



Gestational diabetes mellitus and macrosomia predispose to diabetes in the Lebanese population



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ABSTRACT

Aims: The Middle East has the fastest rising rate of Type 2 Diabetes Mellitus (T2DM) worldwide, with Lebanon having 15.8% of its population affected. This study aims at studying Polycystic Ovarian Syndrome (PCOS), Gestational Diabetes Mellitus (GDM), and macrosomia as risk factors of T2DM in Lebanon. Such epidemiological and statistical study has never been conducted before in the Middle East region and would be useful for clinical diagnosis.

Methods: Our cohort is comprised of 1453 Lebanese individuals, with 897 controls and 556 patients. We tested the correlation between T2DM and the covariates GDM, PCOS, and macrosomia independently. We conducted multinomial logistic regression and cross tabulations with T2DM as an outcome.

Results: The results showed a significant association of the independent factors GDM and macrosomia with T2DM. The risk of having T2DM was increased by 4.192 times with the GDM, and by 2.315 times with macrosomia respectively.

Conclusion: In conclusion, GDM and macrosomia, but not PCOS, are significant risk factors for T2DM in our Lebanese cohort. Our results, reported for the first time in the Middle East, present insights into risk factors management and disease prevention.

Introduction

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by high levels of glucose in the blood [1]. Hyperglycemia may be caused by several factors such as insulin resistance, and impaired insulin secretion. T2DM is one of the major causes of mortality and early formation of disabilities [2]. Severe morbidity factors can develop such as increased risk of heart disease, neuropathy, renal disease, peripheral neuropathy, blindness, amputation of specific body parts, and reduced life expectancy [1].

The Middle East has the fastest rising rate of T2DM development in the world [3]. In Lebanon, 15.8% of the population presents with T2DM [4]. This corresponds to an average of 790,000 affected individuals, given a population size of 5 million habitants. T2DM poses great health and financial burdens on the people and health care system of the country [5]. A recent study done at Rafik Hariri University Hospital Shows that the average mean cost of hospitalizing and managing persons with diabetes in Lebanon is greater than the International Diabetes

Federation estimated cost worldwide which is \$1436 [5].

Due to the major impact T2DM has on Lebanon, we decided to conduct a study on T2DM risk factors that have not been explored in the region. These risk factors are Polycystic Ovarian Syndrome (PCOS), Gestational Diabetes Mellitus (GDM), and macrosomia.

Several risk factors have been associated with T2DM [6]. PCOS is a disorder of the endocrine system, affecting women of reproductive age. While the etiology is poorly defined, prolonged and infrequent menstrual periods as well as excess androgen levels characterize it. The ovaries may develop small follicles and fail to regularly release eggs [7]. Studies in the United States [8,9], as well as in the Netherlands [10], show that women with a history of PCOS are predisposed to T2DM. PCOS causes women to become insulin resistant making them 3–7 times more likely to develop T2DM [9]. A Dutch study also shows that having PCOS puts the individual at a high risk of developing hypertension [11] which is a known risk factor of T2DM [12]. Moreover, the National Institutes of Health states that 4–10% of women who are at a reproductive age suffer from this syndrome [7]. In Lebanon, there are

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no statistics on the exact number of women effected by PCOS.

GDM occurs when a woman develops glucose intolerance during pregnancy [13]. The body of the future mother undergoes several metabolic changes such as insulin resistance due to the placental hormones that stop insulin from functioning properly, leading to glucose build up in the blood [14]. GDM has been suspected as a T2DM risk factor across populations through studies in several countries like the United Kingdom [15], Denmark [16], and the United States [17]. In Lebanon, we lack formal statistics on the prevalence of GDM in the female population.

A third risk factor for T2DM is macrosomia. Macrosomia is a term used to describe a newborn whose birthweight is greater than 4–4.5 kg [18]. This condition affects 3–15% of all pregnancies worldwide [19]. The Center for Disease Control and Prevention has classified giving birth to a macrosomic baby as one of the major risk factors for T2DM [20]. In the Lebanese population however, there have not been any studies done on the association between T2DM and macrosomia.

Since statistical and epidemiological studies would be very useful for clinical diagnosis and management, this article aims at studying PCOS, GDM, and macrosomia as risk factors of T2DM in the Lebanese population. This kind of study has not been conducted before in Lebanon and the Middle East region to our knowledge, and would be crucial since these populations are known for their unique genetic background and ethnic origin [21].

Subjects, materials, and methods

Participants

Our cohort is comprised of 1453 male and female Lebanese individuals over the age of 55. Of these, there are 897 controls and 556 cases of T2DM. The study was conducted in two phases and the data was collected from citizens living in different regions. The first phase occurred in the Lebanese capital Beirut and led to the recruitment of 961 subjects. The second phase occurred in North Lebanon where 492 subjects were recruited. The methods and the research procedures used were carried out using the Helsinki Declaration and under the approval of the Lebanese American University institutional review board as well as the ethics committees. Every participant signed an informed consent [21].

Procedures

The weight and height data of every participant was collected and the Body Mass Index (BMI) was calculated using the standardized formula. A blood sample was used to measure fasting blood sugar (FBS), glycated hemoglobin levels (HbA1C), as well as a lipid profile [21]. The HbA1C cut-off was of 48 mmol/mol which is in compliance with the World Health Organizations (WHO) method for the diagnosis of diabetes [21]. A questionnaire was duly filled where patients were asked about their medical condition, their clinical records, their family history and the age of onset of the disease. According to available data, patients with type I diabetes were excluded from the study. Additional information regarding several parameters including complications during pregnancy such as macrosomia, GDM, and PCOS was collected based on the answers provided in the survey questionnaire.

Statistical analysis

Using the Statistical Package for Social Sciences (SPSS) we tested the correlation between T2DM and the covariates GDM, PCOS, and macrosomia independently on the female cohort of our study population. Since the factors of interest only affect females, the data was split according to the gender and multinomial logistic regression and cross tabulations with T2DM as an outcome were conducted accordingly. In addition, a test was done using multinomial regression with T2DM as

Table 1
Descriptive statistics of the female population.

		T2DM patients (%)	Controls (%)	Total
Gestational diabetes	Yes	13 (81.3%)	3 (18.8%)	16
	No	246 (50.8%)	238 (49.2%)	484
Polycystic ovarian syndrome	Yes	7 (38.9%)	11 (61.1%)	19
	No	246 (51.9%)	228 (48.1%)	474
Macrosomia	Yes	93 (66.0%)	48 (34.0%)	141
	No	159 (45.6%)	190 (54.4%)	349
Hypertension	Yes	209 (58.7%)	147 (41.3%)	356
	No	106 (37.6)	176 (62.4%)	282

the dependent factor and PCOS and hypertension as independent variables.

Results

Descriptive statistics of the population

In our cohort, 89.2% of the individuals had an age of 50 years old or greater. Cross tabulation tables showed that 81.3% of women with GDM had T2DM and 18.8% did not suffer from the condition (Table 1). As for the women who were diagnosed with PCOS, 38.9% of them had T2DM while 61.1% of them did not (Table 1). Regarding women who gave birth to newborns with macrosomia, 66.0% were later diagnosed with T2DM and 34% were unaffected (Table 1).

Multinomial regression coefficients predicting joint exposures with T2DM as an outcome variable

This study shows a significant association of the independent factors GDM and macrosomia with an increased risk of T2DM. Females with GDM showed significant predisposition to T2DM ($\rho = 0.013$) and were 4.192 times more likely to have the condition with a 95% C.I. interval of 1.180–14.90 (Table 2). Macrosomia, showed a significant ρ -value ≤ 0.001 , an OR of 2.315 and 95% C.I. interval of 1.541–3.478 (Table 2).

In parallel, a multinomial regression test was conducted with PCOS and hypertension treated as separate independent variables and T2DM as dependent. Our results show that PCOS did not reach significance. Hypertension was as significantly associated with T2DM ($\rho \leq 0.001$) with an OR of 2.651, and a C.I. of 1.836–3.829 (Table 2). A multinomial logistic regression tested the association of PCOS and hypertension with T2DM and showed that hypertension, regardless of PCOS, increases the risk of T2DM in our Lebanese cohort (Table 2). The same analysis showed that PCOS and gestational diabetes, treated as co-variables as

Table 2
Multinomial regression coefficients predicting joint exposures with T2DM as an outcome variable.

	p-Value	OR	95% C.I.
Gestational Diabetes	0.013	4.192	1.180–14.90
Polycystic Ovarian Syndrome	0.277	0.59	0.225–1.547
Macrosomia	0.000	2.315	1.541–3.478
Hypertension	0.000	1.795	1.427–2.258
<i>Polycystic Ovarian Syndrome & Hypertension</i>			
Polycystic Ovarian Syndrome	0.271	0.577	0.214–1.555
Hypertension	0.000	2.651	1.836–3.829
<i>Polycystic Ovarian Syndrome & Gestational Diabetes</i>			
Polycystic Ovarian Syndrome	0.317	0.614	0.234–1.613
Gestational Diabetes	0.013	4.184	1.176–14.879

Table 3

Demographic, clinical and biochemical features of unaffected controls and patients with T2DM. Data is displayed as means \pm SEM as well as the number of people with their respective percentages.

	Controls	Patients	Male Controls	Male Patients	Female Controls	Female Patients
Number of individuals	897	556	418	236	479	320
<i>Demographics</i>						
Age (years)	62.45 \pm 0.47	63.07 \pm 0.48	60.74 \pm 0.61	61.77 \pm 0.76	64.20 \pm 0.71	64.03 \pm 0.62
Hyperlipidemia Number (%)	248 (45.3%)	300 (54.7%)	129 (52.7%)	116 (47.3%)	119 (39.3%)	184 (60.7%)
Hypertension Number (%)	311 (48.1%)	335 (51.9%)	164 (56.6%)	126 (43.4%)	147 (41.3%)	209 (58.7%)
Cardiac Disease Number (%)	310 (58.2%)	223 (41.8%)	204 (64.6%)	112 (35.4%)	106 (48.8%)	111 (61.2%)
<i>Anthropometric Variables</i>						
Body Weight (kg)	73.37 \pm 0.73	77.10 \pm 0.78	79.92 \pm 1.19	84.05 \pm 1.4	68.17 \pm 0.84	72.75 \pm 0.88
Body Mass Index (kg/m ²)	27.43 \pm 0.23	29.23 \pm 0.27	27.34 \pm 0.36	29.01 \pm 0.44	27.03 \pm 0.34	29.38 \pm 0.35
<i>Metabolic and inflammatory variables</i>						
HbA1C	5.19 \pm 0.02	7.37 \pm 0.08	5.192 \pm 0.031	7.49 \pm 0.13	5.25 \pm 0.02	7.35 \pm 0.10
Plasma Glucose (mg/dL)	96.45 \pm 1.00	155.50 \pm 3.11	158 \pm 4.8	97.04 \pm 1.4	93.30 \pm 0.85	152.52 \pm 4.04
Total Cholesterol (mg/dL)	218.51 \pm 2.61	200.18 \pm 2.68	205.76 \pm 4.0	191 \pm 3.5	233.89 \pm 3.50	207.51 \pm 2.96
HDL Cholesterol (mg/dL)	50.86 \pm 0.75	47.39 \pm 0.64	47.76 \pm 0.97	43.32 \pm 0.88	56.68 \pm 0.95	50.77 \pm 0.84
LDL Cholesterol (mg/dL)	135.29 \pm 2.31	115.89 \pm 1.92	126.32 \pm 3.66	111.49 \pm 3.01	144.96 \pm 3.02	120.27 \pm 2.54
Triglycerides (mg/dL)	154.57 \pm 3.80	188.83 \pm 5.91	148.46 \pm 6.00	183.90 \pm 9.64	152.91 \pm 5.04	188.37 \pm 7.12

they are known to occur together, show an increased risk of T2DM of 4.184 for females with GDM, regardless of PCOS.

Interestingly, an analysis of the demographics of the population shows that the female cohort with T2DM has higher prevalence of both hypertension (58.7%) and hyperlipidemia (60.7%) compared to unaffected female participants where 41.3% had hypertension and 39.3% had hyperlipidemia (Table 3). In addition, individuals with T2DM have a higher HbA1C and glucose blood levels, as well as BMI and total body weight relative to unaffected individuals.

Discussion

This study explored the association of GDM, PCOS, and macrosomia with T2DM. It was performed on a nationally representative sample of female individuals with and without diabetes. Due to the lack of epidemiological and statistical resources in Lebanon concerning GDM, PCOS, and macrosomia, we asked eight gynecologists about their estimation of the prevalence of these conditions in the Lebanese female population. On average, their answer was that approximately 1 in 15 women suffered from PCOS and GDM, and 1 in 50 women gave birth to macrosomic newborns. However, calculating the frequency of each variable in our study population suggests that physicians tend to overestimate the prevalence of PCOS and GDM. In our female cohort, 4% and 3.3% were respectively affected compared to the 6.6% estimation of the physicians. As for macrosomia, physicians greatly underestimated its prevalence, since in our cohort 40.4% had a macrosomic child.

We hypothesized that GDM, PCOS, and macrosomia would behave as risk factors for T2DM. Considering that no statistical or epidemiological studies regarding this topic have been done in Lebanon or in the region, testing the validity of this hypothesis would greatly aid the clinical approaches to managing diabetes. In addition, this study has the power to try to replicate published results by testing if the Lebanese population follows the same T2DM risk factors recognized worldwide.

A large data set was collected to test the correlation between T2DM and GDM, PCOS, and macrosomia using multinomial regression and cross tabulations. Our results demonstrated a strong association of the risk factors GDM and macrosomia with the occurrence of T2DM in the Lebanese population. A statistically significant larger percentage of those who suffered from these disorders predisposing to T2DM developed the condition. The results show that the predisposition of the Lebanese population to T2DM is dictated by the same environmental factors as other western populations.

There is increasing evidence that PCOS has a negative impact on the

development of T2DM [7–11]. Women with PCOS undergo many metabolic alterations [8], one of them being that they are insulin resistant (IR) [22,23], and are at a high risk of having impaired glucose intolerance (IGT) [9,24,25]. The relation of PCOS and IR was established independently of the obesity in women [26]. Considering that IR is a known risk factor for the development of T2DM [27,28], it can be deduced that PCOS in patients increases their risk of T2DM by increasing the risk of having IR. In addition, studies have shown that women diagnosed with PCOS have a pancreatic β -cell defect [29,30]. This decrease in the β -cell function contributes to the advancement of T2DM pathophysiology [31], and makes PCOS even more favorable for T2DM development. In our cohort, there was no correlation between PCOS and T2DM. An increase in the number of individuals may be necessary to have enough statistical power. PCOS has also been linked to various long term consequences like hypertension [11,32] and dyslipidemia [33,34]. A side study was conducted to see if the number of women who suffered from PCOS, T2DM, and hypertension was greater than those who suffered from T2DM and hypertension alone. This would emphasize the role of PCOS in increasing the risk of acquiring hypertension, and consequently predisposing to T2DM when both of the PCOS and hypertension are present. The results of our cohort were significant in stressing the role of PCOS when it came to hypertension, showing that those who suffered from PCOS and hypertension had a greater risk of T2DM than those who suffered from hypertension alone. Studies have shown that with the correct lifestyle alterations and metformin intake, patients with PCOS may be able to combat IR, T2DM, and IGT [24,35].

GDM has been closely linked to T2DM [15,36]. Women who have GDM are seven times more likely to develop T2DM than those who have a normal pregnancy [15]. GDM is defined as a glucose intolerance that begins during pregnancy and recedes after delivery [37]. All pregnancies induce IR [13], however GDM induces several modifications in glucose metabolism [38]. A woman with GDM develops defects in IR and in her insulin secretory response [39], the pancreatic β -cells stop sensing glucose correctly, leading to an inadequate insulin response [17]. The pathophysiology of GDM is similar to that of T2DM since these events occur in patients with T2DM [39]. The metabolic stress that occurs during pregnancy is speculated to lead to T2DM later on [17]. The results of our cohort support this hypothesis with \sim 1.6 more patients with GDM developing T2DM compared to those who did not have the condition [17,39]. Since such information about the female population in Lebanon is now available, work can be done to prevent the progression from GDM to T2DM. The extent of the risk of developing T2DM after GDM depends on several factors, such as glycemia

postpartum [40]. Women are advised to check their oral glucose tolerance six weeks after delivery; however, there are no medical guidelines for such a screening in the Lebanese female population. Similar studies conducted on African American women show that most of them do not attend this follow up appointment [37,41]. This test must be strongly recommended by physicians and its importance in T2DM prevention should be emphasized [15]. Another way for preventing T2DM after GDM is through lactation, since higher frequency and duration of breastfeeding lower T2DM risk [14,42].

Of all pregnancies 6–10% result in macrosomic newborns, however this rate varies between different races and ethnicities [43]. Women who give birth to macrosomic infants are 2–3 times more likely to be diagnosed with T2DM, even after adjusting for GDM [44]. This adjustment is done because macrosomia is a side effect of GDM [45]. The relation between macrosomia and T2DM may be caused by maternal hyperglycemia [44]. T2DM could occur due to the exposure to large amounts of glucose for a prolonged period leading to impaired glucose tolerance in the mother [46], which is a risk factor for T2DM [47]. Our study showed that of those who gave birth to a macrosomic child, 66% had T2DM while 34% did not, and that those who had a macrosomic child had an OR of 2.315 for T2DM. Our results complied with those of the studies done worldwide. In addition, the level of maternal hyperglycemia that leads to fetal macrosomia does not have to meet the level of hyperglycemia that classifies women for having GDM [48], in fact 60% of all macrosomic cases are born to women with unidentifiable risk factors [49]. During pregnancy whether diagnosed with GDM or not, maternal hyperglycemia induces an exaggerated insulin response in the fetus leading to increased use of glucose and thus increasing the adipose tissues [44,45,48]. There are risk factors that women should be aware of to avoid having macrosomic newborns. Age is one of them, women between the ages of 35–39 have a 40% chance of delivering a macrosomic child [48]. Obesity is also a risk factor that doubles the risk of having a macrosomic child [50]. GDM is another risk factor of having macrosomia and T2DM later on due to their combined effect on the body's glucose metabolism. There are also some modifiable risk factors like pre-pregnancy BMI and gestational weight gain. Those who have a pre-pregnancy BMI ≥ 25 kg/m² and those who gain more than 12 kg during pregnancy have a high risk of delivering an infant with macrosomia [46].

Several limitations to this study are observed. First, its cross-sectional nature does not allow assessing the incidence of T2DM. In addition, many of the female participants had not tested for GDM during their pregnancy due to the lack of proper education on this matter and proper blood testing during their pregnancy which is estimated to have occurred approximately 20–30 years ago. Another limitation is that parameters such as macrosomia and PCOS were collected based on the answers of the participants without any access to their old medical records. Thus, an underestimation of the number of cases with respective conditions cannot be excluded.

In conclusion, GDM and macrosomia showed significant results as risk factors for T2DM in our Lebanese cohort. The results of this study are conform to the studies done worldwide. This information may prove to be very valuable in decreasing the prevalence of T2DM in Lebanon. It will aid in the early management of T2DM and in addressing the risks that the Lebanese female population face such that they will be able to take proper precautions and possibly even prevent the occurrence of T2DM.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors contribution

MGS participated in blood samples collection, planning, and analysis of the experiments, as well as manuscript editing; ZM conducted the analysis and wrote the article; LAF helped in the analysis and supervised the work; AKS helped in sample and data collection; PAZ supervised three different aspects of the work.

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Appendix A. Supplementary material

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