Physiological and Metabolic Profiling of Women with Type 2 Diabetes and Former Gestational Diabetes

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ABSTRACT

Objectives: Gestational diabetes mellitus (GDM) represents a variant of Type 2 diabetes with potential health consequences for both mother and baby. GDM is also a risk factor for the later development of Type 2 diabetes in women. The purpose of this study was to compare the physiologic and metabolic profile of women with Type 2 diabetes with a history of GDM to those without a history of GDM. **Patients and Methods:** A retrospective chart analysis was conducted on 176 female patients, including 28 (16%) with a prior history of GDM. A subgroup of 6 non-GDM and 3 GDM had an insulin modified (0.05 U/kg) intra-venous glucose (0.3 g/kg) tolerance test (IVGTT) to assess insulin sensitivity and first phase insulin secretion. **Results:** In our results, a history of GDM was associated with an earlier onset of diabetes (43.4±12.1 vs. 57.4±11.1 years for the GDM and non-GDM groups respectively, $p<0.001$). Despite having a longer duration of diabetes the lipid profile of the GDM group was similar, as was the HbA1c, body mass index, waist-to-hip ratio and blood pressure. The incidence of dyslipidemia (50% vs. 53% for the GDM and non-GDM groups respectively), hypertension (64.2% vs. 76.4%) and cardiovascular disease (14.3% vs. 29.2%) was similar between groups. Fasting plasma glucose was similar but fasting insulin was higher in the non-GDM group. **Conclusion:** Type 2 diabetes patients with a prior history of GDM have an earlier onset of diabetes. Screening for GDM should be universally performed to identify these patients early, and treatment should be instituted to delay or prevent the progression to Type 2 diabetes.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as glucose intolerance that is first detected during pregnancy.[1] It represents an important variant of Type 2 diabetes with potential for morbidity for both mother and baby. It is also recognised to be one of the most important risk factors for the later development of Type 2 diabetes in women. It is often symptomatic and therefore likely that women with GDM are not diagnosed. An earlier pilot study in Ireland has shown that about half of all cases of GDM are missed.[2]

At present, the pathogenesis of GDM is not fully understood. A potential mechanism for GDM is the development of insulin resistance during pregnancy in women whose pancreatic insulin secretion is incapable of adequately compensating to maintain normal glucose homeostasis during gestation. Research indicates that defects in the regulation of glucose clearance, glucose production, and plasma free fatty acid concentrations, together with defects in pancreatic beta-cell function, precede the development of Type 2 diabetes mellitus in women with GDM.[3] One study revealed that insulin sensitivity in a group of pregnant women was reduced to 50%.[4] The increment of insulin resistance was compensated by an enhancement of the first phase of insulin secretion, which was increased more than twofold. This research illustrated that pregnancy is a state of physiologic insulin resistance compensated by an increase of insulin secretion.

There is an immediate return of insulin sensitivity post-partum. The glucose metabolism is restored to a completely compensated non-diabetic baseline similar to original levels which prevailed prior to pregnancy. However, subsequent pregnancies or weight gain, or both, increase the risk of progression to Type 2 diabetes in women with a prior history of GDM.[5-9]

Type 2 diabetes in women is a growing public health problem. Women with Type 2 diabetes have a high risk for cardiovascular and other complications, and have a worse prognosis to these complications than non-diabetic women.[10,11] Women with Type 2 diabetes have a higher relative risk of cardiovascular morbidity and mortality than men with Type 2 diabetes. Early identification of diabetes and early institution of interventions to modify risk factors may be ways to prevent long-term complications and improve the outcomes of Type 2 diabetes. At present, Ireland does not routinely screen for GDM.

HYPOTHESIS

Former GDM subjects with current Type 2 diabetes form a distinct sub-phenotype within the diabetes clinic. Based on evidence from other populations, we expect that women with prior history of GDM have different physical and metabolic profiles, and have more severe defects in insulin secretion in proportion to their degree of insulin resistance.

OBJECTIVES

Our survey involved the complete population of female subjects attending the Diabetes clinic at the outpatients department at St. James Hospital for the treatment of Type 2 diabetes. We compared clinical and metabolic characteristics of these women, specifically demographic data, history of GDM, physical characteristics, metabolic characteristics, the presence of DM complications, and medications used by the patients. In a small number of these women, detailed metabolic studies including an OGTT (with measurement of glucose and insulin) and an insulin-modified three-hours intravenous glucose tolerance test (IVGTT) will be performed.

PATIENTS AND METHODS

The study involves the entire female patient population attending the diabetes outpatient clinic at St. James's hospital. All women surveyed were below the age of 82. A few patients with impaired glucose tolerance (IGT) are also included in the study.

The data collected corresponded to patient's history and characteristics found on their chart. If any of the data from the recent appointment were found missing, incomplete or unavailable, then the patient's data from the previous appointment was used. Relevant information was collected and entered into a clinical data sheet specially designed for this study. The data comprises of six areas: demographic data, gestational history, physical characteristics, metabolic characteristics, the presence of DM complications, and medications used by the patients. The figures from the non-GDM patients were compared with those of GDM patients by performing non-paired t-tests.

The demographic data consisted of the age of patient (calculated based on the corresponding age in year 2001), age of diagnosis of DM, duration of DM (correct to year 2001) and family history of DM (whether none, present in first degree relatives or present in second degree relatives).

The gestational history included the patient's parity (the number of pregnancies including miscarriages, live births and still-births) and the presence or absence of GDM.
The physical parameters examined were the patient's height, weight, body mass index or BMI, waist measurement, hip measurement and waist-to-hip ratio. The metabolic characteristics consisted of total cholesterol level, high-density lipoprotein (HDL) level, low-density lipoprotein (LDL) level, triglycerides (TG) level, microalbumin (Malb) level, urinary creatinine (Ur.Cr), microalbumin-to-urinary creatinine (M/C) ratio, glycosylated haemoglobin (HbA1c) and blood pressure (BP) levels.

Insulin modified intravenous glucose tolerance test (IVGTT) was performed in all subjects to determine acute insulin response to glucose (AIRg) as an index of insulin secretion, and to assess the degree of insulin sensitivity by measuring the insulin sensitivity index (Si). The first step of the procedure was cessation of oral hypoglycaemic agents 5 days before the test. The patients then reported to the laboratory 8 am after an overnight fast. Two antecubital intravenous cannulae were inserted, one in each arm. Base line blood samples were obtained for glucose, insulin and C-peptide measurements. A 50% glucose solution (0.3g/kg) was administered intravenously over one minute and blood samples were then obtained at 2-, 4-, 8-, and 19- minutes. At 20-minutes intravenous short acting human insulin (0.05 u/kg, Actrapid, Novo nordisc, Denmark) was administered intravenously over one minute and blood samples continued to be collected at 22-, 30-, 40-, 50-, 70-, 90-, and 180-minutes. Finally, the serum was separated immediately and stored at -20ºC for analysis at a later date.

An oral glucose tolerance test was performed to measure the blood glucose response to a 75 gm oral glucose load. The procedure began with a three-day diet with at least 300 g of carbohydrates per day. Then, after an overnight fast (12 hours), the patients reported to St. James's Hospital at 8 a.m. They had a cannula inserted and fasting blood sample drawn, and then drank 300 ml of a flavoured glucose drink within 5 minutes. Then a blood sample was drawn every 30 minutes for 3 hours.

RESULTS

A total of 176 patients were included in this study. Of these, 148 were patients without prior history of GDM (non-GDM), while the remaining 28 patients were noted to have had prior history of GDM.

There were differences found between the two groups in terms of the age of the

Table 1. Patient Demographic Characteristics

	Non-GDM (n=148)	GDM (n=28)	p-value
Mean age at diagnosis (years, ± SD)	57.4 ± 11.1	43.4 ± 12.1	< 0.001
Mean current age (years, ± SD)	60.7 ± 11.0	50.7 ± 12.0	< 0.001
Mean duration of DM (years)	3.2 ± 3.1	7.3 ± 9.8	< 0.001

patients, the age at diagnosis of Type 2 diabetes mellitus (DM), and the duration of DM in each patient (Table 1). Non-GDM patients were older than GDM patients (61 ± 11.0 vs. 51 ± 12.0 years, $p<0.001$). Non-GDM patients were diagnosed at an older age (57.4 ± 11.1 years) compared to GDM patients (43.4 ± 12.1 years, $p<0.001$). Non-GDM patients demonstrated a shorter duration of DM (3.2 ± 3.1 years) versus GDM patients (7.3 ± 9.8 years, $p<0.001$). Therefore the trend of GDM is that patients present at a younger age and thus have a longer duration of DM.

Family history characteristics revealed a relation to also have Type 2 DM in 53.4% (first- and second-degree relatives) the non-GDM patients and 82.2% of the GDM patients (Table 2). Of these, positive family history in first-degree relatives contributes the major proportion (43.9% of non-GDM patients vs. 67.9% in GDM patients).

There is little difference in the mean parity of both groups (Table 3). When the patients were grouped together with similar parity and then compared, it was found there were differences in the weight and BMI in the group of women who have a parity greater than 4 (mean parity 7.3 ± 2.3), as represented in Table 4.

The weight in non-GDM patients have a mean of 76.2 ± 13.6 kg versus GDM with mean 88.3 ± 14.4 kg ($p=0.02$) (Table 5). The average BMI in non-GDM patients was 29.90 ± 5.10, in contrast with that of GDM patients 35.60 ± 7.50 ($p<0.05$). We conclude that as the women had more pregnancies, the GDM patients will gain more weight and becoming more obese than the non-GDM patients. In general, patients were overweight, with a mean BMI of 32.8 ± 7.0.

The metabolic profiles were similar between the two groups of patients (Table 6). Separate non-paired t-tests were performed by grouping patients into 5 categories of BMI: (1) Lean (BMI 25-30), (2) Overweight (BMI 31-35), (3) Obese (BMI 36-40), (4) Severely Obese (BMI 41-45) and (5) Morbidly Obese (BMI>45) (Table 7). When all the data were compared between the two groups in each BMI

Table 2. Family History

Family History	Non-GDM (n=148) n (%)	GDM (n=28) n (%)
None	64 (43%)	5 (17%)
Positive: 1st degree relatives	65 (43%)	19 (67%)
Positive: 2nd degree relatives	14 (9%)	4 (14%)
Unknown	5 (3%)	0%

Table 3. Gestational History

	Non-GDM (n=148) n (%)	GDM (n=28) n (%)
Parity = 0	9 (6%)	0 (0%)
Parity = 1	10 (7%)	2 (7%)
Parity = 2	17 (11%)	7 (25%)
Parity = 3	12 (8%)	3 (11%)
Parity = 4	16 (11%)	4 (14%)
Parity > 4	43 (29%)	9 (32%)
Unknown	41 (28%)	3 (11%)
Mean Parity	4.3 ± 3.1	4.2 ± 2.7

Table 4. Weight and body mass index (BMI) of patients with parity > 4.

	Non-GD (n=148)	GDM (n=28)
No. of patients with parity>4	43	9
Weight in kg mean ± SD	76.2 ± 13.6	88.3 ± 14.1
BMI	29.9 ± 5.1	35.6 ± 7.5

Table 5. Physical Characteristics

Characteristic	All Patients	Non-GDM	GDM
Height, mean ± SD (m)	1.59 ± 0.06	1.59 ± 0.07	1.60 ± 0.07
Weight, mean ± SD (kg)	81.3 ± 19.1	80.4 ± 18.5	85.8 ± 21.9
BMI, mean	32.8 ± 7.0	32.5 ± 6.3	33.9 ± 8.9
Waist measurement, mean (cm)	99.6 ± 11.8	99.6 ± 10.6	99.7 ± 14.8
Hip measurement, mean (cm)	110.0 ± 12.1	109.6 ± 11.5	110.9 ± 13.9
Waist/hip ratio	0.89 ± 0.05	0.90 ± 0.04	0.88 ± 0.070

Table 6. Metabolic Characteristics

	Non-GDM	GDM
Mean Total Cholesterol (mmol/l)	5.20 ± 1.07	5.04 ± 0.98
Mean HDL (mmol/l)	1.19 ± 0.33	1.19 ± 0.32
Mean LDL (mmol/l)	3.11 ± 0.89	2.99 ± 0.77
Mean Triglycerides (mmol/l)	2.07 ± 1.51	2.01 ± 1.07
Mean Fasting blood glucose (mmol/l)	9.6 ± 3.6	10.8 ± 6.1
Mean HbA1c (mmol/l)	8.1 ± 1.7	8.1 ± 2.3
Mean Microalbumin	22.8 ± 20.6	19.8 ± 25.9
Mean Urinary Creatinine	9.0 ± 5.8	11.3 ± 5.9
Mean Microalbumin/Urinary Creatinine ratio	3.46 ± 3.11	3.45 ± 1.91
Mean Systolic Blood Pressure	153.5 ± 21.8	148.5 ± 21.2
Mean Diastolic Blood Pressure	81.8 ± 13.3	81.9 ± 13.4

Table 7. Characteristics by BMI stratification

	Lean	Overweight	Obese	Severely Obese	Morbidly Obese
No. non-GDM/GDM	9/3	21/5	25/9	20/2	8/6
BMI	23.04 ± 1.76	27.25 ± 1.43	32.11 ± 1.49	37.87 ± 1.57	45.19 ± 4.99
Total Cholesterol	5.09 ± 1.45	5.21 ± 0.85	5.11 ± 1.15	5.24 ± 1.17	5.08 ± 0.79
HDL	1.42 ± 0.51	1.11 ± 0.23	1.14 ± 0.38	1.17 ± 0.25	1.03 ± 0.20
LDL	3.03 ± 1.05	3.17 ± 0.74	2.97 ± 0.98	3.09 ± 0.88	3.03 ± 0.65
TG	1.41 ± 0.93	2.32 ± 1.92	2.40 ± 1.58	2.32 ± 2.09	2.17 ± 0.88
FBG	-	10.9 ± 4.2	10.1 ± 5.3	9.6 ± 4.7	12.0 ± 4.0
HbA1c	8.0 ± 1.1	8.4 ± 2.3	8.7 ± 1.7	7.7 ± 1.5	7.3 ± 1.4
SBP	155.0 ± 26.7	146.8 ± 17.6	151.8 ± 17.8	152.1 ± 19.3	163.5 ± 18.6
DBP	82.6 ± 14.3	75.7 ± 7.3	84.5 ± 13.8	85.1 ± 12.1	89.5 ± 12.0

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; FBG, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure

category, significant differences were found in the lean group. The level HbA1c in the non-GDM group was lower, (7.6 ± 1.0) compared to the GDM patients (9.1 ± 0.6), $p<0.05$. The systolic blood pressure was higher in the non-GDM group than GDM (163.8 ± 24.2 vs. 128.7 ± 13.3), $p<0.05$. Of note, the non-GDM patients were older than the GDM (66.4 ± 8.2 vs. 36.7 ± 4.0 years old), which may be contributory to their higher systolic blood pressure.

Oral glucose tolerance tests (OGTT) were performed in 3 non-GDM and 4 GDM patients. Meanwhile, intravenous glucose tolerance tests (IVGTT) were performed on 6 non-GDM and 3 GDM patients. Fasting plasma glucose was similar (9.7 ± 1.1 mmol/l in the non-GDM group and 10.2 ± 2.8 mmol/l in the GDM group) but fasting insulin was higher in the non-GDM group (17.7 ± 6 U/ml) compared to the GDM group (10.3 ± 3.1 U/ml, $p<0.05$). The following two graphs depict the glucose and insulin responses derived from the IVGTT.

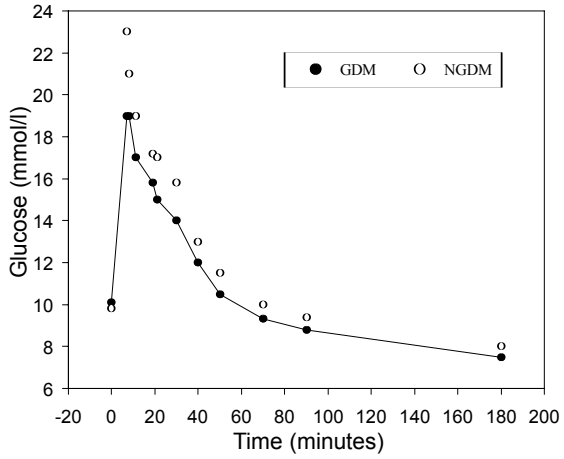

Figure 1. IVGTT Glucose response

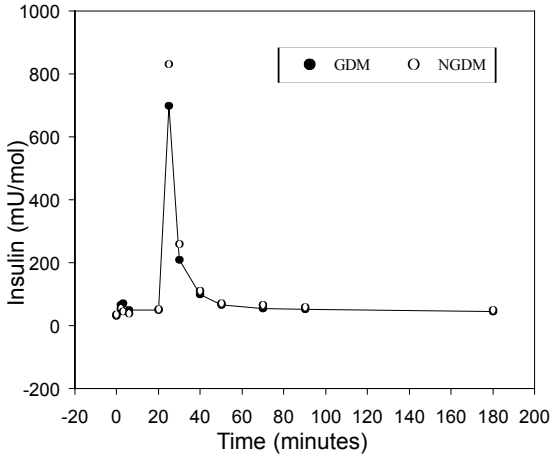

Figure 2. IVGTT Insulin Response

DISCUSSION

From the data analysis we can see that GDM patients tend to present at a younger age and thus have a longer duration of DM compared to the non-GDM patients. Since most patients who had previous history of GDM are at very high risk of developing subsequent DM, every effort should be made to identify them early by screening. The clinicians in Ireland should adopt a universal screening policy on all pregnant women to look for the presence of GDM. A positive history of GDM should alert clinicians that the patient would be prone to develop Type 2 DM in later life and at an earlier age than the general population. These women should have more extensive follow-up by experienced diabetologists after pregnancy; they should be advised to lose weight, exercise regularly and consume healthy diets in hope that these simple, active prevention strategies would prevent or delay the progression to DM. At present, no drug treatment is yet available in preventing the development of DM in non-diabetic women with prior GDM but a research trial has already started in the USA. A randomised, placebo controlled trial of troglitazone is carried out in these women in the hope that chronic administration of this drug may improve insulin sensitivity and reduce the incidence of Type 2 DM.[12] Although the result of this trial is not yet available, it represents an important milestone in pre-emptive treatment of patients with prior history of GDM.

Patients with a history of GDM showed a trend in higher incidence of positive family history, particularly among first-degree relatives. Such a finding may be attributable to an inherited genetic etiology. However, at present, there are still no researches available to identify the genetic causes of GDM.

Overall, the diabetic patients surveyed were mostly overweight, with an average BMI of greater than 30. Parity seems to influence the physical profile of the GDM patients; the more pregnancies they have, the heavier they get and thus attain a greater BMI. As discussed earlier, subsequent pregnancies or weight gain, or both, will increase the rate of progression to the future development of Type 2 diabetes. Therefore, active interventions should target this high-risk group of patients.

The defects in insulin secretion were more pronounced among lean GDM subjects, as evident from a higher level of HbA1c when compared to their counterparts of similar BMI. However, as BMI increases, the physical and metabolic profiles of the GDM patients became similar to those of the non-GDM.

CONCLUSION

This study suggests that GDM patients may be unique in several different aspects. However, more extensive studies on GDM such as molecular, genetic, metabolic, and epidemiological studies are needed to improve our understanding in the characteristics and pathogenesis of GDM. Early identification of GDM status will improve awareness in this subgroup of women and improve preventative strategies including early treatment and follow-up where appropriate.

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