PERINATAL JOURNAL

Original Article

Perinatal Journal 2023;31(3):207-212

Is there a relationship between decreased humanin levels in gestational diabetes mellitus women requiring insulin treatment?

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Abstract

Objective: The aim of this study was to investigate maternal serum humanin levels in pregnant women complicated with gestational diabetes mellitus(GDM) and in healthy pregnant women.

Methods: This cross-sectional study was conducted including 80 pregnant women, 30 with normal pregnancy, 25 with GDM blood glucose regulated with diet alone and 25 with GDM regulated with insulin and diet combination. Maternal serum levels of humanin were measured by using enzyme-linked immunosorbent assay kits.

Results: Serum humanin levels were significantly lower in pregnancies with GDM compared to the control group (p=.004). Moreover, GDM pregnancies requiring insulin to maintain euglycemia had significantly lower humanin levels than GDM pregnancies managed with diet therapy alone (p=.036). Serum humanin levels did not correlate with maternal clinical and biochemical parameters.

Conclusion: Maternal serum humanin levels were significantly lower in pregnancies complicated with GDM. Decreased expression of humanin, considering its regulatory effects, may contribute to the development of pancreatic β-cell dysfunction and GDM.

Keywords: Gestational diabetes mellitus, humanin, mitochondrial dysfunction, insulin, pancreatic b-cell

Introduction

Gestational diabetes mellitus (GDM) is characterized by glucose intolerance of variable severity with onset during pregnancy.[1] Pregnancy is associated with insulin resistant state that escalates as pregnancy progresses.[2] Insulin resistance during pregnancy has been attributed to placental and maternal hormones, TNFa, resistin and chronic low-grade inflammatory state associated with pregnancy.[3,4] During normal pregnancy, pancreatic b cell capacity increases as an adaptive mechanism to compensate for insulin resistance that occurs late in pregnancy.[5,6]. Failure of adequate insulin secretory response by dysfunctional pancreatic β-cell due to occult genetic predisposition leads to the development of GDM.[7]

Mitochondria are the primary energy source for all cellular functions. However, they also play a crucial role in maintaining other critical cellular functions, including calcium homeostasis, synthesis of biomolecules, cell signaling and apoptosis.[8]

Maintaining a healthy and functional mitochondrial network is crucial and provided through coordinating mitochondrial biogenesis, fusion, fission and mitophagy.[9] Proper mitochondrial functioning is a significant determinant of insulin secretion from pancreatic β-cells, and diabetes mellitus develops when β-cells fail to release appropriate amounts of insulin in response to glucose.[10]

The nucleus regulates mitochondrial function through several transcription factors that activate the expression of the mitochondrial genome through the transcriptional induction of several mitochondrial proteins

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How to cite this article: Acar DK, Tayyar A, Aydın AA, Dağ İ. Is there a relationship between decreased humanin levels in gestational diabetes mellitus women requiring insulin treatment? Perinatal Journal 2023;31(3):207-212 DOI: 10.59215/prn.23.0313005

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encoded by nuclear DNA; and by promoting mitochondrial adaptive pathways.[11] Moreover, mitochondria can also communicate with the nucleus and cytosol (which is referred to as retrograde signaling) under physiological and pathological conditions by controlling the levels of various metabolites such as mitochondrial-derived peptides, ATP, NAD+ and reactive oxygen species (ROS).[12]

Humanin (HN) is the first member of retrograde signaling peptides that is encoded by a small open reading frame(sORF) within the mitochondrial 16S ribosomal RNA of mtDNA and was initially identified from surviving neurons in patients with Alzheimer's disease.[13] Humanin was identified as a neuroprotective peptide that could protect neuronal cells from amyloid-β toxicity. In addition to cytoprotection, humanin and its analogs have been demonstrated to have several metabolic effects, such as reducing weight gain and visceral fat and playing a significant role in glucose homeostasis via enhanced insulin sensitivity and increased insulin release.[14-16]

In this study, we measured serum humanin concentrations of pregnant women with GDM and uncomplicated pregnancies. We compared GDM pregnancies and whether humanin levels differ concerning insulin requirement.

Methods

The study was conducted from January 2017 to March 2018 at Istanbul Kanuni Sultan Suleyman Training and Research Hospital, Turkey. Ethical approval for this study was obtained from the local committee. Written informed consent was obtained from all participants for the study following the Declaration of Helsinki.[17] A total of 80 pregnant women were enrolled in the study (50 pregnant women diagnosed with GDM and 30 women with normal blood glucose patterns). Half of the 50 women with GDM were treated with diet and insulin, while the remaining half were treated with diet alone. The control group comprised 30 randomly selected age-matched and gestational-age-matched healthy pregnant women who presented to the antenatal clinic on the same dates as the women in the study group. The women in the control group had no medical, obstetrical or surgical complications. Patients were excluded for chronic maternal disease, pregestational diabetes, hypertension, multifetal pregnancy, or fetal anomalies. The gestational age was determined based on the last day of the menstrual period and confirmed by the first-trimester crown-rump length (CRL) measurement.

Measurements

The examinations were performed with a 3.5MHz color-pulsed Doppler ultrasound (Voluson 730 Expert; GE Healthcare, Chalfont St. Giles, UK). The following parameters were recorded: age, body mass index (BMI) (kg/m2), gestational age at the time of blood sampling, gestational week at birth, and birth weight. A one-step, 2-hour, 75g oral glucose tolerance test was performed following the International Association of Diabetes and Pregnancy Study Group (IADPSG) to all pregnant women between their 24th and 28th gestational weeks. The diagnosis of gestational diabetes was made if any of the plasma glucose values were met or exceeded (fasting: 92 mg/dL, 1 h: 180 mg/dL, 2 h: 153 mg/dL). Serum Humanin (MT-RNR-2 concentrations were measured using an enzyme-linked immunosorbent assay (ELISA) kit (Catalog No: SRB-T-88647, Shanghai Sunred Biological Technology Co., Ltd., China). To produce a standard curve of optical density (OD) versus Humanin concentration, we added specimens, standard samples, and Biotin-labeled antibodies to micropores pre-coated with the Humanin antibody, and the OD values of the standard samples and specimens were then detected with a microplate spectrophotometer (Smart Microplate Reader; USCN KIT INC.) at a wavelength of 450 nm. The concentration of Humanin in the samples was subsequently determined by comparing the OD value of the samples to the standard curve. Glucose, insulin, and hemoglobin A1c (HbA1c) levels were determined using standard laboratory methods. Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) index [HOMA-IR= (fasting plasma glucose (mmol/L) × fasting insulin (μU/mL))/ 22.5].

Statical Analysis

The statistical analyses were performed using the Statistical Package for the Social Sciences, version 20 (SPSS Inc., Chicago, IL). The distributions of all continuous variables were tested using the Kolmogorov-Smirnov test. The variables with normal distributions were compared between groups by the Independent Samples T Test and were expressed as mean + SD. Mann Whitney U Test was applied for non-normal distributed variables, and results were expressed as a median and interquartile range. Pearson's correlation coefficient was used to determine the relationship between the variables. P values less than 0.05 were considered statistically significant.

Results

The demographic characteristics and biochemical values of the GDM and control groups are shown in Table 1. There were no significant differences between GDM and controls for maternal age, gestational age at blood sampling and delivery. The BMI, fetal birth weight, fasting blood glucose, insulin, and HOMA-IR were significantly higher in the GDM group compared to the

control group. Humanin levels were significantly lower in the GDM group compared to the control group. Among women with GDM, 25 had insulin therapy, and 25 were treated with diet alone. Clinical and biochemical characteristics of GDM patients treated with insulin and managed by diet are shown in Table 2. Humanin levels were significantly lower in the group treated with insulin than those managed with diet alone. Maternal serum humanin levels were not associated with patients' clinical and biochemical characteristics (Table 3).

Table 1. The clinical and biochemical characteristics of women diagnosed with gestational diabetes and normal controls

	GDM (n=50)	Control (n=30)	p values
Age (years)	32.7 ± 5.0	31.6 ± 3.8	0.282
BMI at blood sampling (kg/m²)	32.3±4.7	29.5 ± 6.2	0.026
GA at blood sampling (weeks)*	34.4 ± 2.6	34.5± 2.3	0.891
GA at delivery (weeks)	38.4 ±0.8	38.8 ±1.1	0.120
Birth weight (g)	3518.4± 487.2	3253.5 ± 414.4	0.015
Fasting Glucose (mg/dl)	99.2±12.8	80.9 ± 5.3	<0.001
HbA1c (%)	5.5 ± 0.4	5.0 ± 0.4	<0.001
Insulin (mU/l)*	10.6 (8.7)	6.3 (7.4)	0.005
HOMA-IR*	2.46 (2.2)	1.25 (1.6)	<0.001
Humanin (pg/mL)	315.0 ±174.0	436.4 ±188.4	0.004

Statistically significant $p < 0.05$
*Data are expressed as median (interquartile range), and the Mann-Whitney U test was used to analyze non-normally distributed variable
BMI, body mass index; GA, gestational age; HOMA-IR, homeostatic model assessment of insulin resistance.

Table 2. The clinical and biochemical characteristics of GDM patients treated with insulin and managed by diet

	GDM diet (n=25)	GDM Insulin (n=25)	p
Age (years)	31.9 ±7.3	32 ±5	0.964
BMI at blood sampling (kg/m²)	32.2±4.5	32.6±5.1	0.679
GA at blood sampling (weeks)*	34.4 ± 2.8	34.5± 2.5	0.878
GA at delivery (weeks)	38.5 ±0.9	38.5±0.6	0.818
Birth weight (g)	3631.7± 485.6	3405.2 ± 471.2	0.101
Fasting Glucose (mg/dl)	93.1±10.9	105.3±11.7	<0.001
HbA1c (%)	5.4 ± 0.5	5.6 ± 0.5	0.167
Insulin (mU/l)*	12.6 (8.1)	10.5 (10.5)	0.677
HOMA-IR*	2.4 (2.3)	2.5 (2.8)	0.808
Humanin (pg/mL)	366.2 ±141.3	263.8 ± 190.8	0.036

Statistically significant $p < 0.05$
*Data are expressed as median (interquartile range), and the Mann-Whitney U test was used to analyze non-normally distributed variables.
BMI, body mass index; GA, gestational age; HOMA-IR, homeostatic model assessment of insulin resistance.

Table 3. Correlations between serum humanin levels and all the other parameters assessed in all groups

	Whole Group (n=80)		Control Group (n=30)	
	r	p	r	p
Age (years)	-.148	0.190	-.247	.188
BMI at blood sampling (kg/m²)	.011	0.925	.064	.735
GA at blood sampling (weeks)	.049	0.064	.029	.879
GA at delivery (weeks)	.108	0.340	-.051	.789
Birth weight (g)	.006	0.958	.042	.827
Fasting Glucose (mg/dl)	-.215	0.055	-.017	.929
HbA1c (%)	-.80	0.482	-.133	.484
Insulin (mU/l)	-.072	0.528	.095	.616
HOMA-IR	-.114	0.316	.102	.591

r= Pearson's
BMI, body mass index; GA, gestational age; HOMA-IR, homeostatic model assessment of insulin resistance.

Discussion

In this study, humanin levels were significantly lower in patients with GDM than in the nondiabetic control group and in GDM patients requiring insulin to control blood glucose levels. However, there was no significant relationship between humanin and clinical and biochemical characteristics. These results suggest that decreased humanin levels reflect that mitochondrial dysfunction contributes to pancreatic beta cell dysfunction.

Although best known as the primary generators of cellular ATP, mitochondria also play a crucial role in entire cell metabolism through their participation in apoptosis, calcium homeostasis, ROS generation, lipogenesis and the production of steroid hormones.[18] Moreover, pancreatic ß-cell mitochondria play a crucial and dynamic role in insulin secretion.[19] The maintenance of a functional mitochondrial population is critical to cellular fitness. For these reasons, multiple quality control pathways, such as mitochondrial biogenesis, mitochondrial dynamics and autophagy, have evolved to maintain proper function basally and in stress response.[20]

Mitochondrial biogenesis results from coordinated crosstalk between the nucleus and mitochondria.[21] This involves a complex coordination of nuclear, cytosolic and mitochondrial events mediated through energy sensors, transcription factors, coactivators and regulators.

Clinical and experimental studies suggest PGC-1α and its-regulated transcription factors, including TFAM and NRF1, which are master regulators of mitochondrial biogenesis, are downregulated in diabetes mellitus.[22] Moreover, evidence suggests decreased mtDNA content is associated with diabetes mellitus.[23]

In addition to decreased mitochondrial biogenesis, inflammatory and oxidative stresses intrinsic to diabetes may contribute to mtDNA content decline.[24,25] Decreased mtDNA content in pancreatic beta cells compromises bioenergetic functions and constituent protein expression in oxidative phosphorylation. This reduces glucose-stimulated ATP generation and impaired β-cell insulin secretory capacity.[26] Humanin plays a crucial role in preserving essential mitochondrial functions related to energy production. In a well-designed study, exogenous administration of humanin was demonstrated to improve pancreatic beta cell function through increased mitochondrial mass and efficiency. Exogenous administration of humanin promoted mitochondrial biogenesis by activating the PGC-1α -NRF1-TFAM pathway after stimulation of AMPK phosphorylation. Moreover, humanin treatment increases mtDNA copy numbers and intracellular ATP generation; hence, this mechanism alters the molecular mechanism of diabetes mellitus.[27]

Gestational diabetes is associated with a chronic inflammatory state, where TNF alpha levels were inversely correlated with insulin sensitivity.[3] A role for humanin in the down-regulation of inflammatory responses has been demonstrated. Humanin attenuates inflammatory response by suppressing the secretion of pro-inflammatory cytokines such as IL-6, IL-1beta and TNF alfa in astrocytes induced by lipopolysaccharides.[28] Hence it may be speculated that decreased humanin levels in pregnancy may contribute to the inflammation associated with gestational diabetes. In line with this suggestion, in an experimental study in non-obese diabetic (NOD) mice, a 6-week humanin treatment was demonstrated to suppress inflammation and cytokine-induced apoptosis in pancreatic beta cells and improve glucose tolerance.[29]

Autophagy plays a crucial role in the function and survival of pancreatic beta cells by clearing misfolded proteins and dysfunctional organelles, and it has been demonstrated that impaired autophagy results in beta cell apoptosis and impaired insulin secretion.[30] A recent study demonstrated that humanin activates autophagy by stabilizing the binding of the chaperone HSP90 to substrates destined to lysosomes and protects multiple cell types against oxidative stress-induced cell death.[31]

Human studies reported lower circulating humanin levels both in prediabetic[32] and Type 2 diabetic[33] patients. A recent study also showed decreased humanin levels in pregnant with GDM compared with healthy controls. Moreover, they found a negative correlation with HOMA-IR and argued that decreased humanin levels might contribute to insulin resistance in GDM.[34] In contrast, we found no association between HOMA-IR and humanin levels but significantly decreased humanin levels in pregnant women requiring insulin treatment to maintain euglycemia. This finding aligns with the evidence suggesting that GDM results from insufficient insulin response to overcome insulin resistance due to pancreatic β-cell dysfunction.[35]

The mechanism of decreased humanin expression in diabetes mellitus has not yet been fully elucidated; however, it may reflect diminished mtDNA content due to the downregulation of mitochondrial biogenesis. Mitochondrial SNP within the coding region of the humanin gene is implicated with lower circulating humanin levels and cognitive decline.[36] It is thus tempting to speculate that such mtDNA variations may be associated with decreased expression of humanin and the development of GDM.

Study Limitations

As this was a cross-sectional study, a cause-and-effect

relationship between decreased humanin levels and GDM could not be demonstrated. Another limitation is the small number of included patients. The strength of our study was the first study to investigate humanin levels in pregnant with gestational diabetes requiring insulin treatment compared to those treated with diet alone.

Conclusion

In conclusion, the present study demonstrates that humanin levels were significantly lower in pregnant with gestational diabetes compared to the control group. Further clinical studies with larger cohorts are required to determine how humanin can be used as a diagnostic marker and potent therapeutic agent for GDM.

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