hair dye had effect in birth outcomes, either macrosomia or low birth weight, examples of some chemical ingredient within hair dye: (aromatic amines, organic solvents, phthalates, formaldehyde, and other compounds). (Jiang et al., 2018), limited study was found about hair saloon chemicals and pregnancy. The researcher hypothesize that using hair dye may interact with other factors that lead to T1DM.

Negative Emotion (stress) during pregnancy

A cross sectional study of 4400 individual to evaluate the effect of parenting stress effect in developing T1DM, it found an association between parental stress and presence of GAD autoantibodies at age 1 year, also mothers who exposed to violence and experience divorce were associated with islet autoimmunity in the children age 2.5 years (Rewers et al., n.d.).

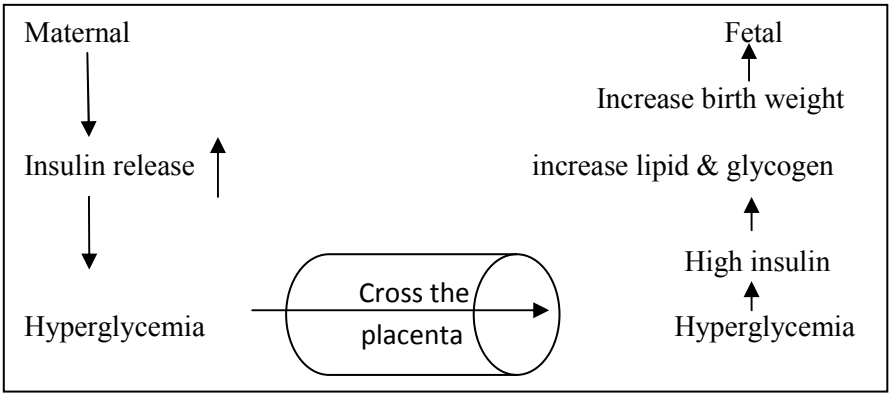
According to a population based family design cohort study, concluded that maternal anxiety/ depression during pregnancy seems to be associated with offspring T1DM (Smew et al., 2023)

Diabetes or gestational diabetes in pregnancy

High level of glucose in pregnancy can lead to increase insulin (hyperinsulinemia) which lead to high level of protein and fat storage in the baby so the baby birth weight will be high, more than 4 kg (macrosomia) (Kc et al., 2015), macrosomia is linked to T1DM (Harder et al., 2009).

Figure 7

Maternal hyperglycemia result in fetal



Hypertension and preeclampsia

Hypertensive is one of the chronic disease characterized by systolic blood pressure above 140 mm Hg or diastolic blood pressure of 90 mm Hg. Preeclampsia happened when pregnant women after 20 weeks of gestation suddenly have hypertension with several complication for both mother and fetus, pulmonary edema, renal and retinal injury, for fetus a growth restriction may occurred and placental disruption, also fetal and mother death (Karrar., et al, 2023).

Preeclampsia is also associated with preterm birth, which mean that the baby development is not completed and the birth weight may be less than the normal range, also preeclampsia increase the opportunity of caesarian section rather than normal delivery.

Smoking during pregnancy & passive smoker

Maternal smoking during pregnancy has a high risk for developing T1DM according to study was done in Sweden, a case control study that take into account HLA typing and same birth year for participant, each child with diabetes has 3 controls to matched with,

an odds ratio of 2.83 for 1-9 cigarettes smoking per day and odds ratio 3.91 for more than 9 cigarettes per day (Mattsson et al., 2015).

Lifestyle during pregnancy

Mother lifestyle during pregnancy including her nutrition and physical activity affect short and long term birth outcome, western countries are facing the challenge of obesity while other developing countries are facing under nutrition problems (Soltani et al., 2017).

Chapter Four

Methodology

4.1 Study design

An analytical case- control study was performed to achieve the aim of the study. As the study aim at looking for the risk factors associated with T1DM. 2 groups were included, the cases who developed T1DM, and controls who are healthy. Age of participants (1-22 years).

4.2 Setting

The study was implemented at 2 health care centers, in Nablus Governorate, the first is the governmental Nablus Public Health Centre (PHC)/ Al-Makhfya branch and the Palestine Diabetes Institute.

Palestine Diabetes Institute

A charitable non-profit centre that follows administratively and financially the Jerusalem Fund for Education and Community Development It provides many medical services a diabetic clinic for early detection and treatment of diabetes mellitus types, Ophthalmic clinic for diagnosis of diabetic retinopathy and vision examination, endocrinology and diabetic clinic for children, nutrition department that provide food program for diabetics, and lab for all laboratory analysis needed in diabetes care. The centre runs by 2 main diabetic doctors, Dr. Intesar Alalim for Type 2 diabetes and Dr. Mona Sharaf for type 1 diabetes and endocrinology, in addition to Dietician who help the newly diagnosed patients in preparing their food program and to calculate the carbohydrate in their meals. the canter also provide laboratory services.

Palestine Diabetic Institute has three branches, at Al-Bireh, Nablus and Hebron all provide the same services.

Governmental health care centre (Al-Makhfya branch)

Non-profit governmental organization that belongs to Ministry of health, the only governmental centre in Nablus that provides services for patient with T1DM, it provides many other medical services:

- Medical laboratory test in which a wide range of blood and body fluid test is available.
- Nursing services: there is regular recording for patients high, weight and blood pressure in special nurse room.
- Pharmacy: that provides several kinds of drugs for a wide range of diseases and insulin pin monthly for patient of T1DM.
- Nutritional: to follow up with all diabetic patients.
- Other services for all types of diabetes and other health conditions. Services for T1DM were only performed on Monday each week.

4.3 Study population

The study population consisted of the patients diagnosed with T1DM and their mothers. For control healthy participants and their mothers. The size of study population was 118, the cases was taken from newly diagnosed T1DM after COVID-19.

4.4 Sample size and sampling technique

The sample size was 118 participants (68 diagnosed with T1DM and 50 control), convenience sampling was used, each Monday every week the governmental health center receive T1DM patients only, every patient meet the criteria for research was included, also every Sunday and Tuesday the sample were gathered from the Palestinian diabetic institute. The control was also gathered from the same health centers, as there was other department than diabetes in the governmental health center, from the pregnancy clinic or from insurance clines.

The data was collected at the health centers in Nablus city, information was gathered through researcher by face-to-face meeting with the mothers and their sons, if the mother is absent the researcher call her by phone.

4.5 Inclusion and exclusion criteria

The study includes male and female, who were diagnosed after April 2020 to August 2022, and age between 1 and 22 years old, from Nablus city, any other health condition will be excluded any diagnoses with T1DM done before April 2020 will be excluded, any patient with other disease along with diabetes will be excluded like endocrine disease, any questionnaire was not completed was excluded from the study.

In control group, all participants are healthy with no previous history of disease till the time of taking the questionnaire, almost at the same age group of the cases (1 – 22) years, from both genders.

4.6 Data collection tools

Structured questionnaire was used to collect the data, the questionnaire (annex 1 and 2) developed based on theoretical framework that includes genetics and environmental risk factors (Saberzadeh-Ardestaniet al., 2018), and after reviewing other related risk factors, (Maahs et al., 2010; Norris et al., 2020; Primavera et al., 2020; Rewers et al., n.d.).

The tool consisted of maternal and patients parts, each included questions about environmental and genetics factors in addition to the sociodemographic data, 3 sections. The first category (The demographic data) include groups of: gender, maternal education, parental education, age of having diabetes, age, date of diagnoses, number of children and economic status. The second category includes two sections the both sections the maternal and patient part included questions about the environmental and genetics factors that related to T1DM. All participating were tested by the study tool (the questionnaire).

4.7 Reliability and validity of the tool

The questionnaire was reviewed by 6 doctors, and gave the possible modification or additions:

A doctor at Al-Najah National University, head of division of immunology, microbiology and pathology, PhD Degree in health sciences molecular microbiology, reviewed the questionnaire with some modification, for the microbiota section he added the questions about if the child had took several antibiotic in his childhood and if he suffer from regular diarrhea, for COVID-19 section he add the symptoms to see if there is a relation between specific symptoms and the disease occurrence.

A diabetic specialist and endocrinologist at Palestinian diabetic institute reviewed the questionnaire and added some questions and details, type of delivery, if there is antibiotic medication was took in pregnancy mention the name, if there was genetic testing and the result.

Diabetologist and head of the Palestine Diabetic Institute- Nablus branch, reviewed the questionnaire with no additions.

A diabetic specialized at Ministry of health also reviewed with no additions.

Assistance professor at Al-Najah national university- public health department, also reviewed with no additions.

Assistance professor at Al-Najah national pharmaceutical sciences, head of pharmaceutical chemistry and technology, he reviewed the questionnaire with no modifications.

The added questions were; if there was too much use for antibiotic in early childhood and if the child had frequent diarrhea, mode of delivery also was added, if there was genetic testing, if there was using for antibiotic in pregnancy and COVID-19 symptoms.

A pilot study was performed on 15% of the study sample to test the questionnaire, no modification was done and so the pilot study was included in the total sample. The reliability of the study was calculated using Cronbach's Alpha: for prenatal factors (15 items) the result was 0.513, and for the child factors (18 items) the result was 0.800.

4.8 Ethical considerations

The approval of Institutional Review Board (IRB) at An-Najah National University was obtained to conduct the study, (Annex 2), the IRB consent and the approval from Ministry of health at Nablus was obtained to collect the data (Annex 3), Consent form was read for the participants to ensure their acceptance to participate (Annex1). The collected data was anonymous and confidentially kept no names or any signs that may reveal the identity of the participants. The participants were informed of the study objectives to reassure them of in-existence of any harm or risk from their information, also the participants were informed that they have the right to ask any questions or to withdraw at any time.

4.9 Field work

The study was run over a period of 6 month from March 2022 to the end of August 2022. The visits held on each Monday to the governmental center where patients living with diabetic are followed up. And the visits for the PDI, were programmed each Sunday and Tuesday of each week. 7 visit was made to MOH clinic and 10 visit to Palestinian diabetic institute. Face to face interview was done with each participant who met the criteria of the study at the two health centers, at the beginning the study name and purposes was read for each participant, a consent form was also read and they were asked if they want to participate, then the questionnaires were filled by the researcher.

4.10 Study variables

In this study environmental factors including viruses and COVID-19 virus, with familiar symptoms for COVID-19 was included (diarrhea, dry cough, high body temperature, and loss of taste and smell), also breastfeeding, early induction to Bovine milk or gluten and fruit, vitamin D deficiency, decrease in gut micro biota and genetic factors.

Dependent variable: Proved diagnosed of T1DM.

Independent variables: environmental and genetic factors at maternal and child level.

Table 3

Study variables (Maternal factors) with their conceptual and operational definition

Variable	Conceptual definition	Operational definition
1. BMI	statistical index that use the body weight and high to generate an estimate of body fat for both male and female, the equation of calculation is {weight (in kg)/ height^2 (in m^2) }. (Weir et al., 2023)	Underweight less than 18.5 Normal 18.5-24.9 Overweight 25-29.9 Obese greater than or equal 30.0
2. Preeclampsia	Gestational hypertension systolic above 140mmHg and diastolic above 90mmHg after 20 weeks of gestation and with proteinuria. (Karrar., et al, 2023)	Yes: if she had experience preeclampsia. No: if not
3. Hypertension	Blood pressure above 130/80 mmHg (NHLBI/2022)	Yes: if she is hypertension patient. No: if not
4. Gestational diabetes	Diabetes that developed during pregnancy and usually disappear after delivery ("Diagnosis and Classification of Diabetes Mellitus," 2014)	Yes or no question
5. Chemicals in beauty centers	Substance that has a defined composition that can change the hair nature (Health line/2020)	Yes: if she exposed to hair or no if not exposed.
6. Smoking	The act of inhaling and exhaling the fumes of burning plant material. (Henningfield., et al, 2023)	Yes or no question
7. Passive smoking	Second hand smoke, the smoke exhaled by the smoker (mainstream smoke) and the smoke that rises directly from the smoldering tobacco (sidestream smoke) (Henningfield., et al, 2023)	Yes: if she lived at the same environment with smoker at the time of pregnancy, and inhaled directly the smoke of the smoker while being close to him. No: if not

Table 4

Study variables (patient factors) with their conceptual and operational definition

Variable	Conceptual definition	Operational definition
1. Birth weight	The first weight of the baby, taken just after being born (Medline plus/2022)	Less than 2.5 low 2.5-4 normal Above 4 overweight
2. Covid-19 (for the patient)	Infectious disease caused by SARS-COVID2, appear in December 2019 and spread worldwide (News medical 2020)	Yes: exposed to covid-19 infection before having T1DM. No: didn't exposed to COVID-19 before diagnosis of T1DM.
3. Breastfeeding	Process of feeding a mother's breast milk to her infant (WHO/ 2015)	Yes: breastfeeding only without formula milk not less than 6 months. No: not complete breastfeeding/ or there is no breastfeeding.
4. Cow milk	Milk obtained from dairy cows (white liquid), containing proteins, lactose, fat and minerals.	Yes: if he had drunk earlier than 1 year. No: after 1 year
5. Fruit earlier than 6 month	According to CDC recommendations, the baby can be introduce to fruit after 6 month (CDC / 2021)	Yes: if introduce to fruit earlier than 6 months. No: if not.
6. Gluten	Protein found naturally in some grains including wheat, barley, and rye (Saberzadeh-Ardestani et al., 2018)	Yes: if the baby had eaten any food before 3 month of age including cereal and bread. No: if not
7. Family history of diabetes	Record of the disease and health conditions of individual and his biological family members.	Yes: if there is other family member has T1DM. NO: IF NOT
8. Negative emotions during pregnancy	The once that can be unpleasant to experience and can cause disruption to daily life include: anger, sadness and fear… (Very well mind/2023)	Yes: if she experience any emotional event fear sadness, death of someone dear during pregnancy… No: if not

4.11 Data analysis

Data were analyzed by using Statistical Package for Social Sciences (SPSS) version 21, (mean SD for continuous data), (frequencies and percentage for categorical data). The Chi- squire test was used for testing relationship between categorical variables. The statistical significance was set at $P < 0.05$.

Chapter Five

Results

Sociodemographic data

This study includes 118 participant: 53.4 % are male (50.8% are cases and 49.2% are controls), 46.6% are female (65.5% are cases and 34.5% are controls), the number of male to female is not matched in both groups. In maternal education level 50.8% are elementary (60.0% are cases and 40.0% are control), while paternal education level 65.3% are elementary educated level (54.5% are cases and 45.5% are control), elementary education levels was the higher proportion at both maternal and paternal in cases. 89% of economic status is in the middle, age of participant 1-22 years with mean of age 8.8703, see table (5).

Table 5

Distribution of percentage of participants according to their demographic data

Variable	Category	Case	Control	Total	Chi square p.value
		No. (%)	No. (%)	No. (%)	
Gender	Male	32 50.8% 27.1%	31 49.2% 26.3%	63 100.0% 53.4%	0.077
	Female	36 65.5% 30.5%	19 34.5% 16.1%	55 100.0% 46.6%	
Maternal education level	Elementary/secondary	36 60% 30.5%	24 40% 20.3%	60 100.0% 50.8%	0.465
	Diploma	7 63.6% 5.9%	4 36.4% 3.4%	11 100.0% 9.3%	
	B.A	19 48.7% 16.1%	20 51.3% 16.9%	39 100.0% 33.1%	
	M.A and higher	6 75.0% 5.1%	2 25.0% 1.7%	8 100.0% 6.8%	
Paternal education level	Elementary/secondary	42 54.5% 35.6%	35 45.5% 29.7%	77 100.0% 65.3%	0.172
	Diploma	7 63.6% 5.9%	4 36.4% 3.4%	11 100.0% 9.3%	
	B.A	13 54.2% 11%	11 45.8% 9.3%	24 100.0% 20.3%	
	M.A and higher	6 100.0% 5.1%	0 0.0% 0.0%	6 100.0% 5.1%	
Economic status	Low	6 85.7% 5.1%	1 14.3% 0.8%	7 100.0% 5.9%	0.156
	Middle	60 47.1% 5.8%	45 42.9% 38.1%	105 100.0% 89.0%	
	High	2 33.3% 1.7%	4 66.7% 3.4%	6 100.0% 5.1%	
Mean of age /case		8.8703±5.2053			0.101
Mean of age /control		8.5600±5.83938			

Table (6) show that 75% of the underweight mothers from the cases compared to 25% underweight of the mother of controls (p 0.009). 42.9% of obese mothers are from cases and 57.1% are control. 87.5% of the mothers of cases had hypertension compared to 12.5% in mothers of controls (OR 5.623, p 0.077). 84.6% of the mothers of cases had exposed to hair saloon chemicals during their pregnancy compared to 15.4% in mothers of control (OR 4.632, p 0.033). 73.6% of the mothers of cases had passive smoking compared to 26.4% in the mothers of control (OR 3.458, p 0.002). 70% of the mothers of cases had consumed soft drinks during pregnancy compared to 30% in the mothers of controls (OR 2.217, p = 0.051).

Table 6

Distribution of percentage of participants and p value according to their maternal factors

Variables	Category	Case N0. (%)	Control No. (%)	Total No. (%)	chi square p.value	Odd ratio	95% CI lower	95% CI Upper
1. BMI pre-pregnancy	Underweight	3 (75.0)	1 (25.0)	4 (100)	0.009	-	0.4544	2.0456
	Normal	43 (71.7)	17 (28.3)	60 (100)			1.1659	1.4007
	Overweight	16 (40)	24 (60.0)	40 (100)			1.4413	1.7587
	Obese	6 (42.9)	8 (57.1)	14 (100)			1.2749	1.8679
2. Extra weight gained during pregnancy	Yes	16 (64.0)	9 (36.0)	25 (100)	0.311	1.4017	0.5622	3.4946
	No	52 (30.0)	41 (70.0)	93 (100)				
3. Preeclampsia	Yes	1 (33.3)	2 (66.7)	3 (100)	0.386	0.358	0.2324	4.064
	No	67 (59.3)	48 (40.7)	115 (100)				
4. Hypertension	Yes	7 (87.5)	1 (12.5)	8 (100)	0.077	5.623	0.8294	1.4206
	No	61 (55.5)	49(44.5)	110 (100)				
5. Gestational diabetes	Yes	5 (55.6)	4 (44.4)	9 (100)	0.843	0.731	1.0393	1.8496
	No	63 (57.8)	46 (42.2)	109 (100)				
6. Exposed to hair saloon chemicals	Yes	11 (84.6)	2 (15.4)	13 (100)	0.033	4.632	0.9269	1.3808
	No	57 (54.3)	48 (45.7)	105 (100)				
7. Experience negative emotional events in pregnancy	Yes	27 (60.0)	18 (40.0)	45 (100)	0.415	1.171	1.2512	1.5488
	No	41 (56.2)	32 (43.8)	73 (100)				
8. Smoker	Yes	5 (55.6)	4 (44.4)	9 (100)	0.896	0.913	1.0393	1.8496
	No	63 (57.8)	46 (42.2)	109 (100)				
9. Passive smoker	Yes	39 (73.6)	14 (26.4)	53 (100)	0.002	3.458	1.1415	1.3868
	No	29 (45.5)	36 (54.5)	65 (100)				
10. Consumption of soft drinks	Yes	28 (70.0)	12 (30.0)	40 (100)	0.051	2.217	1.1516	1.4484
	No	40 (51.3)	38 (48.7)	78 (100)				
Total		68 (57.6)	50 (42.4)	118 (100)				

Table (7) show that 100% of cases had family history of T1DM (p 0.000, OR 42.6907).

Table 7

Distribution of percentage of patient risk factors & chi square p. value

Variable		Case No. (%)	Control No. (%)	Total No. (%)	chi square & p.value	Odd ratio	95% Confidence Interval CI	
							lower	Upper
Birth weight	Low	7 (77.8)	2 (22.2)	9 (100)	0.171	-	0.8833	1.5612
	Normal	54 (54.0)	46 (46.0)	100 (100)			1.3606	1.5594
	High	7 (77.8)	2 (22.2)	9 (100)			0.8833	1.5612
Exposed to COVID-19	Yes	26 (59.1)	18 (40.9)	44 (100)	0.804	1.101	1.2579	1.5603
	No	42 (56.8)	32 (43.2)	74 (100)				
Other viral infection	Yes	2 (100)	0 (0.0)	2 (100)	0.221	0.971	1.3396	1.5225
	No	66 (56.9)	50 (43.1)	116 (100)				
Breastfeeding	Yes	63 (57.8)	46 (42.2)	109 (100)	0.896	1.096	1.3278	1.5162
	No	5 (55.6)	4 (44.4)	9 (1000				
Cow milk earlier than 1 year	Yes	3 (50.0)	3 (50.0)	6 (100)	0.698	0.723	0.9252	2.0748
	No	65 (58.0)	47 (42.0)	112 (100)				
Induction to fruits earlier than 6 months	Yes	21 (50.0)	21 (50.0)	42 (100)	0.213	0.617	1.3423	1.6577
	No	47 (61.8)	29 (38.2)	76 (100)				
Induction to gluten earlier than 3 month	Yes	2 (66.7)	1 (33.3)	3 (100)	0.748	1.485	0.1009	2.7676
	No	66 (57.4)	49 (42.6)	115 (100)				
Family history	Yes	20 (100)	0 (0.0)	20 (100)	0.000	42.6907	1.4095	1.6109
	No	48 (49.0)	50 (51.0)	99 (100)				
Total		68 (57.6)	50 (42.4)	118 (100)				

Chapter Six

Discussion and Conclusion

This study is one of the fewest studies that report the risk factors of T1DM, either genetically or environmentally at maternal level and child level, and may be the only in Palestine.

Among 118 participants, 68(57.6%) were diagnosed with T1DM patients and 50(42.4%) were controls. Maternal risk factors, hypertension, hair saloon chemicals, passive smoker, and consumption of soft drinks were the main risk factors associated with T1DM in this study. For patients risk factors family history with T1DM was the main significant risk factor in this study.

Most of the previous studies about association of pre pregnancy BMI and T1DM results were focusing on obesity of the mothers and offspring later developing of T1DM. A nationwide, prospective, population base case control study, in Sweden. To investigate the influence of maternal BMI and gestational weight gain on the subsequent risk of children T1DM. It concluded that maternal obesity is a risk factor for T1DM in the offspring, and influence the age of onset of T1DM which emphasis the importance of a normal maternal BMI to decrease the incidence of T1DM. Also among children in age group (15-19) years, there were more mothers who had been underweight in their pregnancy, while in the youngest age group (0-4) years, the pattern was reversed (Lindell et al., 2018). In our study, 75% of the underweight mothers from the cases compared to 25% of the mother of controls (p 0.009, CI of 95% 0.4544-2.0456). 42.9% of obese mothers are from cases compared to 57.1% obese of the mothers of controls (p 0.009, CI of 95% 1.2749-1.8679)

A population case control study was done in U. K. from hospital abstracted data found that older mother and mother of preeclampsia increase the risk of T1DM, while breastfeeding decrease the risk (McKinney et al., 1999). A little evidence of an increase of the risk of T1DM in children born to mothers who had preeclampsia during pregnancy (OR 1.10, P 0.17) (Henry et al., 2011). Hypertension in pregnancy can lead to decrease blood flow in placenta which affect nutrition delivery to the fetus. In this study there is a significance association between hypertension and T1DM (P 0.077, OR

5.623, and CI of 95% 0.8294 - 1.4206). While preeclampsia was not significant (P 0.386, OR 0.358, and CI of 95% 0.2324-4.064).

Exposure to hair salon chemicals during pregnancy: there are no studies on occasional use of hair products during pregnancy and future developing of T1DM. In this study 84.6% of the mothers of cases had exposure to hair salon chemicals during pregnancy compared to 15.4% in the mothers of controls (P 0.033, OR 4.632, and CI of 95% 0.9269-1.3808). Hair dye can contain potentially harmful chemicals. The chemicals can be absorbed by the skin, and could cause harm to the fetus. Nowadays the use of hair saloon chemical increase wildly, including hair dye and straitening. This field should have attention in future studies to evaluate any health consequences on the offspring of exposed mothers during pregnancy.

Maternal smoking in pregnancy has a high risk for developing T1DM according to study was done in Sweden, taken into account HLA typing and same birth year. For each child with diabetes 3 controls was matched, an odds ratio of 2.83 for 1-9 cigarettes smoking per day and odds ratio 3.91 for more than 9 cigarettes per day (Mattsson et al., 2015). As smoking for women conceder to be not accepted culturally but for men is accepted and familiar in our culture. The passive smoking gives a significant relationship with T1DM in this study (P 0.002, OR 3.458, and CI of 95% 1.1415 - 1.3868). While being smoking in pregnancy didn't give a significant relationship (p 0.896, OR = 0.913, CI of 95% 1.0393 - 1.896). However other studies support that fetal exposure to smoking is associated with a reduce risk of T1DM. A systematic review and meta-analysis was done to synthesize current evidence on the association between perennial smoking and incidence of T1DM in the offspring. The study include 535 records including 25 927 T1DM cases. It conclude that maternal smoking during pregnancy may associated with reduced risk of T1DM, n = 22, RR 0.78, CI 0.71– 0.86, I2=69% (Edstorp et al., 2022). A nationwide register based study with family based design, case control (quasi experiment) was done in Sweden, it included 2995321 children who were born between 1983 and 2014 and followed them for the diagnosis of T1DM until 2020, the results support for a protective effect of maternal smoking on offspring T1DM (22% lower risk, Hazard Ratio 0.78) compared to their sibling. This inverse relationship between smoking and risk of T1DM could hypothetically be attributed to nicotine. Studies show that nicotine can suppress systematic inflammation

and autoimmunity. The association between smoking and diabetes could be related to immunity rather than diabetes, because there was lack for association between maternal smoking and T2DM (Wei et al., 2022).

Consumption of soft drinks: Mother life style and nutrition affect her baby health as Baker developing theory that was previously mentioned proposed that mother nutrition affect her baby future life including the risk of metabolic syndrome (diabetes, hypertension, insulin resistance and obesity) (Wadhwa et al., 2009). High amount of energy is present in soft drinks, and as the pregnant women consuming more energy more weight gain is occurs for both mother and fetus and high amount of triglyceride and glucose is transferred to the fetus, as a result high birth weight will associated with consuming high energy food (Coelho et al., 2015), and the birth weight is mentioned as one of the risk factor that is associated with T1DM (Huang et al., 2021). Another point about those drinks that it containing high amount of sugar and sweetened. The infant of the mother that consume high amount of sugar is called (second hand sugar) just like second hand smoker. The glucose and fructose can cross the placenta and reach to the baby blood stream, with various effects for example: preterm delivery, preeclampsia, gestational diabetes, increase birth weight, child obesity and other effects (Goran et al., 2019).

A qualitative research was done in 2018 for the last 10 years to assess the effect of low vitamin D levels in mothers, neonates, and children, it conclude that in the middle east there was a widespread for low level of serum vitamin D, which is directly associated with developing many serious health conditions. In pregnant women it increase possibility of gestational diabetes, osteoporosis and hypertension (Elsori et al., 2018). It's worth mentioning that the majority of people have insufficiency and deficiency of vitamin D level in Palestine. Severe vitamin D deficiency is highly prevalence among pregnant women in Palestine according to study was done in 2021(Saabneh et al., n.d.). Highly intake of vitamin D either supplementation or in dietary in pregnancy conceder to be prenatal protective factor against T1DM (Rewerts et al., 2016). In this study unfortunately not all the participant were tested previously for their vitamin D level, but all who were tested were having deficiency in their vitamin D levels, 34.7% of the mothers were tested for their vitamin D level, while the other didn't test their levels. So

the overall association can't be evaluated, and the question about vitamin D was excluded from the study analysis section.

Genetically, HLA is responsible for almost 50% of genetic in T1DM, several studies support the fact of monitoring autoantibodies of beta cell, by detect genetic susceptibility and inhibiting the autoimmune process and preserve beta cell in early detection of genetic susceptibility (Dayan et al., 2021). Over than 60 non HLA loci are associated with increased risk of T1DM, any family history of T1DM or HLA was used to predict occurrence of T1DM in future, also HLA and non HLA loci can be used together as a risk factor for T1DM, but non HLA alone cannot be used alone for this prediction due to its relation to other disease (DiMeglio et al., 2018). According to our study, family history of T1DM was associated with increased risk of T1DM (p 0.000, OR 42.6907, CI of 95% 1.4095 - 1.6109).

According to this study no provided significance between previous exposed to COVID-19 and T1DM (p 0.804, OR 1.101, CI of 95% 1.2579-1.5603). Actually the real association between T1DM and COVID-19 can be estimated by molecular method through testing viral RNA presenting in the blood or stool or tissue of newly diagnosed T1DM patient. Also same HLA typing should be take into account in control group for more accuracy in result. But in this study the questionnaire was the main tool in extracting the data, so further studies should be done to estimate the association.

No significance association was found with the other risk factors for mothers and patient included in this study. Sample size was small, if the size was more there could be other significant risk factor associated with T1DM.

Finally T1DM is a result of several risk factors which all together enhance the disease, wither genetically or environmentally from the starting point of pregnancy to the time of disease occurrence.

6.1 Limitation

Several limitations should be noted:

- 3 participants from the cases, and 1 from the control didn't answer all the questions so their questionnaire was eliminated. Also 3 questionnaire was excluded from the study due to their ages (above 22 years).
- Recall bias, the answers depend on the participant memory so one of the limitation for this study was memory bias.
- At diabetic center the load of patient was low, so long time was needed to gather the information. Many patient have combination of diabetes and endocrine disease, also patient with history of having diabetes before 2020 were excluded, the time for gathering information was long, as a result the number of cases was declined from 100 to 71 which is another limitation for this study (small sample size).
- In seasonality of the disease the date of diagnosis was recorded for each patient but unfortunately many of them were having the symptoms months before going to any health center and diagnosed, till they developed DKA and coma then admitted to the hospital. So the time of diagnosis doesn't represent the actual time of developing the disease.
- In vitamin D previous cheek, not all the mothers have tested their vitamin D level only 34.7% of the mothers were tested for the level of serum vitamin D. So the relationship between vitamin D and T1DM can't be estimated in this study.
- In COVID-19 section many patient may expose to the disease without knowing or testing, so the real significance for COVID-19 in T1DM need to be estimated with antibody titer or other COVID-19 test (example: PCR).
- Loose definition, and open questions, make the conclusion very week, extracting data from mothers using retrospective study from several years ago, depending on the mothers memory make the conclusion very week. Trying to minimize this limitation the researcher exclude some questions from the analysis, like using antibiotic during pregnancy, obesity in early childhood, and other open questions.
- Genetic testing for T1DM: not all the patient have previously done any genetic testing to estimate if there was genetic factor associated with the disease development, so this question was excluded from the analysis, and the researcher

deepened on previous family history of T1DM to estimate the genetic risk in T1DM development.

Despite the limitation, the study provide basis for further studies about maternal factors and environmental factors in T1DM pathogenesis.

6.2 Recommendations

The results is important in future studies of mothers during pregnancy lifestyle and exposing to chemicals in further health problems in there fetus life, so the researcher recommend further studies to be undertaken to take more sample size. In COVID-19 section sample testing for antibodies presentation in newly diagnosed T1DM patient may be done, also PCR testing.

In chemical section an expanding in details of chemicals names and at which trimester the exposure was, and even a prospective study for the pregnant women who intended to do any hair treatment method may be useful more.

Even preconception questions should be take into account in further studies about the risk factors for T1DM, specially the mother and father diet and weight.

In disease like T1DM in which not only the high risk group are susceptible to the disease, more researches should be done that include large sample size of pregnant women's and following them and their children prospectively to investigate the effect of exposing to several environmental risk factors in future developing of T1DM.

In general, studying multifactorial disease like T1D conceder to be not easy with a poorly understood pathophysiology, the disease is very complicated many axis play role in the developing of the disease, but detecting the highly significant factors and the high risk group could be helpful in future prevention or delaying of T1DM.

List of Abbreviations

Abbreviation	Meaning
T1DM	Type 1 Diabetes Mellitus
COVID-19	Corona Virus Disease of 2019
BMI	Body Mass Index
WHO	World Health Organization
CDC	Centers for Disease Control and prevention
HLA	Human Leukocyte Antigen
MHC	Major Histocompatibility Complex
IDF	International Diabetic Federations
APC	Antigen Presenting Cells
PDI	Palestine Diabetic Institute
ACE-2	Angiotensin Converting Enzyme-2
OR	Odd Ratio
SLE	Systematic Lupus Erythematous

Definition of Term

Type 1 Diabetes Mellitus (T1DM): a chronic condition where's the pancreas doesn't make insulin or make very little insulin, which in term help in regulating blood glucose level, usually developed in children, teen, and young adult, also called Juvenile Diabetes. (CDC, 2022)

Case control study: study design to determine if an exposure is associated with the outcome or disease. The cases are a group already have the outcome, and the controls are a group known to be free of the outcome. By looking back in time, we know which group had the exposure and then comparing the frequencies in each one, if the exposure found more in cases this mean the exposure may be linked to the outcome. (Tenny et al., 2023)

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Appendices

Appendix A

Consent form & questionnaire

An-Najah National University

Faculty of Graduate Studies

Public Health Department

A questionnaire

Dear participant,

The researcher is carrying a study exploring risk factors associated with Type 1 Diabetes Mellitus, your completion of this questionnaire is a valuable contribution to the research field of diabetes in Palestine and is appreciated by the researchers, honesty and transparency in answering the questions is necessary. The information you are providing is confidential and is collecting only for research purposes, you have the right to withdraw at any moment without any explanations

Appreciating your participation

The researcher: Bara'a Rawajbeh

Supervisor: Dr. Mariam Al-Tel

Demographic information

- **Participant No.:**
- **Gender: Male female**
- **Maternal educational level**

- Elementary/secondary
- Diploma
- BA
- Master or higher

- **Paternal educational level**

- Elementary/secondary
- Diploma
- BA
- Master or higher

- **Age of having diabetes:**
- **Age:**
- **Date of diagnosing: / /**
- **How do you discover the disease?**
- **No. Of children: () Male () female**
- **What is the family economic status?**

- Low
- Middle
- High

Risk factors associated with type 1 diabetes

❖ **Mother questions**

1. Weight gained during pregnancy……..Kg. Height:……. BMI:…….
2. Weight pre pregnancy…….

BMI pre pregnancy being pregnant:

Do you gain high weight during pregnancy? Yes no

If yes how much?.....Kg

If yes at which trimester was the main gain

Questions	Yes	No	uncertain	Note
1. Do you gain too much weight during pregnancy? If yes how much?				
2. Have you experienced preeclampsia during pregnancy?				
3. Have you experienced gestational diabetes?				
4. Have you exposed to chemicals during pregnancy? Ex, hair salon(proteins, hair color)				
5. Did you have infections like UTI or others during pregnancy?				
6. Did you have medication during pregnancy? For example antibiotic, if yes name them.				
7. Have you experience emotional disorders events?				
8. Do you have hypertension? If yes and you took medication mention them..				
9. Do you have any pulmonary infections influenza or COVID during pregnancy?				
10. Do you have diabetes? If yes which type and mention your medication….				
11. Do you smoke?				
12. Are you a negative smoker?				
13. Did you took mineral and vitamins during pregnancy?				

14. Did you check vitamin D level? If yes what's the level?				
15. Do you consume soft drink?				
16. Do you relay on fast food in your eating?				
17. Do you play sport?				

- **1st trimester …….**
- **2nd trimester …….**
- **3rd trimester ……..**

❖ **Diabetic child questions:**

Do your child have any health conditions other than diabetes? ……. (The answer should be no to be included in the study)

Part 1: Environmental factors

a- Obesity

Questions	**Yes**	**No**	**Uncertain**	**Notes**
1. Was your child obese when he diagnosed with diabetes? If yes his weight?				……kg
2. Was his birth weight above 4 kg?				
3. Were your child obese in early childhood? If yes at which age you start to gain weight?				

➢ **What was the birth weight for the child?.....**

- Less than 2.5(low)
- Between 2.5-4 (normal)
- More than 4(high)

Do you deliver your baby premature or not?

What was the gestational age?

0b- Viral infections

Questions	Yes	No	Uncertain	Notes
1. Do your child expose to coved-19 infection before having diabetes? If yes				
2. Dose it confirmed with PCR?				
3. Was the result positive?				
4. Were the symptoms extreme?				
Fever				
Diarrhoea				
Dry cough or shortness of breath				
Loss of taste or smell				
Headache				
Sore throat				
Feelings very tired				
Other symptoms not mention				
5. Do you expose to other viral infections before having diabetes? (ex. Mumps, Rubella)				

c- Breastfeeding and early bovine milk, gluten and fruit induction

Questions	Yes	No	Uncertain	Notes
Were your child breast feed? How long? (……)				
Was there combination between breastfeeding and formula feeding?				
Did your child drink cow milk earlier than 1 years old?				
Did he inducted to fruit early then 6 months?				
Did he inducted to gluten containing foods earlier than 3 month ex. Cereals?				

d- Vitamin D deficiency

Questions	Yes	No	Uncertain	Notes
Did you took recommended vitamin D supplement regularly at first year of life?				
Do you expose to sunlight well?				

e- Decrease gut micro biota

Questions	Yes	No	Uncertain	Notes
Do you have too much diarrhoeas before having diabetes?				
Do you have too much medication before having diabetes, like antibiotics? If yes mention them……				

Part 2: Genetic factors

Questions	Yes	No	Uncertain	Notes
Do you have any family history or relatives with T1DM? If yes mention the kinship…….. Male or female At which age?				
Have you done any genetic testing for diagnosis diabetes? If yes was the result positive……..				

Appendix B

Questionnaire in Arabic

رقم المريض: العمر:

الجنس:

المستوى التعليمي للاب

- اساسي
- دبلوم
- بكالوريوس
- ماستر او اعلى

المستوى التعليمي للام

- اساسي
- دبلوم
- بكالوريوس
- ماستر او اعلى

عمر الاصابة بالسكري:

تاريخ التشخيص:

كيفية اكتشاف المرض؟

عدد الاطفال الاخوة: الذكور ( ) الاناث ( )

الوضع الاقتصادي

- منخفض
- متوسط
- مرتفع

قسم الاسئلة الخاصة بالام في فترة الحمل:

الوزن المكتسب خلال فترة حملها في الطفل المصاب بالسكري.....كغم طول الام.....

BMI في نهاية الحمل.....

الوزن قبل الحمل مباشرة.....

BMIقبل الحمل.....

في اي قسم من الحمل كانت الزيادة اكثر؟

الاول.....

الثاني.....

الثالث.....

السؤال	نعم	لا	غير متأكد	غير ذلك
1. هل ازداد وزنك خلال فترة الحمل كثيرا؟ اذا نعم كم كانت الزيادة؟				
2. هل اصبتي بتسمم الحمل؟				
3. هل كان لديك سكري حمل؟				
4. هل تعرضتي للمواد الكيميائية في صوالين تصفيف الشعر خلال فترة الحمل؟مثال الصبغات وبروتين الشعر				
5. هل عانيت من التهابات البول خلال فترة الحمل؟				
6. هل اخذت ادوية خلال فترة الحمل تبعا لمشكلة الالتهابات بكثرة(مضادات حيوية) مع ذكر الاسم ان امكن؟				
7. هل عانيت من مشاكل نفسية او صدمة عاطفية/فقدان شخص خلال فترة الحمل؟				
8. هل انت مريض ضغط؟ اذا نعم ما الادوية؟				
9. هل اصبت باي امراض تنفسية مثل الانفلونزا خلال الحمل؟				
10. هل انت مريضة سكري اذا نعم ما نوع السكري وما هي الادوية؟....				
11. هل انت مدخة؟				
12. هل انت مدخن سلبي؟				
13. هل التزمتي باخذ الادوية والمعادن المطلوبة خلال فترة الحمل؟				
14. هل فحصتي فيتامين دال من قبل؟ اذا نعم كم النسبة؟				
15. هل تستهلكين مشروبات غازية خلال فترة الحمل				
16. هل تعتمدين على الوجبات السريعة في نظامك الغذائي بكثرة؟				
17. هل تمارسين الرياضة؟				

❖ **قسم اسئلة الطفل:**

هل لدى الطفل اي مرض غير السكري نوع الاول؟ يجب ان تكون الاجابة لا حتى يتضمن في البحث

القسم الاول: العوامل البيئية

السمنة

السؤال	نعم	لا	غير متأكد	ملاحظة
1. هل كان الطفل سمين عند التشخيص بالسكري؟				.....kg
2. هل كان وزنه اكثر من 4 كغم عند الولادة؟				
3. هل كان طفلك لديه سمنة في فترة طفولته اذا نعم فـــي اي عمر بالضبط؟				

➢ **وزن ولادة الطفل.....**

- اقل من 2.5 منخفض-
- طبيعي – بين 2.5الى 4
- مرتفع- اكثر من 4

هل ولد الطفل قبل التاسع وهل الولادة طبيعي ام قيصري

قسم الامراض الفيروسية

السؤال	نعم	لا	غير متأكد	ملاحظة
1. هل تعرض طفلك للاصابة بكورونا قبل الاصابة بالسكري؟				
2. هل تم عمل فحص PCR				
3. هل كانت النتيجة ايجابية؟				
4. هل كانت الاعراض حادة				

حرارة				
اسهال				
كحة ناشفة				
فقدان حاسة الذوق اوالشم				
الم في الراس				
احتقان حلق				
الشعور بالارهاق				
غير ذلك				
5. هل اصيب باي مرض فايروسي اخر؟				

الرضاعة الطبيعية والتعرض لاغذية معينه قبل اوانها

السؤال	نعم	لا	غير متأكد	ملاحظات
هل كانت رضاعة طفلك طبيعية فقط؟ و كم المدة				
هل كان هناك رضاعة طبيعية وصناعية معا؟				
هل شرب الطفل حليب البقر قبل عمر السنة؟				
هل تم تقديم الفواكه للطفل قبل الستة اشهر؟				
هل تم تقديم الاغذية التي تحتوي جلوتين قبل الثلاث اشـــهر ؟ مثال الخبز السيرلاك..				

نقص فايتمن دال

السؤال	نعم	لا	غير متاكد	ملاحظة
هل تم اخذ نقاط فيتامين دال خلال اول سنة ؟من عمر الطفل				
هل يتعرض لاشعة الشمس بشكل جيد ؟				

e- Decrease gut micro biota

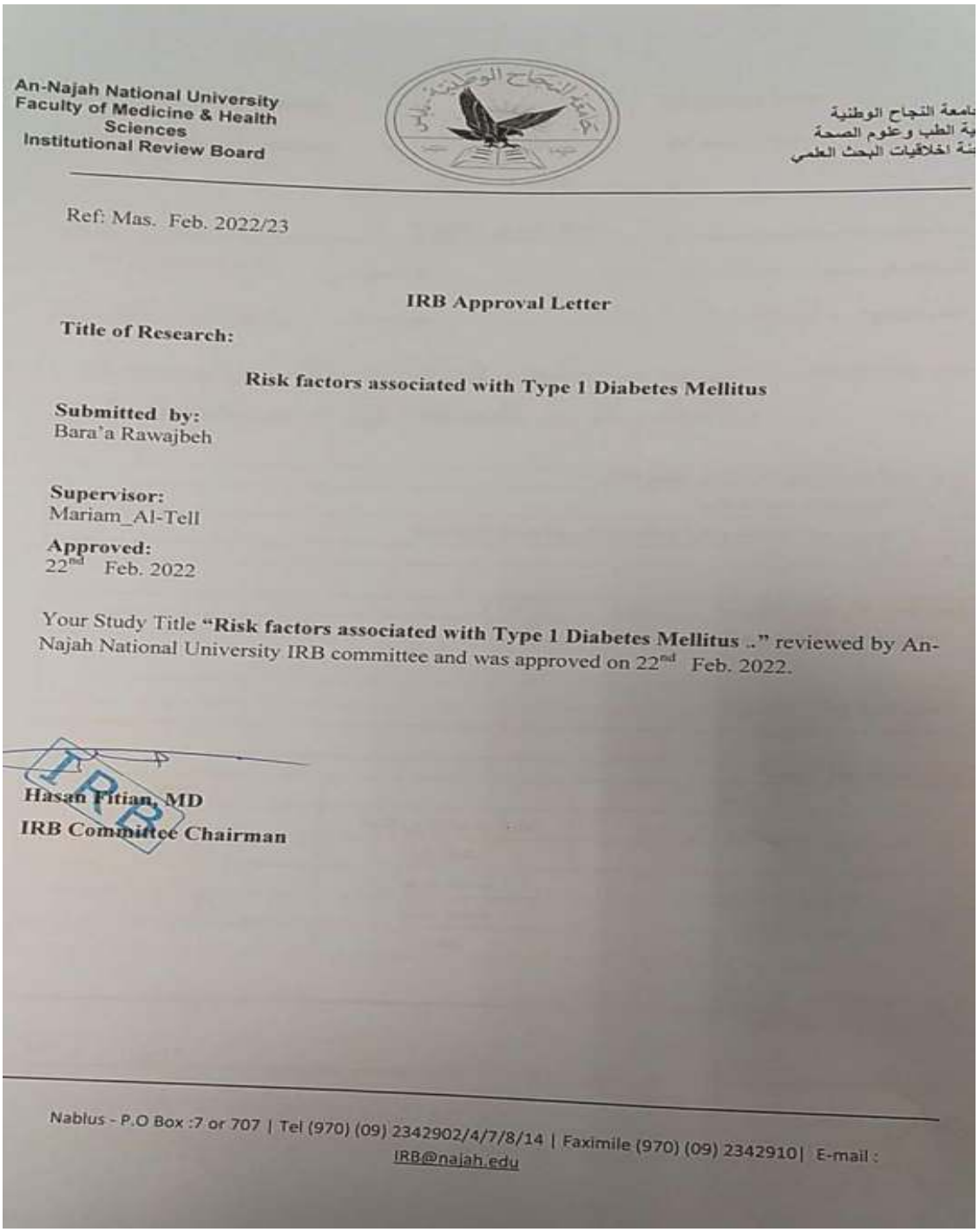
السؤال	نعم	لا	غير متاكد	ملاحظة
هل اصيب الطفل بالاسهال كثيرا في فترة طفولته؟				
هل اخذ الطفل الكثير من المضادات الحيوية قبل اصابته بالسكري وما الاسماء؟				

القسم الثاني: العوامل الجينية

السؤال	نعم	لا	غير متأكد	ملاحظة
هل لديك اي اقارب مصابين بالسكري نوع الاول؟اذا كانت الاجابة نعم اذكر نوع القرابة ذكر ام انثى ما هو عمر الاصابة للقريب؟				
هل تم عمل فحص جيني من قبل واذا نعم هل كانت النتيجة ايجابية؟				

Appendix C

IRB form



An-Najah National University
Faculty of Medicine & Health Sciences
Institutional Review Board

جامعة النجاح الوطنية
كلية الطب وعلوم الصحة
لجنة اخلاقيات البحث العلمي

Ref: Mas. Feb. 2022/23

IRB Approval Letter

Title of Research:

Risk factors associated with Type 1 Diabetes Mellitus

Submitted by:
Bara'a Rawajbeh

Supervisor:
Mariam_Al-Tell

Approved:
22nd Feb. 2022

Your Study Title **"Risk factors associated with Type 1 Diabetes Mellitus .."** reviewed by An-Najah National University IRB committee and was approved on 22nd Feb. 2022.

IRB

Hasan Fitian, MD
IRB Committee Chairman

Nablus - P.O Box :7 or 707 | Tel (970) (09) 2342902/4/7/8/14 | Faximile (970) (09) 2342910| E-mail : IRB@najah.edu

Appendix D

Task facilitation model

An-Najah
National University
Faculty of Graduate Studies

جامعة
النجـــاح الوطنية
كلية الدراسات العليا

التاريخ : 2021/12/27م

حضرة الدكتور عبد الله القواسمي المحترم
مدير عام التعليم الصحي / وزارة الصحة الفلسطينية

الموضوع: تسهيل مهمة الطالبة/ براءة خليل غالب رواجبة رقم تسجيل (11750748)
تخصص ماجستير الصحة العامة

تحية طيبة وبعد ،،،

الطالبة/ براءة خليل غالب رواجبة، رقم تسجيل 11750748، تخصص ماجستير الصحة العامة في كلية الدراسات العليا، وهي بصدد اعداد الاطروحة الخاصة بها والتي عنوانها:

عوامل الخطورة في السكري من النوع الاول
Risk Factors among Type 1 Diabetes Mellitus

يرجى من حضرتكم تسهيل مهمتها في جمع العينة في الفترة الزمنية الواقعة بين (2022/2/30 – 2022/1/2) والفئة المستهدفة هم المرضى المصابون بسكري نوع الاول والذين يزورون الرعايات الصحية الأولية / عيادة السكري علما بانه سيتم تعبئة الاستبانات معوائي امر المريض او المريض نفسه وجها لوجه من خلال الباحث وكذلك من خلال مراجعة الملفات الكترونيا او ورقيا.

علماً بأن البيانات والمعلومات سوف تستخدم لأغراض البحث العلمي واستكمال مشروع البحث فقط.

شاكرين لكم حسن تعاونكم.

وتفضلوا بقبول فائق الاحترام ،،،

أ.د. وليد صوبلح
عميد كلية الدراسات العليا

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جامعة النَّجاح الوطنيَّة

كليَّة الدّراسات العليا

عوامل الخطورة البيئية والجينية المرافقة لحدوث السكري النوع الأول / دراسة الحالات والشواهد في مدينة نابلس

إعداد

براءة رواجبه

إشراف

د. مريم الطل

قدمت هذه الرسالة استكمالاً لمتطلبات الحصول على درجة الماجستير في الصحة العامة من كلية الدراسات العليا، في جامعة النجاح الوطنية، نابلس – فلسطين.

2023

عوامل الخطورة البيئية والجينية المرافقة لحدوث السكري النوع الأول / دراسة الحالات والشواهد في مدينة نابلس

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إشراف

د. مريم الطل

الملخص

السكري من النوع الأول(سكري الأطفال)، هو من امراض المناعة الذاتيه حيث ان جهاز المناعة يهاجم الجسم نفسه بدلاً من الدفاع عنه، العامل الحقيقي او العوامل المؤديه لهذا التحفيز ليست واضحة كما الأمر في سكري الكبار او النوع الثاني من السكري، في هذه الدراسة تم تتبع المرضى منذ كانوا أجنة حتى لحظة الإصابة بالسكري في اسئله تشمل العوامل البيئية والجينية للأم والطفل ونقارن الإجابات مع حالات أطفال اصحاء.

تهدف الدراسة الى التعرف على العوامل المرافقة لحدوث السكري من النوع الأول بيئيا وجينياً في فلسطين وخصيصاً مدينه نابلس.

تم اعتماد تصميم دراسة الحالة والشواهد لجمع المعلومات حول العوامل المرتبطة بحدوث سكري الأطفال، العينة كانت (181) قسمت إلى:((68 أمهات الأطفال المرضى بسكري الأطفال، و(50) أمهات أطفال اصحاء، تم تعبئة استبيان صمم من قبل الباحث مكون من خمس صفحات وحللت البيانات باستخدام برنامج ال.SPSS

مؤشر كتلة الجسم قبل الحمل، وتعرض الام خلال فترة الحمل للمواد الكيميائية مثل صبغات الشعر، الاصابة بمرض الضغط خلال الحمل واستهلاك المشروبات الغازية كانت من العوامل المرتبطة في تطور السكري نوع الاول للاطفال لاحقا في حياتهم، الوراثة بوجود اقارب مصابين بالسكري نوع الاول كانت من العوامل المرتبطة في حدوث المرض.

مرض السكري هو نتيجة لعدة عوامل بيئية وجينية على مستوى الام خلال حملها وعلى مستوى الطفل، على مستوى الام: مؤشر كتلة الجسم قبل الحمل، والتعرض لمواد كيميائية بالحمل والاصابة بمرض الضغط، و كون

الأم مدخنة سلبية، واستهلاك المشروبات الغازية، وعلى مستوى الطفل التاريخ العائلي للاصابة بالمرض، كــل هذه العوامل ارتبطت بحدوث السكر نوع الاول لاحقا للطفل. يوصى بعمل العديد من الابحاث على النتائج التي اثبتت وجود علاقة بين عوامل الخطورة و السكري في هذا بالبحث بشكل ادق وعلى نطاق اوسع وعدد اكبر من المرضى.

الكلمات المفتاحية: النوع الاول من السكري؛ السكري وعوامل الخطورة.