

Positive correlation between serum omentin and thrombospondin-1 in gestational diabetes despite lack of correlation with insulin resistance indices

Dodatnia korelacja pomiędzy osoczymym stężeniem omentyny i thrombospondyny-1 u kobiet z cukrzycą ciążową pomimo braku korelacji z insulinoopornością.

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Abstract

Gestational Diabetes (GDM) is characterized by insulin resistance and a pro-inflammatory state, both factors possible related to adipokine expression.

Subjects and Methods: *The study included 20 women with GDM, diagnosed according to the WHO criteria, and 23 matched for age and BMI women with normal glucose tolerance. Omentin and TSP-1 were measured by ELISA assays. Insulin resistance was assessed by HOMA and Insulin Resistance Index (IRI).*

Results: *There were no significant differences in omentin and TSP-1 levels between subjects with GDM and controls (48.0±12.0ng/ml versus 50.2±7.9ng/ml and 2150±1661ng/ml versus 1569±1160ng/ml, p=0.64 and p=0.29, for omentin and TSP-1 in GDM and control subjects, respectively). There was no significant correlation between either omentin or TSP-1 with HOMA or IRI, however, there was a significant positive correlation between thrombospondin-1 and omentin (r=0.49, p=0.010). There was also a positive correlation between serum omentin and glucose levels at 60 and 90 minutes of OGTT, however, in the control group only (p<0.05).*

Conclusions: *Concentrations of omentin and thrombospondin-1 seem to be inter-related in pregnancy, however, there are no differences in serum levels between women with normal glucose tolerance and those with glucose intolerance. These observations suggest that regulation of concentrations of these adipokines in pregnancy might be mediated through different mechanisms than in non-pregnant subjects.*

Key words: **omentin / thrombospondin-1 / gestational diabetes / insulin resistance /**

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Streszczenie

Cukrzyca ciążowa (GDM) charakteryzuje się insulinoopornością i zmianami o charakterze prozapalnym, za co prawdopodobnie odpowiedzialne są adipocytokiny.

Materiał i metody: Do badania włączono 20 kobiet z cukrzycą ciążową, rozpoznaną na podstawie kryteriów WHO i 23 kobiety dobrane odpowiednio pod względem wieku i BMI z prawidłową gospodarką węglowodanową. Stężenia omentyny i TSP-1 mierzono metodą ELISA. Insulinooporność oznaczono metodą HOMA i Insulin Resistance Index (IRI).

Wyniki: Nie stwierdzono znamienych różnic w stężeniu omentyny i TSP-1 pomiędzy kobietami z GDM a zdrowymi (48.0±12.0 ng/ml versus 50.2±7.9 ng/ml i 2150±1661 ng/ml versus 1569±1160 ng/ml, p=0.64 i p=0.29, dla omentyny i TSP-1 w grupie GDM i zdrowych, odpowiednio). Także nie stwierdzono znamienych korelacji zarówno między stężeniem omentyny i TSP-1 a HOMA i IRI, jednak, stwierdzono znamiennej pozytywną korelację pomiędzy trombospondyną-1 a omentyną (r=0.49, p=0.010). Stwierdzono także znamiennej pozytywną korelację pomiędzy omentyną a stężeniem glukozy w 60. i 90. min OGTT, aczkolwiek tylko w grupie kontrolnej (p<0.05).

Wnioski: Stężenia omentyny i trombospondyny-1 wydają się być zaburzone w ciąży, jednak nie stwierdza się różnicy stężeń w osoczu między kobietami z prawidłową i nieprawidłową tolerancją glukozy. Ta obserwacja może sugerować, że regulacja tych adipokin w ciąży może być spowodowana na drodze innych mechanizmów niż poza ciążą.

Słowa kluczowe: **omentyna / trombospondyna-1 / cukrzyca ciążowa / insulinooporność /**

Background

Secretory products from adipocytes or from macrophages infiltrating the adipose tissue, contribute to deterioration in glycaemic control and increased insulin resistance (IR), with complications, such as type 2 diabetes and atherosclerosis [1, 2, 3]. Gestational Diabetes (GDM) is characterized by insulin resistance and a pro-inflammatory state, both factors possible related to adipokine expression [4, 5, 6].

Omentin is a putative insulin-sensitiser, while omentin concentrations are decreased in some insulin-resistant states, such as polycystic ovary syndrome, and are downregulated by insulin and glucose [7]. Thrombospondin (TSP-1) is an adipokine that is highly expressed in obese, insulin-resistant subjects. TSP-1 gene expression correlates with adipose inflammation and inversely with insulin sensitivity [8]; and is decreased by pioglitazone [9]. Regulation of several adipokines in pregnancy may be, however, different than in non-pregnant state e.g. due to possible placental contribution and other non-identified factors. Furthermore, the model of the relationship between insulin resistance indices and serum concentrations of omentin and TSP-1 has not been validated in Gestational Diabetes Mellitus (GDM), i.e. the state characterized by hyperglycaemia, and increased IR in comparison to healthy pregnant women [10].

In our study we have therefore endeavoured to assess serum levels of insulin-sensitising omentin and pro-inflammatory thrombospondin-1 in women with GDM and their possible correlation with insulin resistance indices.

Subjects and Methods

The study included 20 white, Caucasian women with GDM, diagnosed according to the WHO criteria [11], age 29.7±5.5 years (mean±SD), BMI 28.1±4.7kg/m² and 23 normal glucose tolerance controls (NGT) matched for age (28.3±3.9 years), and BMI (28.3±4.8 kg/m²), p=ns. The blood for all study parameters was obtained during an oral glucose tolerance test (OGTT), which was performed between 26 and 28 weeks of gestation in all women. Demographic data of the control group and women with GDM are presented in Table I.

Table I. Demographic characteristics of subjects participating in the study (mean ±SD).

Parameter	GDM (n=20)	NGT (n=23)	p
AGE (years)	29.7 ± 5.5	28.3 ± 3.9	0.63
BMI - before pregnancy (kg/m ²)	24.2 ± 4.7	24.8 ± 5.0	0.75
BMI -current (kg/m ²)	28.1 ± 4.7	28.3 ± 4.8	0.99

Serum omentin levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA kit; Axxora, Nottingham, U.K.), with an intra-assay coefficient of variation of 6%. Serum TSP-1 concentrations were measured with commercially available ELISA kits (R&D Systems, Abingdon, UK), according to the manufacturer's protocol, with an intra-assay coefficient of variation of less than 7%. Insulin was measured by ELISA (DakoCytomation Ltd, Denmark House, Angel Drove, Ely CB7 4 ET, UK).

Insulin resistance was assessed by HOMA [12], where HOMA = fasting insulin concentration [μU/mL] x fasting glucose concentration [mmol/L]/22,5 and Insulin Resistance Index (IRI), i.e. a method based on changes of glycaemia and insulinemia during 75 OGTT.

IRI was calculated through the formula: 2/[1/(INSp x GLYp)]+1, where INSp and GLYp are the measured insulin and glycaemic areas [13]. The study has been approved by the Ethics Committee of the "Polish Mother" Memorial Research Institute.

Statistical Analysis

The data were analysed by means of simple descriptive statistics and non-parametric methods: Mann-Whitney U test for comparison of distributions in two independent groups (GDM and NGT) and Spearman rank correlations for qualifying associations between covariates of interest.

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In all analyses, statistical significance was considered attained for $p \leq 0.05$. Calculations were derived by means of Statistica v8.0 software.

Results

Results of the study are presented in Table II.

There was no difference in fasting glucose levels between women with normal glucose (NGT) tolerance and those with GDM. Women with GDM had higher glucose levels at 60, 90, and 120 minutes of OGTT. Insulin levels were non-significantly higher in the NGT group at the beginning of OGTT, reaching borderline statistical significance at 60 minutes of OGTT ($67.1 \pm 43.7 \mu\text{IU/ml}$ versus $85.5 \pm 38.6 \mu\text{IU/ml}$, $p=0.06$, for GDM and NGT, respectively).

This was reversed at the end of the OGTT, where insulin levels were significantly higher in women with GDM ($93.5 \pm 59.1 \mu\text{IU/ml}$ versus $59.9 \pm 32.4 \mu\text{IU/ml}$, $p=0.016$, for GDM and NGT, respectively). There were no significant differences in insulin resistance parameters (HOMA & IRI) between analysed groups. (Table II).

There were also no significant differences in omentin and TSP-1 levels between subjects with GDM and controls ($p=0.64$ and $p=0.29$, respectively). (see Table II).

There was no significant correlation between either omentin or TSP-1 and insulin resistance parameters i.e. HOMA or IRI, both for all subjects analysed as a whole (Table IIIA) and for a subgroup analyses (GDM and NGT groups) – see Table IIIB.

There was however, a positive correlation between thrombospondin-1 and omentin ($r=0.49$, $p=0.01$) (Table IIIA, Figure 1).

Omentin concentrations correlated positively with glucose levels at 60 minutes of OGTT ($r=0.34$, $p=0.025$). This was the result of positive correlation between serum omentin and glucose levels in women from NGT group, where positive correlation between serum omentin and glucose was also present at 90 minutes of OGTT (Table IVA, Figure 2A and 2B).

Interestingly there was also a positive correlation between serum TSP-1 and glucose at 60 minutes of OGTT in the GDM group only (Table IVB). There were no significant correlations between either serum omentin or TSP-1 and BMI both before pregnancy and at 26-28 weeks of gestation.

Table II. Comparison of analysed parameters (mean \pm SD) during 75 gram oral glucose tolerance test in women with gestational diabetes (GDM) and in normal glucose tolerance controls (NGT) (mean \pm SD).

Parameter	GDM (n=20)	NGT (n=23)	p
OMENTIN (ng/ml)	48.0 \pm 12.0	50.2 \pm 7.9	0.64
TSP-1 (ng/ml)*	2150 \pm 1661	1569 \pm 1160	0.29
Glucose_0' (mg/dl)	76.9 \pm 8.2	78.9 \pm 6.5	0.87
Glucose_30'	132.1 \pm 18.2	135.4 \pm 20.4	0.71
Glucose_60'	165.1 \pm 21.6	149.9 \pm 21.8	0.029
Glucose_90'	169.5 \pm 17.6	137.1 \pm 25.5	0.0001
Glucose_120'	162.9 \pm 16.6	117.0 \pm 15.7	<0.0001
Insulin_0' ($\mu\text{IU/ml}$)	8.54 \pm 4.30	11.31 \pm 6.83	0.21
Insulin_30'	43.3 \pm 18.3	61.6 \pm 34.1	0.14
Insulin_60'	67.1 \pm 43.7	85.5 \pm 38.6	0.06
Insulin_90'	88.1 \pm 59.6	84.0 \pm 48.1	0.96
Insulin_120'	93.5 \pm 59.1	59.9 \pm 32.4	0.016
IRI	1,11 \pm 0,25	0,97 \pm 0,33	0.13
HOMA	1,69 \pm 0,93	2,21 \pm 1,54	0.28

*For thrombospondin-1 (TSP-1) n=14 for GDM and n=13 for NGT.

Table IIIA. Spearman rank correlations between serum omentin and thrombospondin-1 and insulin resistance indices (HOMA and IRI) in all subjects analyzed together.

	n	r _s	p-value
TSP-1 & IRI	27	0.119	0.346
TSP-1 & OMENTIN	27	0.495*	0.012
TSP-1 & HOMA	27	0.012	0.954
OMENTIN & IRI	43	0.016	0.921
OMENTIN & HOMA	43	0.273	0.076

Statistical significance for $p < 0.05$ is marked with *.

Table IIIB. Spearman rank correlations between serum omentin and thrombospondin-1 and insulin resistance indices (HOMA and IRI) – separately for women with Gestational Diabetes Mellitus (GDM) and with Normal Glucose Tolerance (NGT).

	GDM			NGT		
	n	r _s	p-value	n	r _s	p-value
TSP-1 & IRI	14	-0.106	0.719	13	0.286	0.344
TSP-1 & OMENTIN	14	0.622*	0.018	13	0.538*	0.049
TSP-1 & HOMA	14	0.121	0.681	13	0.236	0.437
OMENTIN & IRI	20	0.093	0.698	23	-0.032	0.883
OMENTIN & HOMA	20	0.275	0.240	23	0.264	0.224

Statistical significance for p < 0.05 is marked with *.

Table IVA. Spearman rank correlations between serum omentin and glucose during 75 gram OGTT (Table 4A) and between serum thrombospondin-1 (TSP-1) – Table 4B.

	n = 43		GDM (n = 20)		NGT (n = 23)	
	r _s	p-value	r _s	p-value	r _s	p-value
Glucose 0'	0,262	0,089	0,382	0,097	0,125	0,570
Glucose 30'	0,277	0,073	0,277	0,237	0,262	0,227
Glucose 60'	0,343	0,025*	0,350	0,130	0,423*	0,044*
Glucose 90'	0,164	0,295	0,070	0,769	0,428*	0,041*
Glucose120'	-0,106	0,497	-0,278	0,236	0,089	0,685

Table IVB.

	n = 27		GDM (n = 14)		NGT (n = 13)	
	r _s	p-value	r _s	p-value	r _s	p-value
Glucose 0'	-0,076	0,705	0,144	0,623	-0,094	0,760
Glucose 30'	-0,182	0,363	0,178	0,543	-0,391	0,187
Glucose 60'	0,115	0,566	0,541	0,046*	-0,297	0,325
Glucose 90'	0,183	0,362	0,515	0,060	-0,033	0,915
Glucose120'	0,133	0,507	0,240	0,409	-0,353	0,237

Discussion

Concentrations of novel adipokines – omentin and thrombospondin-1 (TSP-1) seem to be inter-related in pregnancy, however, there are no differences in serum levels between women with normal glucose tolerance and those with glucose intolerance, i. e. features characteristic of gestational diabetes. The reasons for this phenomenon might be complex. In non-pregnant subjects omentin is preferentially produced in visceral rather than by subcutaneous adipose tissue [14] and is downregulated by glucose and insulin [7]. Omentin plasma levels are decreased in obesity [15] and increased after weight loss [16].

TSP-1 gene expression, on the other hand, correlated positively with obesity and PAI-1 concentrations, i.e. a marker of metabolic syndrome [17].

One should note, that though our subjects with GDM fulfilled the diagnostic criteria for this condition, the degree of glucose intolerance was relatively mild. In particular, there were no differences in fasting glucose and the main difference was in post glucose load values at 60, 90, and 120 minutes of OGTT, while insulin levels were significantly raised in GDM subjects only at 120 minutes of OGTT. This also explains the lack of significant differences in insulin sensitivity indices (HOMA and IRI) between the groups.

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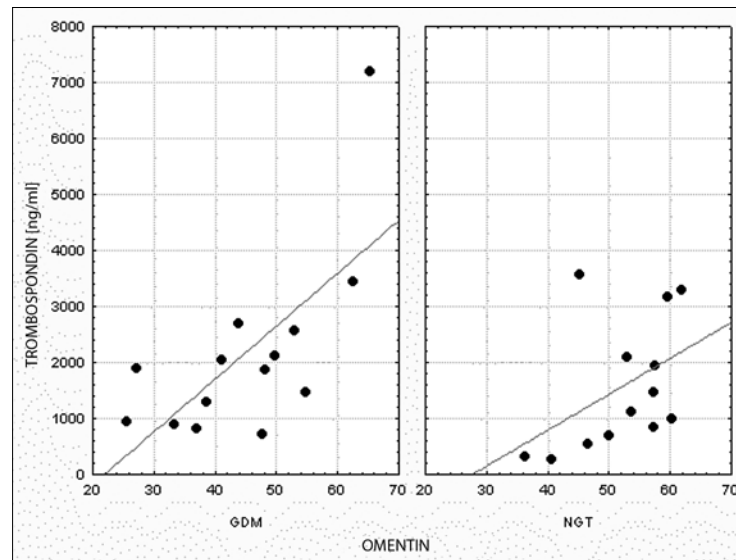


Figure 1. Positive correlation between omentin-1 and thrombospondin (TSP-1) (both expressed in ng/ml) in women with gestational diabetes (GDM) and in normal glucose tolerance controls (NGT). The above mentioned correlation was significant for both groups analyzed as a whole ($r=0.49$, $p=0.01$, $n=23$) as well as for the subgroup analysis: (GDM group: $r=0.62$, $r=0.01$, $n=14$, NGT group: $r=0.53$, $p=0.049$).

To some degree, such situation reflects the success of GDM screening protocols employed at our countries, where women are diagnosed with GDM relatively early and still only with minor degrees of glucose intolerance. On the other hand this might have potentially blunted the differences in adipokine levels between the investigated groups.

In our opinion, however, the above mentioned lack of significant differences in serum omentin and TSP-1 concentrations also is likely to be influenced by other factors. First, in case of application of the non-pregnant model one should expect a negative i.e. and inverse correlation between serum omentin and TSP-1, rather than a positive correlation observed in our study. In non-pregnant subjects there was a positive correlation between TSP-1 and BMI and insulin resistance indices [9], while there was a negative correlation between omentin and HOMA [7, 18]. In contrast, in pregnant subjects there was no correlation between both omentin and TSP-1 and insulin resistance indices (possibly with exception of a trend towards weak correlation between omentin and HOMA, $r=0.27$, $p=0.076$). Interestingly, the lack of correlation with insulin resistance indices in pregnant women, in contrast to the data from non-pregnant individuals was also observed for several other adipokines [19, 20].

Furthermore, correlation between TSP-1 and HOMA was also not observed in insulin-resistant subjects with polycystic ovary syndrome [21]. We also notice that in contrast, to the data from non-pregnant subjects, where omentin was suppressed by glucose (within 24 hours) and by insulin (within 30 minutes) [7], in pregnant women with normal glucose tolerance, there was a positive correction between serum omentin and glucose levels at 60, and 90 minutes of OGTT, i.e. at the time of the highest post-OGTT glucose excursion observed in that group. Interestingly, the effect of glucose on serum omentin might be different in women with GDM, where there was no correlation between glucose and serum omentin at any time-point.

It is also worth to mention that in non-pregnant subjects ($n=20$), where there was no change in omentin during OGTT [22], but the authors of this study measured plasma omentin only at 0 and 120 minutes of OGTT.

On the strength of the above data we suggest, that physiological role of adipokines in pregnancy may differ from a non-pregnant state and hence the mechanisms involved in regulation of adipokine concentrations may be also different; in most cases still awaiting to be fully elucidated. Omentin enhances insulin-stimulated glucose uptake in subcutaneous as well as in human omental adipocytes [23] and recently was also found to induce vasodilatation in isolated rat blood vessels through an endothelium-derived nitric oxide mediated mechanism [24]. Thrombospondin-1, on the other hand, apart from direct involvement in insulin resistance and TGF- β related inflammatory pathways [25] displays pleiotropic actions including inhibition of angiogenesis, regulation of cell proliferation and wound healing [26]. We speculate that some of the above-mentioned actions of omentin and TSP-1 might be more pertinent in pregnancy apart from the contribution to insulin resistance. Elucidation of the precise role of these adipokines in human pregnancy requires, however, further extensive research.

Conclusions

To the best of our knowledge this is the first study on omentin and thrombospondin-1 concentrations in gestational diabetes. Our study demonstrated positive correlation between novel adipokines omentin and thrombospondin-1 in pregnancy, both in women with and without gestational diabetes. On the other hand there were no differences in serum levels of both omentin and thrombospondin-1 between women with normal glucose tolerance and those with gestational diabetes. There was also no correlation between serum concentrations of these adipokines and insulin resistance indices (HOMA and Insulin Resistance Index).

This implies that pregnancy-related increase in insulin resistance is unlikely to be directly mediated through alterations of concentrations of either omentin or thrombospondin-1. Elucidation of the precise role of these adipokines in human pregnancy requires further study.

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