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ORIGINAL ARTICLE

Placental expressions and serum levels of adiponectin, visfatin, and omentin in GDM

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Abstract

Aims Adiponectin, visfatin, and omentin have been shown to be associated with insulin sensitivity and might have a role in the pathophysiology of gestational diabetes mellitus (GDM). This study aimed to (1) compare *adiponectin*, *visfatin*, and *omentin* mRNA expressions in placenta and their serum levels between normal pregnancy (NP) and GDM class A1 (GDMA1) pregnancy and (2) determine correlations between placental gene expressions as well as serum levels with maternal and neonatal clinical parameters in all, NP, and GDM subjects.

Methods NP subjects ($n=37$), who had normal medical history during their pregnancies without diagnosis of any abnormalities and GDMA1 subjects ($n=37$), who were diagnosed since they had antenatal care, were recruited when they were in labor with a gestational age of at least 34 weeks. Clinical parameters and serum adiponectin, visfatin, and omentin levels were measured in the delivery room.

Results GDMA1 subjects had higher serum visfatin and plasma glucose levels, but lower serum omentin levels ($p < 0.05$ all) compared to controls, with comparable levels of placental *adiponectin*, *visfatin*, and *omentin* expressions, plasma insulin, and indices of insulin sensitivity and insulin resistance. Serum visfatin was negatively correlated with neonatal weight and length in the GDM group ($p < 0.05$ all). Serum omentin was negatively correlated with pre-pregnancy body mass index and waist circumference only in the NP group ($p < 0.05$ all). Serum adiponectin was negatively correlated with maternal age and HOMA-IR in the NP group ($p < 0.05$ all) and with placental weight and serum omentin in the GDM group ($p < 0.05$ all).

Conclusions In conclusion, in GDMA1, increased serum visfatin, which has insulin-mimetic effect, might be associated with a compensatory mechanism that improves the impaired insulin function. Decreased serum omentin in GDMA1, which is normally found in visceral obesity, might lead to insulin resistance and contribute to the pathophysiology of GDM.

Keywords GDM · Insulin resistance · Obesity · Adiponectin · Visfatin · Omentin

Introduction

Pregnancy is a condition defined as "low" or "high" risk, depending on the possible disadvantages for the maternal or neonatal outcomes [1]. Gestational diabetes mellitus (GDM) is one of the most common medical complications of pregnancy that threaten the mother and her neonate [1]. Pregnancy is associated with the accumulative deposition of visceral adipose tissue [2]. The total and visceral adipose tissue depths are key pathogenic indicators of abnormal glucose homeostasis and GDM [2]. Abnormal production of adipokines might characterize a pathophysiological relationship between obesity and GDM [3]. Adipokines, including adiponectin, visfatin, and omentin, have been shown to be

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involved in the regulation of insulin sensitivity by modulating the insulin signaling pathway implicated in glucose metabolism [3].

Adiponectin is encoded by the adiponectin gene and has 247 amino acids [4]. The adiponectin gene is expressed in adipose tissue [4] and placenta [5]. Binding of adiponectin to its receptors results in an increase in the oxidation of fatty acid and glucose uptake in skeletal muscle, inhibition of gluconeogenesis in the liver, and a decrease in triglyceride accumulation in skeletal muscle [6]. Adiponectin was decreased in obese compared to non-obese subjects [7, 8] and was negatively correlated with BMI, insulin levels and homeostasis model assessment of insulin resistance (HOMA-IR) [7, 9, 10]. Additionally, adiponectin levels were shown to be decreased in patients with type 2 diabetes mellitus (T2DM) [9]. Previous studies found significantly lower adiponectin levels in GDM women compared to their BMI-matched controls [11–14]. Women with low adiponectin levels were 5–6 times more prone to the risk of GDM than women with high levels [15].

Visfatin is encoded by the *nicotinamide phosphoribosyltransferase* (*NAMPT*)/*pre-b cell colony-enhancing factor 1* (*PBEF1*) gene and composed of 491 amino acids [16]. Visfatin was found to be expressed comparably in both subcutaneous and visceral adipose tissues [7] and can be produced by the placenta [17]. In 2006, Chan et al. reported that visfatin had insulin-mimetic activity [18] since it can bind to the insulin receptor at a distinct site from insulin binding, resulting in glucose uptake by adipose tissue and skeletal muscle [19]. Visfatin decreases hepatic glucose release and enhances glucose consumption by adipose tissue and muscle [19]. Visfatin levels were increased in both type 1 and 2 diabetes mellitus patients [20, 21]. Serum visfatin levels were found to be increased [22], not different [23], or decreased [24, 25] in obese compared to non-obese subjects. Furthermore, previous studies have found either elevated [26], comparable [27], or decreased [18] visfatin concentrations in women with GDM compared to healthy pregnant controls.

Omentin is encoded by omentin-1 and omentin-2 genes [28] and has 295 amino acids [29]. Omentin-1 is mainly expressed in visceral, not subcutaneous, adipose tissue [30]. Hyperinsulinemia significantly reduces omentin levels and secretion [31]. Previous studies reported that lower serum omentin levels were found in impaired glucose tolerance, T2DM, and obese subjects and had negative correlations with insulin, HOMA-IR and BMI [7, 28, 32]. In GDM, circulating omentin was found to be either decreased [33] or unchanged [34] compared to controls.

To summarize, adiponectin, visfatin, and omentin are 3 interesting adipokines which are associated with obesity, insulin resistance, the development of T2DM and GDM. As dysregulation of placental function might contribute to the pathogenesis of GDM [35], identification of the relevance of the adiponectin, visfatin, and omentin expressions in placenta and maternal serum levels of adiponectin, visfatin, and omentin might contribute to the pathophysiology of GDM. Furthermore, interactions and comparisons of placental gene expressions and their serum comparison among these 3 adipokines have not been determined in a single setting. The current study aimed to (1) compare the placental expressions of *adiponectin*, *visfatin*, and *omentin* in placental tissue, as well as their maternal serum levels between the NP and GDM pregnant women and (2) determine correlations between 2 factors including these parameters and maternal and neonatal clinical parameters. GDM is categorized into class A1 and class A2. Class A1 can be controlled with diet therapy alone, while class A2 is being treated with insulin therapy [36]. Most previous studies quantified *adiponectin*, *visfatin*, and *omentin* gene expressions and blood levels of adiponectin, visfatin, and omentin in GDMA1 and A2 subjects pooled together. The current study focused only on GDM class A1 subjects so that confounding factors from insulin injection in GDM class A2 could be avoided. Revelations of alterations in the expression and secretion of hormones from adipose tissue as well as from placenta might lead to the disclosure of pathophysiology of GDM [37].

Materials and methods

Subjects

The study protocol was approved by the Siriraj Institutional Review Board (COA no. Si.545/2015) of the Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. Informed consent was obtained from all participants included in the study. Written informed consents and questionnaires were collected from all subjects prior to blood and placenta collection after admission to the delivery room at Siriraj Hospital. In this study, there were 37 gestational diabetes mellitus (GDM) and 37 normal pregnant (NP) subjects.

Healthy and GDMA1 pregnant women undergoing either cesarean or vaginal delivery were recruited in this study when they were in labor. The inclusion criteria for all subjects were pregnant women aged at least 18 years who started their antenatal care before 20 weeks of gestation and were in labor at Siriraj Hospital, and having a gestational age of at least 34 weeks. For the NP group, healthy pregnant women who had normal medical history during their pregnancies without diagnosis of any abnormalities were recruited. For the GDM group, patients who were diagnosed with GDMA1 since they had antenatal care were recruited. There were no pre-specified matching criteria between the GDM and NP groups. GDM screening and diagnosis were performed during the antenatal care period in pregnant women who

had risk factors including maternal age ≥ 30 years, pre-pregnancy BMI ≥ 27, previous GDM history, a history of giving birth to a large-for-gestational-age baby, and a family history of DM [38] during their first visit and again at 24–28 weeks of gestation if the initial tests were normal [38]. For the screening test, the blood sample was drawn before and at 1, 2, and 3 h after an oral 50-gram glucose challenge test (GCT) [38]. Glucose values of > 95 mg/dl at the fasting state, > 140 mg/dl at 1-h postprandial, or > 120 mg/dl at 2-h postprandial were classified as abnormal glucose tolerance test results. Then, a 100-gram oral glucose tolerance test (OGTT) was performed to identify GDM, in accordance with the Carpenter and Coustan criteria [38], with fasting glucose ≥ 95 mg/dl, 1 h ≥ 180 mg/dl, 2 h ≥ 155 mg/dl, and 3 h ≥ 140 mg/dl. GDM class A1 is identified when the fasting plasma glucose < 105 mg/dL, 2-h postprandial blood glucose < 120 mg/dL, and the subject's blood glucose level is being controlled with diet therapy alone. GDM class A2 is diagnosed when the fasting plasma glucose > 105 mg/dL, 2-h postprandial blood glucose > 120 mg/dL, and the subject is being treated with insulin therapy to control maternal blood glucose levels [36]. The current study focused only GDM class A1, which is regarded as the mild form, to avoid confounding factors from the insulin injection of GDM class A2. Exclusion criteria were subjects who had human immunodeficiency virus infection; type 1 or 2 diabetes mellitus; hypertension; other endocrine disorders; a previous history of chronic diseases; smoking habits; malignancies; pre-term membrane rupture; fetuses with malformations; and fetal distress during delivery; used drugs that might affect blood glucose and insulin levels; or received drugs for pre-term delivery risk. Withdrawal or termination criteria were subjects who did not want to further participate at any time during the study, and those who were not willing to have their blood or placenta collected.

Tissue and blood collection

Before delivery, 2 ml of blood was collected for glucose assay, 4 ml for insulin assay, and 8 ml for hormonal assay. Blood samples for glucose and insulin analysis were sent to the central laboratory at the Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. The 8-ml sample was weight-balanced and separated by centrifugation at 3000 rounds per minute at 4 °C for 15 min. The serum sample was stored at − 70 °C until analysis of adiponectin, visfatin, and omentin.

After delivery, the whole placenta tissue was collected, processed for cleaning with normal saline, and snap frozen in liquid nitrogen to preserve RNA from RNase action. The placenta was cut into small pieces and kept at − 70 °C until analysis of the gene expressions of *adiponectin*, *visfatin,* and *omentin.*

Demographic details

Maternal history including maternal age, gestational age, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), height, pre-pregnancy body weight and BMI, pre-delivery body weight and BMI, and waist and hip circumferences were obtained from the questionnaire and medical record. Body weight change was calculated from the pre-delivery body weight minus the pre-pregnancy body weight. Neonatal clinical data including weight, length, head circumference, and placental weight were obtained from the medical record.

RNA extraction

Adiponectin, visfatin, and *omentin* mRNA expressions were quantified as described previously [7]. The reference gene was *TOP1*, which is the most stably expressed gene in the placenta [39]. The primer sequences of *TOP1* were designed by the authors and blasted to confirm primer specificity using published nucleotide sequences from the PubMed database as follows: Forward–5′TCCAAGCATAGCAACAGTGAACA3′ and Reverse–5′AATAGCCATCATCTTCAGGTTCATC3′. The primer sequences of *adiponectin, visfatin,* and *omentin* were obtained by a previously published article [7]. For all genes, PCR amplification was performed under the following conditions: Taq DNA polymerase activation at 95 °C for 10 min, 40 cycles of DNA denaturing at 95 °C for 15 s, and annealing at 58 °C for 60 s with a final extension at 72 °C for 30 s. For every RT-PCR reaction, no template control was performed as a negative control, and fat tissues were used as positive controls. The actual real-time PCR product size of *adiponectin* (132 bp), *visfatin* (148 bp), *omentin* (149 bp), and *TOP1* (238 bp) genes in placental tissue was proven by gel electrophoresis (Bio-Rad, Hercules, CA, USA) as shown in Fig. 1.

Hormonal assay

Analysis of plasma glucose and insulin

Plasma glucose was determined by an enzymatic reference method with hexokinase by Cobas Integra 800 analyzer (Roche Diagnostics, Tokyo, Japan). Plasma insulin was determined by a sandwich electrochemiluminescent immunoassay by Cobas 8000 modular analyzer series module e602 (Roche Diagnostics, Tokyo, Japan). The homeostasis model assessment of insulin resistance (HOMA-IR) is calculated by the multiplication of fasting glucose (mg/dl) and fasting insulin (μU/ml) divided by 405. The quantitative

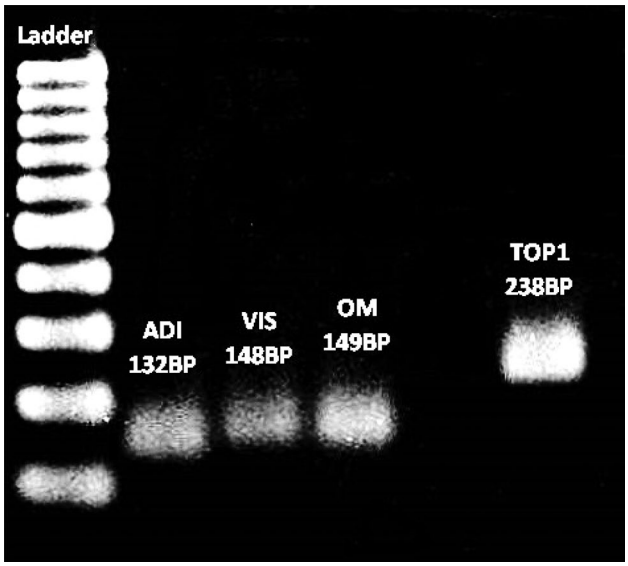

Fig. 1 Gel electrophoresis revealing amplicon size of *adiponectin* (ADI) (132 bp), *visfatin* (VIS) (148 bp), *omentin* (OM) (149 bp), and *TOP1* (238 bp)., *BP* base pair

insulin sensitivity check index (QUICKI) is calculated by the inverse of the sum of the logarithms of the fasting insulin (μU/ml) and fasting glucose (mg/dl).

Analysis of serum adiponectin, omentin, and visfatin

The serum adiponectin (Phoenix Pharmaceuticals Inc., Burlingame, CA, USA) and omentin (Elabscience Biotechnology Co. Ltd., Wuhan, People's Republic of China) levels were analyzed by a commercial enzyme-linked immunosorbent assay (ELISA) kit. The serum visfatin levels were analyzed using an enzyme immune assay kit (Phoenix Pharmaceuticals Inc., Burlingame, California, USA). The range of detection was 0.15–10 ng/ml for adiponectin, 0.63–40 ng/ml for omentin, and 0.1–1000 ng/ml for visfatin. The minimum detectable level was 0.15 ng/ml for adiponectin, 0.38 ng/ml for omentin, and 1.9 ng/ml for visfatin. The intra-assay and inter-assay variations were 9.28% and 14.79%, respectively, for adiponectin, 4.00% and 9.66%, respectively, for omentin, and 3.64% and 8.78%, respectively, for visfatin. The absorbance was read at 450 nm using a Synergy HT Multi-Detection Microplate Reader (BioTek Instruments, Inc., Winooski, VT, USA).

Statistics

Data were presented as mean ± standard error of mean (SEM), using SPSS 18.0 software. To test the normality, a Kolmogorov–Smirnov test was performed. For normally distributed data, comparisons between NP and GDM groups were made by Student's unpaired *t*-test. For non-normally distributed data, the Mann–Whitney U test was performed. Comparisons of the gene expressions as well as serum levels for adiponectin, visfatin, and omentin in all, NP, and GDM subjects were made using one-way repeated-measures analysis of variance (ANOVA). Correlations for all variables were studied in all, NP, and GDM subjects using 2-tailed Pearson's product-moment correlation for normally distributed data or Spearman's rank correlation coefficient for ranked or non-normally distributed data. Only variables that provide significant correlations were shown in the results. Multivariate linear regression analyses were performed to determine the factors that contributed to serum levels of adiponectin, visfatin, and omentin by the stepwise method. A p value less than 0.05 was considered to be statistically significant.

Results

Comparisons between NP and GDM subjects

Pre-pregnancy BMI tended to be higher in the GDM group compared to the NP group ($p = 0.071$) (Table 1). Fasting plasma glucose ($p < 0.05$) and serum visfatin levels were significantly higher ($p < 0.001$), but serum omentin levels ($p < 0.01$) were significantly lower in GDM compared to NP subjects (Table 1). Serum omentin levels were comparable between the NP and GDM groups. After adjustment for BMI or insulin levels or gestational age, the results of adipokine levels compared between NP and GDM subjects remained same.

Comparisons between adiponectin, visfatin, and omentin

For placental gene expressions in all (Fig. 2A), NP and GDM (Fig. 2B) subjects, the expression of *visfatin* was highest, followed by *adiponectin*, and then by *omentin* ($p < 0.001$ all). Placental *adiponectin*, *visfatin*, and *omentin* gene expressions were not significantly different between NP and GDM subjects (1.058 ± 0.195 and 0.93 ± 0.21, respectively, for adiponectin; 4.098 ± 0.78 and 0.09 ± 0.04, respectively, for visfatin; and 0.023 ± 0.01 and 0.02 ± 0.003, respectively, for omentin; Fig. 2B). For maternal serum levels in all (Fig. 2C) and NP (Fig. 2D) subjects, levels of adiponectin were highest, followed by omentin, and then by visfatin ($p < 0.001$ all). In GDM subjects (Fig. 2D), serum levels of adiponectin were significantly higher than visfatin and omentin ($p < 0.001$), with comparable serum levels for visfatin and omentin. Serum adiponectin was comparable between NP (2258.66 ± 196.85) and GDM (2745.89 ± 243.74) subjects (Fig. 2D). Serum visfatin was significantly higher in GDM (10.14 ± 1.47) compared to NP (4.95 ± 0.59) subjects

Table 1 Comparison of parameters between NP and GDM groups

Parameters	NP ($n=37$)	GDM ($n=37$)	p value
Maternal age (year)	30.4 ± 5.02	32.1 ± 3.59	0.109
Gestational age (week)	38.2 ± 1.05	38.2 ± 1.37	0.924
Systolic blood pressure (mmHg)	117.8 ± 7.87	117.7 ± 9.72	0.958
Diastolic blood pressure (mmHg)	76.4 ± 6.73	76.5 ± 7.85	0.924
Heart rate (bpm)	84.8 ± 8.56	84.0 ± 7.93	0.678
Pre-pregnancy body weight (kg)	57.3 ± 12.30	60.1 ± 13.35	0.343
Pre-pregnancy BMI (kg/m^2)	22.7 ± 3.88	24.6 ± 4.84	0.071
Pre-delivery body weight (kg)	72.5 ± 13.05	71.0 ± 14.32	0.640
Pre-delivery BMI (kg/m^2)	28.8 ± 4.08	29.0 ± 4.97	0.842
Fasting plasma glucose (mg/dl)	76.3 ± 9.66	86.1 ± 25.03	0.031*
Fasting plasma insulin (μU/ml)	13.2 ± 7.42	13.0 ± 13.77	0.944
HOMA-IR	2.34 ± 1.19	3.47 ± 6.57	0.316
QUICKI	0.34 ± 0.03	0.36 ± 0.11	0.339
Waist circumference (cm)	98.6 ± 9.51	98.6 ± 9.82	0.996
Hip circumference (cm)	101.7 ± 9.02	99.6 ± 8.71	0.327
Neonatal weight (g)	3025.4 ± 366.5	3087.3 ± 407.5	0.494
Neonatal length (cm)	49.8 ± 2.08	49.7 ± 2.18	0.828
Neonatal head circumference (cm)	33.2 ± 1.28	33.2 ± 1.48	0.867
Placental weight (g)	638.7 ± 93.55	673.5 ± 132.61	0.196
Adiponectin gene expression	1.06 ± 1.17	0.93 ± 1.19	0.650
Visfatin gene expression	4.10 ± 4.53	3.97 ± 5.14	0.915
Omentin gene expression	0.023 ± 0.032	0.016 ± 0.015	0.289
Serum adiponectin levels (ng/ml)	2258.7 ± 1197.4	2745.9 ± 1482.6	0.124
Serum visfatin levels (ng/ml)	4.95 ± 3.59	10.1 ± 8.81	<0.001***
Serum omentin levels (ng/ml)	14.2 ± 5.12	11.2 ± 7.99	0.002**

Values are expressed as mean (± S.D.), *$p<0.05$ compared between normal NP and GDM groups, *BMI* body mass index; *GDM* gestational diabetes mellitus; *HOMA-IR* homeostasis model assessment of insulin resistance; *NP* normal pregnancy; *QUICKI* quantitative insulin sensitivity check index; *SD* standard deviation

($p<0.01$, Fig. 2D), but serum omentin-1 was significantly higher in NP (14.24 ± 0.85) than GDM (11.21 ± 1.37) subjects ($p<0.01$, Fig. 2D).

Correlations between placental gene expressions as well as serum levels with maternal and neonatal clinical parameters

The correlations in all, NP, and GDM subjects between placental gene expressions as well as serum levels and maternal and neonatal clinical parameters are shown in Table 2.

In all, NP, and GDM subjects, *visfatin* expression was positively correlated with *adiponectin* expression ($p<0.001$ all), and *omentin* expression ($p<0.05$ all). As well, *omentin* expression had a negative correlation with placental weight ($p<0.05$) in NP subjects only (Table 2). Serum adiponectin levels tended to have a negative correlation with body weight change in NP subjects ($p=0.054$) and were significantly negatively correlated with body weight change only in all subjects ($p<0.05$) (Table 2). Furthermore, serum adiponectin levels had negative correlations with maternal age and HOMA-IR ($p<0.05$ all) only in NP subjects and had negative correlations with placental weight ($p<0.05$) and serum omentin levels ($p<0.01$) only in GDM subjects (Table 2). Serum visfatin levels had negative correlations with gestational age and neonatal weight but had a positive correlation with serum omentin levels ($p<0.05$ all) only in the GDM group (Table 2). Serum omentin levels were negatively correlated with gestational age only in all subjects and were negatively correlated with pre-pregnancy BMI and maternal waist circumference only in NP subjects ($p<0.05$ all) (Table 2). Placental weight was negatively correlated with maternal fasting plasma glucose levels ($p<0.05$) only in GDM subjects (Table 2).

Multivariate regression analyses for serum levels of adiponectin, visfatin, and omentin

Multivariate regression analyses for serum levels of adiponectin, visfatin, and omentin are shown in Table 3. By setting serum adiponectin levels as a dependent variable, models of significant interactions were observed by setting body

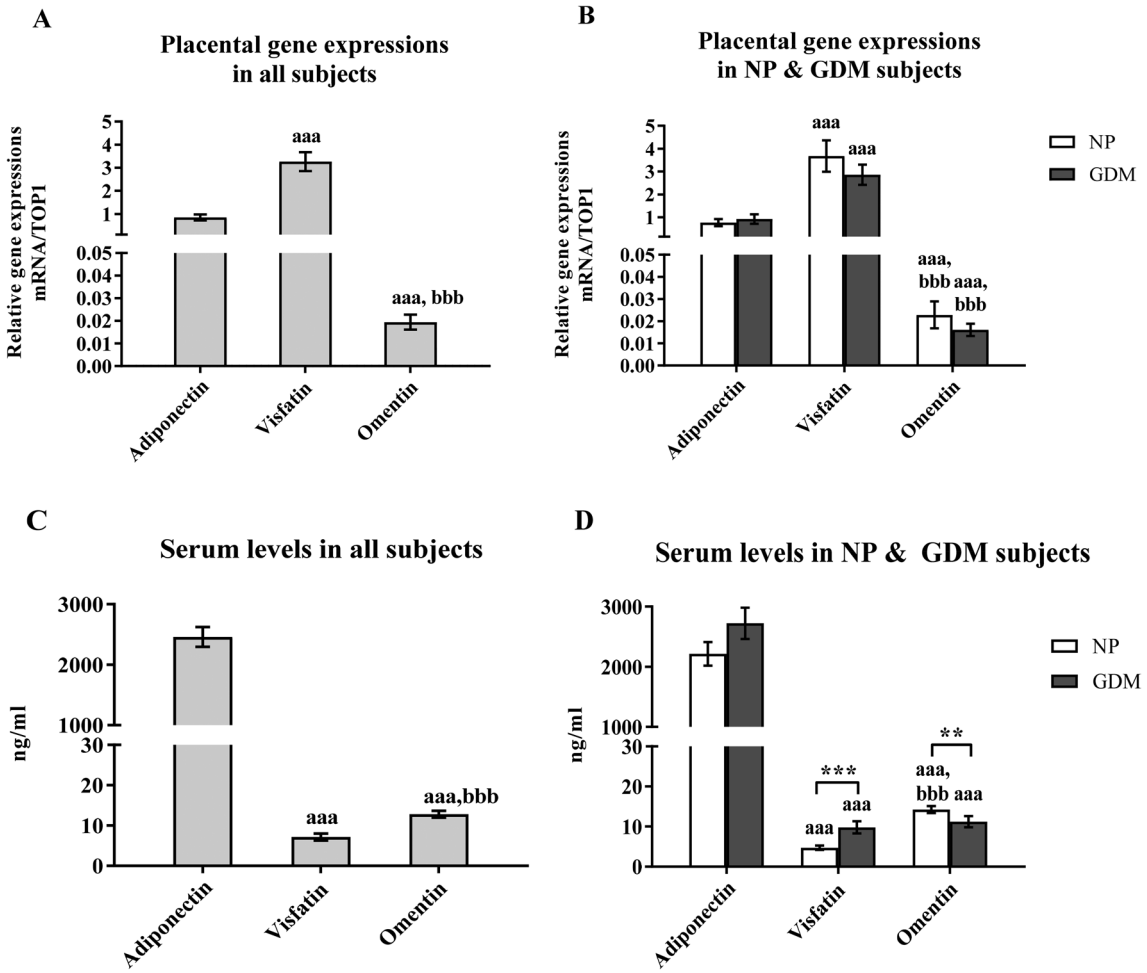

Fig. 2 Mean (±S.E.M.) placental expressions and serum levels of adiponectin, visfatin, and omentin in all (**a** and **c**, respectively) and normal pregnancy (NP) and gestational diabetic mellitus (GDM) (**b** and **d**, respectively) subjects, $^{aaa}p<0.001$ compared to adiponectin, $^{bbb}p<0.001$ compared to visfatin, $^{**}p<0.01$, $^{***}p<0.001$ compared between NP and GDM groups., *S.E.M.* standard error of mean

weight change (model 1) or placental weight (model 2) as independent variables for all subjects; body weight change (model 1) as an independent variable for NP subjects; and placental weight (model 1) as an independent variable for GDM subjects ($p<0.05$ all) (Table 3). Taking serum visfatin as a dependent variable, models of significant interactions were found by using gestational age as an independent variable for all and GDM subjects ($p<0.01$ all) (Table 3). When serum omentin levels were set as a dependent variable, models of significant interactions were observed by setting gestational age (model 1) as an independent variable for all subjects; gestational age (model 1) or gestational age and waist circumference (model 2) as independent variables for NP subjects ($p<0.05$ all) (Table 3).

Discussion

The current study is the first study that simultaneously determined placental expressions and serum levels of 3 hormones involved in insulin sensitivity, including adiponectin, visfatin, and omentin, as well as compared these parameters between NP and GDM pregnant women. This is also the first study that recruited only GDM class A1 to avoid confounding factors from the insulin injection of GDM class A2. Moreover, this study determined correlations between these factors and maternal and neonatal clinical parameters.

In this study, fasting plasma glucose was higher in the GDM than the NP group which was consistent with a previous study [26, 40]. However, fasting insulin levels were not higher in the GDM than the NP group, which is inconsistent with previous studies [26, 40]. This might be because the present study recruited only GDMA1, whereas other studies recruited both classes pooled together. GDMA1 is

Table 2 Correlations between 2 factors in all, NP, and GDM subjects

Factors	All subjects ($n=74$)		NP subjects ($n=37$)		GDM subjects ($n=37$)	
	R	*p* value	*R*	*p* value	*R*	*p* value
Visfatin expression						
Adiponectin expression	0.653	<0.001***	0.640	<0.001***	0.852	<0.001***
Omentin expression	0.247	0.046*	0.408	0.020*	0.477	0.004**
Omentin expression						
Placental weight	−0.191	0.113	−0.335	0.049*	−0.016	0.927
Serum adiponectin						
Maternal age	−0.185	0.115	−0.383	0.019*	−0.068	0.691
Body weight change	−0.232	0.047*	−0.319	0.054	−0.007	0.968
HOMA-IR	−0.105	0.374	−0.332	0.045*	−0.121	0.476
Placental weight	−0.209	0.073	−0.048	0.777	−0.356	0.031*
Serum omentin	−0.229	0.057	0.097	0.572	−0.489	0.003*
Serum visfatin						
Gestational age	−0.208	0.078	−0.189	0.262	−0.364	0.029*
Neonatal weight	−0.077	0.516	0.010	0.954	−0.387	0.020*
Serum omentin	−0.149	0.221	−0.288	0.088	0.429	0.013*
Serum omentin						
Gestational age	−0.295	0.013*	−0.300	0.075	−0.307	0.077
Pre-pregnancy BMI	−0.191	0.113	−0.334	0.046*	0.034	0.850
Waist circumference	−0.157	0.204	−0.361	0.039*	−0.076	0.668
Placental weight						
Glucose	−0.220	0.060	−0.024	0.886	−0.348	0.035*

*$p<0.05$, **$p<0.01$, and ***$p<0.001$, BMI = body mass index; GDM = gestational diabetes mellitus; HOMA-IR = homeostasis model assessment of insulin resistance; NP = normal pregnancy

considered to be a mild form of GDM which has an abnormal OGTT only, but fasting blood glucose levels that are still normal [41]. In this study, the blood glucose levels of all subjects were still in the normal range, which might lead to comparable levels of insulin, HOMA-IR and QUICKI in both groups. Pre-pregnancy BMI had a trend to be higher in GDM compare to NP subjects. This result corresponds with the hypothesis stating that pre-pregnancy obesity specifically maternal BMI is one of key pathogenic factors of abnormal glucose homeostasis and GDM [2, 42].

Please note that since these measurements were taken in patients already in labor, the labor process including labor pain and stages of labor could have influenced adiponectin, visfatin, and omentin levels. Serum visfatin levels were higher in GDM than in control subjects. Previous evidences revealed that glucose exposure increased visfatin secretion from subcutaneous and visceral adipocytes [43] and the administration of glucose to humans increased blood visfatin concentrations [43, 44]. Moreover, circulating visfatin is increased with progressive ß-cell deterioration and independently associated with insulin secretion but not with insulin sensitivity [20]. Therefore, high glucose levels in the GDM group in our study, probably due to impaired ß-cell function, might lead to increased visfatin levels. Unlike adiponectin and omentin, visfatin exerts insulin-mimetic activity by binding to insulin receptors at a distinct site from insulin binding [18], resulting in increased glucose uptake into adipose tissue and skeletal muscle leading to increased insulin sensitivity [19]. Therefore, the increased serum visfatin levels may indicate a compensatory mechanism that improves the impaired insulin function [19] in the GDM condition. Our result was consistent with at least 2 studies [26, 45], but was contrary to other 2 studies reporting unchanged [27] or decreased [18] visfatin levels in GDM subjects. The inconsistencies of the results might be because previous studies recruited both GDMA1 and GDMA2 subjects probably having confounding effects from insulin treatment [18, 27]. Furthermore, serum visfatin levels had a negative correlation with gestational age in GDM subjects. Multivariate regression analyses showed that serum visfatin levels had significant interactions with gestational age in GDM and all subjects. These results suggested that increased gestational age was related to decreased visfatin levels, especially in GDM subjects. This association was not found in NP subjects which is consistent with a previous study stating that plasma visfatin levels of GDM women were diminished in the third trimester [46].

Table 3 Multivariate regression analyses for serum adiponectin, visfatin, omentin levels in all, NP, and GDM subjects

Model for serum adiponectin levels								
No.	*R*	R^2	*P* value	Variables	Coefficient	Standard error	*T* value	*P* value
For all subjects								
1	0.248	0.062	0.038*	(Constant)	3424.846	460.963	7.430	< 0.001***
				Body weight change	− 71.297	33.725	− 2.114	0.038*
2	0.259	0.067	0.031*	(Constant)	4468.664	901.635	4.956	< 0.001***
				Placental weight	− 2.992	1.356	− 2.207	0.031*
For NP subjects								
1	0.492	0.242	0.003**	(Constant)	4317.308	678.897	6.359	< 0.001***
				Body weight change	− 138.842	43.463	− 3.194	0.003**
For GDM subjects								
1	0.356	0.127	0.031*	(Constant)	5425.720	1211.753	4.478	< 0.001***
				Placental weight	− 3.979	1.766	− 2.253	0.031*
Models for serum visfatin levels								
For all subjects								
1	0.314	0.098	0.009**	(Constant)	77.613	25.828	3.005	0.004**
				Gestational age	− 1.828	0.676	− 2.704	0.009**
For GDM subjects								
1	0.435	0.189	0.008**	(Constant)	115.711	37.543	3.082	0.004**
				Gestational age	− 2.766	0.983	− 2.814	0.008**
Models for serum omentin levels								
For all subjects								
1	0.286	0.082	0.019*	(Constant)	73.429	25.282	2.904	0.005**
				Gestational age	− 1.590	0.661	− 2.404	0.019*
For NP subjects								
1	0.388	0.150	0.026*	(Constant)	87.152	31.155	2.797	0.009**
				Gestational age	− 1.907	0.814	− 2.342	0.026*
2	0.508	0.258	0.011*	(Constant)	100.119	30.240	3.311	0.002**
				Gestational age	− 1.767	0.777	− 2.275	0.030*
				Waist circumference	− 0.185	0.089	− 2.087	0.046*

*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$

This study found lower serum omentin levels in GDM compared to control subjects, which was similar to a previous finding [33]. Interestingly, omentin is known to be mainly expressed by visceral, not subcutaneous, adipose tissue [30]. The visceral adipose tissue has been found to be more related to insulin resistance than subcutaneous adipose tissue [47]. Furthermore, visceral obesity has also been found to be related to decreased omentin secretion in adipose tissue [7]. In visceral fat accretion, free fatty acids and inflammatory cytokines are released from the visceral fatty tissue into the portal vein resulting in increased oxidative stress [48] and the development of hepatic insulin resistance [49]. In this study, the pre-delivery body weight, pre-delivery BMI, and waist and hip circumferences were not different between GDM and NP groups, suggesting that subcutaneous adipose tissue might not differ between groups. The lower omentin levels found in the GDM group might be related to increased visceral obesity as increased visceral adipocyte size was related to decreased serum omentin levels [7]. This could probably be explained by the evidence showing that increased pro-inflammatory cytokines suppressed adipokine secretion such adiponectin from human adipocytes [50]. However, this result was inconsistent with another finding reporting unchanged circulating omentin in GDM compared to normal glucose tolerant subjects [34]. The inconsistencies of the results might be due to the difference in the period of gestation, glucose level outcome, and methods of screening diagnosis of GDM [34]. Collectively, the decrease in omentin levels, probably caused by visceral obesity, might result in insulin resistance causing GDM.

Serum omentin was negatively correlated with pre-pregnancy BMI and waist circumference in the NP, but not in the GDM subjects, which was similar to results obtained from

non-pregnant subjects [7]. In addition, multivariate regression analysis showed that serum omentin levels were negatively associated with gestational age and/or waist circumference only in the NP group. Furthermore, serum adiponectin was negatively correlated with serum omentin in the GDM group only. A previous study reported a positive correlation between serum adiponectin and omentin levels in non-pregnant subjects [7]. These results suggest that there is a possible dysregulation of omentin levels in the GDM group.

Serum adiponectin levels were comparable between GDM and NP groups. Our result was inconsistent with previous findings showing that adiponectin concentrations were lower in the GDM compared to the NP group [11, 12, 14]. The inconsistency might be due to the different diagnostic method, the GDM classification, and the measurement method. Furthermore, insulin levels in our study were comparable between the GDMA1 and the NP group, but other studies showed higher insulin levels in the GDM group [11, 12, 14]. As hyperinsulinemia was found to reduce plasma adiponectin levels in humans [51], the unchanged insulin levels in our study might result in unchanged plasma adiponectin levels. Interestingly, in multivariate regression analysis, serum adiponectin levels had a negative association with body weight change only in NP, not GDM subjects. These results were in accordance with previous findings in non-pregnant women showing that adiponectin levels had a significant negative correlation with weight change in women who developed diabetes but not in women who did not [52]. The results suggested that weight gain was associated with decreased adiponectin levels in only non-diabetic subjects. This might be explained by the evidence that fat accretion is known as the process of chronic inflammation in adipose tissue which elevated expressions of pro-inflammatory cytokine levels including IL-6, TNF-α, and IL-1β [53]. Furthermore, TNF-α, IL-1β, and IFN-γ had been shown to suppress the release of total adiponectin in dose-dependent manner [54]. On the other hand, in women who were susceptible to develop diabetes, there might be a metabolic dysfunction of adipose tissue in early pre-diabetic stage. Thus, such correlation was not found in diabetic subjects. Instead, serum adiponectin levels were negatively associated with placental weight only GDM, not NP subjects in both correlation and multivariate regression analyses. A previous study in neonates showed that high molecular weight adiponectin levels had a weak, not significant negative correlation with placental weight [55]. However, the underlying mechanism of the negative correlation is unknown.

When compared between maternal serum levels of adiponectin, visfatin, and omentin, the same trend of results was observed in all and NP subjects but not in GDM subjects. In all, NP, and GDM subjects, serum adiponectin had the highest levels, being approximately 193, 156, and 243 times, respectively, higher than omentin, and 344, 469, and 278 times, respectively, higher than visfatin. The serum pattern in this study differed from the placental expressions pattern. Interestingly, the maternal serum levels pattern showed the same trend with a previous study in the visceral adipose tissue of non-pregnant subjects [7], indicating that the circulating levels of these peptides were not related to placental expressions, but rather to visceral expressions. In the NP subjects, serum omentin levels were higher than visfatin levels; however, in the GDM group, serum omentin levels were decreased, comparable to the visfatin levels. This might be because visfatin can be synthesized by both visceral and subcutaneous fat while omentin is synthesized mainly from visceral fat. The lower omentin levels in GDM group might reflect higher visceral fat accretion in GDM subjects [7].

The placental *adiponectin, visfatin,* and *omentin* expressions were similar in the NP and GDM subjects. Furthermore, no correlations were found between placental *adiponectin, visfatin,* and *omentin* expressions with plasma glucose and insulin levels, HOMA-IR, and QUICKI. Therefore, we postulate that the placental *adiponectin, visfatin,* and *omentin* expressions might not mainly contribute to the pathophysiology of GDMA1.

Visfatin expression was positively correlated with the *adiponectin* and *omentin* expressions in all, NP, and GDM subjects. These correlations suggest that the expressions of these hormones were linked to each other in the placental tissue. A previous study [7] found that subcutaneous *visfatin* expression was positively correlated with subcutaneous expressions of *adiponectin* and *omentin*. Moreover, visceral *visfatin* positively correlated with both visceral *adiponectin* and *omentin* without any cross-correlations between the types of adipose tissue. Therefore, these results indicate that the expression of these 3 genes might be linked in a tissue-specific fashion. The underlying mechanism of the relationship is unknown.

When compared placental expressions between *adiponectin*, *visfatin*, and *omentin*, the same trend of results was observed in all, NP and GDM subjects. *Visfatin* showed the highest expression in placenta, being approximately 4, 5, and 3 times higher than *adiponectin* and 168, 161, and 178 times higher than *omentin* in all, NP and GDM subjects, respectively. This placental expression pattern was inconsistent with the patterns found in subcutaneous and visceral adipose tissues in non-pregnant subjects [7]. In both subcutaneous and visceral adipose tissues, *adiponectin* showed the highest expression, followed by *visfatin* then *omentin* [7]. In conclusion, GDMA1 subjects had higher serum visfatin and plasma glucose levels, but lower serum omentin levels compared to controls. Increased levels of serum visfatin in GDM subjects are considered as a compensatory mechanism because visfatin has insulin-mimetic effects and its levels were shown to be elevated along with blood glucose levels.

The decrease in omentin levels in GDM might be caused by visceral obesity resulting in insulin resistance, thus possibly contributing to the pathophysiology of GDM. Further investigations are required to confirm whether a reduction in circulating omentin levels is associated with visceral obesity and is the pathophysiology of GDM. Decreasing visceral obesity and abdominal fat should be considered to prevent GDM.

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Author Contributions All authors participated in the design, interpretation of the studies and analysis of the data and review of the manuscript; XS-V, CS, RK, CS, and IK conducted the experiments. XS-V and CS wrote the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest.

Ethical approval The study has been approved by the the Siriraj Institutional Review Board (COA no. Si.545/2015) of the Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand and has been performed in accordance with the Declaration of Helsinki.

Informed consent Written informed consents were obtained from all subjects prior to the study.

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