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Pancreatic Duodenal Homeobox Factor-1 and Neurogenin-3 Serum Expression in Gestational Diabetes

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ABSTRACT

Objectives: Pancreatic duodenal homeobox factor-1 (*PDX-1*) and neurogenin-3 (*NGN-3*) are progenitor cell markers in the pancreas. The aim was to compare their serum levels in women with and without gestational diabetes mellitus (GDM).

Material and Methods: This prospective, cross-sectional study included two groups: (a) Women with normal gestation and (b) with GDM. *PDX-1* and *NGN-3* serum expression was determined by qRT-PCR. Student's *t*-test or the Mann–Whitney U-test was used to contrast both groups and the Pearson or Spearman correlation was used. A multiple regression was done introducing body mass index and the relative expression of both genes as independent variables and glucose as dependent variable. Statistical significance was tested at $P \leq 0.05$ level.

Results: Thirty-eight patients (mean age was of 29.00 ± 7.74 years) were included, 22 belonged to the normal pregnancies, and 16 to GDM. Using the ΔΔCt method, the expression fold change for *PDX-1* was 0.458 and for *NGN-3* it was 0.361. There was a significant positive correlation between the expressions of both genes. The multiple regression was significant for both genes expression and glucose levels in case of having normal weight.

Conclusion: *PDX-1* and *NGN-3* low serum expression could be predictors of higher glucose levels in normal pregnancies.

Keywords: Gestational diabetes mellitus, Neurogenin-3, Pancreatic duodenal homeobox factor-1

INTRODUCTION

Pregnancy is considered a diabetogenic state and starting it with overweight or obesity causes an increase in insulin resistance, which leads to the ß-cells ability depletion of insulin synthesis and secretion in sufficient quantities to manage the metabolic requirements triggered in pregnancy. This extra demand on maternal physiology is one of the causes that lead to the development of gestational diabetes mellitus (GDM).[1] As a matter of fact, the worldwide GDM prevalence shows a wide spectrum of prevalence, ranging from 5.4% in caucasian women to 11.9% in Asian and Pacific Islander women.[2] In Mexico, GDM complicates 12.9% of pregnancies[3] being a health challenge.

It is recognized that GDM and Type 2 diabetes mellitus (T2DM) share part of the pathophysiology and it has been shown that several genes of susceptibility to T2DM are associated with GDM.[4]

There are two pancreatic progenitor cell (stem cell) markers that stand out neurogenin-3 (*NGN-3*) and pancreatic duodenal homeobox factor-1 (*PDX-1*) which are also expressed in the adult pancreas.[5] Besides the corroborated function of *PDX-1* as a necessary transcription factor for insulin, it also participates in the pancreas development and β-cell maturation.[6] On the other hand, it has been stated that pancreas islet progenitor cells are those *NGN-3*-positive cells in pancreases of embryonic or adult rats; thus, neurogenin-3 protein is considered an endocrine differentiation marker for β-cells.[7]

In general, glucose-stimulated insulin secretion is decreased after repeated exposure of β-cells to fatty acids, but this last high exposure diminishes the *PDX-1* nuclear translocation and MafA (a β-cell-specific activator) expression, downregulates insulin expression, and induces apoptosis.[8,9] A compensatory response when β-cells decrease in adult animals is β-cell neogenesis activation. During the pancreas regeneration process, *PDX-1* is reexpressed in proliferating cells of this gland[10,11] and it's ducts,[12] and such cells gain a multipotent property to differentiate into any type of cell in the pancreas.

Within the pancreatic islets, Ngn3+ cells have been previously described as progenitor cells involving the ability to generate all endocrine cell lineages, including insulin-producing β-cells.[13] The aim of this study was to compare the *PDX-1* and *NGN-3* serum expression levels in women with and without GDM.

MATERIAL AND METHODS

Setting

This was a prospective, clinical, cross-sectional study performed at the third level "Mónica Pretelini Sáenz" Maternal-Perinatal Hospital (HMPMPS), Health Institute of the State of Mexico (ISEM), Toluca, State of Mexico, Mexico, in the year 2018.

Patients

The invitation was made to all women who attended the Maternal Medicine Service of the HMPMP. The conditions required to exclude them from the study were autoimmune diseases, heart disease, nephropathy, liver disease, or any other chronic condition. If there were incomplete clinical files, they were discarded from the final analysis. Two groups were integrated: (a) Patients with normal gestation and (b) patients with GDM.

Sample

Sample calculation was performed using the next formula:

$$n_0 = \frac{2(Z_\alpha + Z_\beta)^2 S^2}{d^2}$$

Where, n_0: necessary size of the sample, S: Standard deviation, d: Difference to find, Z_α = 1.96, and Z_β: 0.482. Our measure to contrast was the relative units (RUs) of gene expression. Introducing 0.05 for the alpha risk, 0.2 for the beta risk, and a standard deviation (SD) of 4, a sample size of 16 subjects per group was necessary to detect an equal or greater difference at 4 RU.

Physical exploration

Body weight was measured with a digital scale (Tanita) with precision of 0.1 kg and the height was measured with accuracy of 0.1 cm with a Holtain stadiometer (Holtain Ltd., Crymych, United Kingdom). Body mass index (BMI) was calculated as usual, and other anthropometrics parameters were ideal weight based on the formula of Lorentz = ((Height (cm))-100)-((Height (cm)-150)/2.5) and weight gain (kg) per month.

Laboratory

Blood samples were collected in Vacutainer tubes, after a fasting period of 8–12 h. Laboratory tests of albumin (mg/dL), creatinine (mg/dL), electrolytes (Na, Cl), glucose (mg/dL), total cholesterol (mg/dL), triglycerides (mg/dL), and aminotransferases (ALT and AST) were done at the Clinical Laboratory of the HMPMPS. The GDM diagnosis was based on the criteria of the American Diabetes Association (ADA) with an oral glucose load of 75 g with one or more values above the following ranges: 5.1 mmol/L (92 mg/dL) fasting, 10.0 mmol/L (180 mg/dL) at 1 h, and 8.5 mmol/L (153 mg/dL) at 2 h (16). All studies were carried out following the recommendations of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC).

RNA extraction

RNA was extracted from a peripheral blood sample using the using a Norgen's Total RNA Purification Kit (Norgen Biotek Corp.) following the manufacturer's protocol at the Laboratory of Genetics, Faculty of Medicine, Autonomous University of the State of Mexico (UAEMéx). The concentration and purity were quantified in a spectrophotometer (NanoDrop ND-100).

Real-time PCR expression

In the Research Laboratory of Ciprés Grupo Médico S.C. (CGM) using a real-time PCR PrimeQ (Techne, UK) equipment, the gene expression was determined with primers synthesized at the Synthesis and DNA Sequencing Unit of the National Autonomous University of Mexico (UNAM), Institute of Biotechnology (Cuernavaca, Morelos, Mexico). The QuantiNova SYBR Green RT-PCR Kit (Qiagen) was used with the following oligonucleotides:

PDX-1 5' GGATGAAGTCTACCAAAGCTCACGC 3'and 3' CCAGATCTTGATGTGTCTCTCGGTC 5', *NGN-3* 5' CAATCGAATGCACAACCTCA 3' and 3' GGGAGA CT GGGGAGTAGAGG 5'.[14] The reaction was done with a final volume of 20 µl, with primer concentrations of 200 nM and RNA samples of 100 ng. Cycling was programmed as follows: Denaturation (95°C 15 s), alignment (95°C 15 s), extension (50°C 15 s), and melting curve (72°C 15 s) all for 35 cycles. The fold changes of every gene were normalized against glyceraldehyde-3-phosphate dehydrogenase (*GADPH)* 5'CTTGGTATCGTGGAAGGACTC 3' and 3'GTAGAGGCAGGGATGATGTTCT 5' and then compared with the controls through the $2^{-\Delta\Delta CT}$ method.

Statistical analysis

Continuous data were expressed as means ± SD. Once the Kolmogórov test has been performed for the normality of the variables, either the Student's t-test or the Mann–Whitney U-test was used to compare both groups. With the same criteria for normality, either Pearson or Spearman correlation was used among the genes' relative expression and anthropometric variables. Point-biserial correlation was used to determine the correlation between the dichotomous variable GDM presence/absence and the relative quantification of any of both genes of interest. Furthermore, a multiple regression was done introducing BMI and the relative expression of both genes as independent variables and glucose as dependent variable. Statistical significance was tested at $P \leq 0.05$ level using SPSS ver. 23.0 software (IBM Corp., Armonk, NY, USA).

Ethics

All participants gave their informed consent, and both the Research Committee and the Ethics on Research Committee of the HMPMPS approved the protocol (code: 2010-00-91). All procedures were performed in accordance with the Declaration of Helsinki (Fortaleza, Brazil, 2013) and the General Health Law in Mexico.

RESULTS

Data were obtained from 38 patients of whom 22 belonged to the control group and 16 to the experimental group. The mean age was of 29.00 ± 7.74 years. The general characteristics of the patients are shown in Table 1. The distribution of age, height, BMI, and cholesterol was normal, for the rest of the variables, a free distribution was identified and the appropriate statistical analysis was applied.

About family history, in the GDM group, three women mentioned a first degree relative that suffered the same metabolic complication, while in the control group, only one patient had known a similar case in her family.

Women with GDM had significantly higher serum glucose concentrations than patients in the control group and 100% of them had concentrations above 100 mg/dl (or 5.5 mmol/L) while only two patients in the control group had high concentrations. Cholesterol and triglycerides concentrations were within the normal parameters and there were no significant differences between the groups.

Taking into account the ideal weight (54.93 ± 4.95 kg) of the whole population, the average increase in weight

Table 1: Basal characteristics of the patients.

Variable	General	Control group (*n*=22) Mean±SD	GDM (*n*=16) Mean±SD	*P*-value
Age (years)	29.0±1.2	27.3±1.5	31.2±2.1	0.249[a]
BMI (kg/m^2)	26.2±0.3	26.8±0.4	25.5±0.6	0.760[a]
Pregestational BMI (kg/m^2)	26.8±5.0	29.3±5.6	24.4±3.5	0.094
Albumin (mg/dL)	2.3±0.1	2.3±0.1	2.2±0.1	0.243[a]
ALT (mg/dL)	44.0±8.5	39.4±0.9	50.4±18.8	0.895
AST (mg/dL)	34.4±3.3	36.7±4.2	31.1±5.2	0.234
Cholesterol (mg/dL)	182.1±6.1	182.4±8.6	181.8±9.1	1.00
Creatinine (mg/dL)	0.79±0.1	0.87±0.1	0.7±0.6	0.781
Gestational age (weeks)	32.9±5.0	34.5±3.0	30.7±6.5	0.190
Glucose (mg/dL)	133.9±13.0	86.5±2.1	199.2±22.3	0.001
Hemoglobin A1C (%)	6.5±1.3	5.9±1.4	7.1±1.1	0.04
Triglycerides (mg/dL)	243.8±14.9	241.5±14.8	247.0±29.7	0.115[a]
Urea (mg/dL)	28.6±3.4	33.2±5.5	22.2±2.4	0.285
K (mg/dL)	3.8±0.1	3.9±0.1	3.7±0.1	0.162
Na (mg/dL)	134.7±1.1	135.0±1.3	134.2±2.0	0.715
PDX-1 (RU)	3.6±1.5	5.9±2.7	1.3±0.4	0.246
NGN-3 (RU)	1016±373.5	1556.1±595.1	477.6±152.0	0.455

[a]Student's *t*-test. ALT: Alanine transaminase, AST: Aspartate transaminase, BMI: Body mass index, *PDX-1*: Pancreatic duodenal homeobox factor-1, *NGN-3*: Neurogenin-3, RU: Relative units

gain was of 18.47 ± 12.96 kg. Furthermore, for weight and height, no significant differences were observed, in fact, the weight gain per month was similar in both groups 1.56 ± 0.07 kg in the GDM group and 1.60 ± 0.08 kg in the normal gestation group, however, 50% of the GDM patients had a BMI classified as overweight and only 36% of the control patients were identified within the same category. As far as obesity cases, the control group had more cases with Grade 1 (27.3%) and morbid obesity (13.6%) compared to the GDM group which had no cases of morbid obesity and only 18.8% of Grade 1 cases [Table 2].

The point-biserial correlation between the GDM presence/absence and the RU of *NGN3* showed an r of –0.24311 ($P = 0.14136$), the same test between the GDM presence/absence and the RU of *NGN3* showed an r of –0.23264 ($P = 0.15986$).

Using the ΔΔCt method, the expression fold change for *PDX-1* was 0.458 and for *NGN-3*, it was 0.361. In the Spearman correlation analysis, there were no significant results between the clinical variables and the gene expression in any group, but there was a statistically significant correlation between the expression values of both genes in both groups [Table 3].

At last, the multiple regression per BMI classification, for glucose, showed that the model constructed with both *PDX-1* and *NGN-3* was significant in women with normal weight [Table 4].

Table 2: BMI by group.

BMI category	Control group frequency (%)	GDM group frequency (%)	Total frequency (%)
Normal	5 (22.7)	4 (25.0)	9 (23.7)
Overweight	8 (36.4)	8 (50.0)	16 (42.1)
Obesity Grade 1	6 (27.3)	3 (18.8)	9 (23.7)
Obesity Grade 2	0 (0.0)	1 (6.3)	1 (2.6)
Morbid obesity	313.6	0 (0.0)	3 (7.9)
Total	(22)	16	38

Table 3: Spearman correlation between the variables and each gene.

Variable	Gene	Correlation	
		R2	*P*
Age (years)	*PDX-1*	0.076	0.648
	NGN-3	0.052	0.758
BMI (kg/m^2)	*PDX-1*	0.061	0.716
	NGN-3	0.021	0.898
Glucose (mg/dL)	*PDX-1*	–0.072	0.666
	NGN-3	–0.221	0.182
Cholesterol (mg/dL)	*PDX-1*	–0.154	0.356
	NGN-3	–0.154	0.357
Triglycerides (mg/dL)	*PDX-1*	–0.16	0.339
	NGN-3	–0.134	0.421
ALT (mg/dL)	*PDX-1*	–0.254	0.124
	NGN-3	–0.064	0.704
Albumin (mg/dL)	*PDX-1*	–0.157	0.346
	NGN-3	–0.049	0.771
AST (mg/dL)	*PDX-1*	–0.21	0.206
	NGN-3	–0.094	0.573
Creatinine (mg/dL)	*PDX-1*	–0.066	0.692
	NGN-3	–0.058	0.731
K (mg/dL)	*PDX-1*	–0.166	0.319
	NGN-3	–0.058	0.731
Na (mg/dL)	*PDX-1*	0.188	0.257
	NGN-3	–0.058	0.731
Urea (mg/dL)	*PDX-1*	–0.112	0.505
	NGN-3	–0.082	0.624
PDX-1 (RU)	*NGN-3*	0.751	0.001

ALT: Alanine transaminase, AST: Aspartate transaminase, BMI: Body mass index, *PDX-1:* Pancreatic duodenal homeobox factor-1, *NGN-3:* Neurogenin-3, RU: Relative unit

DISCUSSION

Until now, hundreds of genetic variations related with T2DM or glucose/insulin have been identified by genome-wide association studies.[15,16] Most of these genes perform biological processes which affect the pancreatic β-cell number or function.[17] It has been known that overweight and obesity are factors linked to various types of diabetes and here we found that the majority (75.1%) of the GDM patients had a BMI corresponding to overweight, Grade 1 obesity or Grade 2 obesity; interestingly, the control group had a higher percentage of Grade 1 obesity and morbid obesity and the combined percentage with overweight cases was slightly higher overall (77.3%), this could be explained by the treatment of GDM patients since they have to follow a stricter dietetic plan to keep their glucose levels in good targets, whereas the control group patients only followed the general dietetic recommendations for pregnancy, it is also possible that the weight estimation required additional corrections for the expected changes of pregnancy and BMI does not take into account the adipose tissue distribution. With these findings, it is once again clear that GDM and T2DM are multifactorial diseases, and the genetic factors must be taken into account to understand them.

Following the previously mentioned arguments, interactome studies of GDM are still in their phase of increase [Table 5].

The identification of additional genetic markers that could explain the differences in the susceptibility to GDM would represent a crucial point to establish a strategy for prevention, early diagnosis, and treatment of this condition.

In the present study, although it was not reached a statistical difference, both *PDX-1* and *NGN-3* showed a tendency to be underexpressed in patients with GDM compared with patients who had a normal pregnancy, these results are in line with the findings of Wang *et al.* (2018) where *PDX-1* was underexpressed in the fetal side of placental tissue of patients

with GDM, and they also reported *PGC-1α* mutilation.[18] Interestingly, the fact that in the group of pregnant women with normal weight, the serum levels of both genes showed a significant value in the regression for glucose could be a tool to predict a future β-cell failure.

NGN-3 studies in humans are rare and even rarer during pregnancy because they would require a pancreas sample, which is not a viable procedure for diagnosis during pregnancy. The alternative approach proposed here is to use blood samples to perform the mRNA quantification and our findings suggest that it is possible to obtain similar results to those previously reported for the *NGN-3* protein that is present in adult human pancreas from surgical and cadaveric tissue. In fact, in murine models for pregnancy and diabetes, the results suggest a similar expression decrement but the mice usually go through experimental manipulation to achieve the *NGN-3* expression and the systemic response of such manipulation in humans would most likely be different.[19]

The potential *NGN-3* expression manipulation in non-β-cells could greatly improve the treatment for T2DM and GDM but the current evidence *in vivo* is not enough to warrant beneficial results without negative side effects, for this study, we limit our scope to use these molecular tests as potential diagnosis tools that ensure an accurate treatment throughout pregnancy, both genes had a similar expression behavior and the statistical correlation between their expression values suggests that they might share more pathways than we currently know, more interactomes studies are necessary to fully understand this possible relation.

Some final remarks deserve to be mentioned. It is a bit risky to propose a specific stage of the pregnancy to request the quantification of the relative expression of *NGN-3* and *PDX-1*, but pretending to have enough time for a prevention intervention, it could be suggested to measure them after the 20th week of gestation.

Table 4: Multiple regression per BMI classification for glucose.

BMI category	Model		Standardized coefficient	
			Beta	*P*-value
Normal	1	(Constant)		0.067
		NGN-3	–3.130	0.002
		PDX-1	3.348	0.001
Overweight/obesity	1	(Constant)		0.000
		NGN-3	–0.407	0.432
		PDX-1	0.170	0.742

BMI: Body mass index, *PDX-1*: Pancreatic duodenal homeobox factor-1, *NGN-3*: Neurogenin-3

Table 5: Review of genes related to GDM.

Genes	Reference	Sample	Findings
IRS-1 and *PPARγ*	Cheng *et al.* (2017). Fasting mimicking diet promotes ngn3-driven β-cell regeneration to reverse diabetes	Human	Decreased expression of *IRS-1* (might reduce insulin suppression of lipolysis) and *PPARγ* in GDM patients compared with non-pregnant controls
PGC-1α and *PDX1*	Wang *et al.* (2018). Altered expression of PGC-1α and *PDX1* and their methylation status are associated with fetal glucose metabolism in gestational diabetes mellitus	Human	Lower levels of *PGC-1α* and *PDX1* in the GDM group compared with the non GDM group as well as higher methylation levels of the *PGC-1α* gene on the GDM group but lower on *PGC-1α* and *PDX1* mRNA
NGN-3	Toselli *et al.* (2014). Contribution of a non-β-cell source to β-cell mass during pregnancy	Mice	Decreased expression of *Ngn3* in pancreatic islets during pregnancy
GCK	Zubkova *et al.* (2019). High frequency of pathogenic and rare sequence variants in diabetes-related genes among Russian patients with diabetes in pregnancy	Human	28 pathogenic variations of which the majority occurred in the *GCK* gene
ACLY	Mac-Marcjanek *et al.* (2018). Expression profile of diabetes-related genes associated with leukocyte sirtuin 1 overexpression in gestational diabetes	Human	In groups with GDM and over expression of *SIRT1, ACLY* was under expressed compared with the group with normal *SIRT1*
TCF7L2 SLC30A8 KCNQ1 KCNJ11 and *GCK (SNPs)*	Khan *et al.* (2019). Genetic confirmation of T2DM meta-analysis variants studied in gestational diabetes mellitus in an Indian population	Human	Positive association of GDM with the polymorphisms
Multiple SNP's of *TCF7L2* and *KCNQ1*	Huerta-Chagoya *et al.* (2015). Genetic determinants for gestational diabetes mellitus and related metabolic traits in Mexican women	Human	Strong association of the *TCF7L2* and *KCNQ1* variants with risk of developing GDM and higher frequency of family history of diabetes in cases, compared to controls

The association of *PDX-1* and *NGN-3* with the GDM severity should be a complementary analysis but was beyond the scope of this initial approach. To set up the cutoff value for these genes as predictors of high glucose levels, it will be necessary to perform a longitudinal study. However, with the information obtained in this initial study, there is a possibility that these genes could indeed have a place in clinical practice, as predictors for a high glucose value during pregnancy, although much remains to be done and demonstrated.

If the correlation between the decrease of *PDX1* and *NGN-3* with the condition of hyperglycemia and the appearance of GDM is corroborated, one could be witnessing the same phenomenon that occurs with patients with T2DM, in whom the decrease or loss of these transcription factors has been demonstrated with the chronicity of the disease (between 10 and 15). This highly accelerated process of β-cell loss in pregnancy can be visualized as an accelerated burnout state, potentiated by the appearance of insulin counterregulatory hormones in gestation: Cortisol (serum level doubles in pregnancy), placental lactogen (main increase in the second half of pregnancy), estrogens, and progesterone.

A limitation of the study is the variability in the evolution of BMI during pregnancy, however, it is a simple and practical tool that allows us to monitor when it comes to the care of thousands of patients as it is our case. The same variable has previously been considered for regressions with other parameters with useful results.[20] Of course, to carry out a more precise study to determine the association between gestational weight gain and the genes of interest, ideally, it would be necessary to quantify the increase in visceral adipose tissue. Finally, the next steps in our line of research will be the construction of the *NGN-3* and PDX1 recombinant proteins to expand the analytical options to corroborate our hypothesis.

CONCLUSION

In normal weight pregnant women, *PDX-1* and *NGN-3* serum levels might be related with the glucose serum concentration.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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