Title: The association between dysregulated adipocytokines in early pregnancy and development of Gestational Diabetes

Short title: Adipocytokines in gestational diabetes

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Abstract

The association between dysregulated adipocytokines in early pregnancy and development of Gestational Diabetes

Sally K Abell, Soulmaz Shorakae, Cheryce L Harrison, Danielle Hiam, Alba Moreno-Asso, Nigel K Stepto, Barbora De Courten and Helena J Teede.

Background

To investigate the association of adipocytokines and other inflammatory markers with development of GDM.

Methods

Serum adipocytokines and inflammatory markers were studied at 12-15 weeks gestation using biobanked control samples from a randomised trial. Study participants were identified as high risk for GDM using a validated clinical risk prediction tool. Markers were tested using commercial ELISA kits for high molecular weight (HMW) adiponectin, interleukin-6 (IL-6), plasminogen activator inhibitor-1, visfatin, omentin-1, sex-hormone binding globulin, monocyte chemoattractant protein and asymmetrical dimethylarginine. The association between each biomarker and development of GDM at 24-28weeks was evaluated using multivariable logistic regression analysis adjusted for maternal factors.

Results

There were no differences in age, parity, country of birth, smoking, body mass index or family history of diabetes in women with normal glucose tolerance (n=78) and women who developed GDM (n=25). Women with GDM were more likely to have a past history of GDM

($p=0.004$). HMW adiponectin (odds ratio OR 0.37 [95% confidence interval 0.19-0.74]), omentin-1 (0.97[0.94-0.99]) and IL-6 (1.87[1.03-3.37]) were associated with development of GDM, after adjustment for maternal age, body mass index and past history of GDM. The other markers were not associated with GDM development.

Conclusions

Decreased HMW adiponectin and omentin-1 and increased IL-6 may enhance sensitivity of early risk prediction tools for women at high risk of GDM. This may allow early identification and opportunities for prevention of GDM and adverse outcomes. Further research is required in large validation studies to confirm these results.

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Keywords

adipocytokines, biomarkers, pregnancy, prediction, gestational diabetes

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Introduction

Gestational diabetes mellitus (GDM) is increasingly regarded as an inflammatory condition, where a combination of hormonal changes and inflammatory mediators lead to insulin resistance and glucose intolerance.^{1,2} The prevalence of GDM is rising³ and the need for early identification of women at risk is well recognised. Early prediction enables risk stratification of women, facilitates opportunities for prevention of GDM, and may improve clinical outcomes.⁴ Screening methods using clinical risk factors have reasonable predictive ability, but may be improved by combining inflammatory biomarkers that precede the onset of hyperglycaemia. This may allow early identification of women at risk of glucose intolerance in late pregnancy.⁵

Prospective studies have shown that GDM is linked to the down-regulation of anti-inflammatory cytokines and upregulation of pro-inflammatory cytokines.¹ Alterations in adipose tissue derived adipocytokines including high molecular weight (HMW) adiponectin^{6,7,8}, interleukin-6 (IL-6)^{9,10}, plasminogen activator inhibitor-1 (PAI-1)¹¹, visfatin^{12,13} and omentin-1¹⁴ are associated with inflammation, insulin resistance and reduced insulin sensitivity in GDM.¹ Other biomarkers that may be associated with GDM include sex-

hormone binding globulin (SHBG)^{15,16,17} and endothelial function markers monocyte chemoattractant protein (MCP-1)¹⁸ and asymmetrical dimethylarginine (ADMA).¹⁹ However, it is unclear whether these markers can be used for early prediction of GDM. Current literature is limited by small sample sizes, confounding factors (diverse ethnicity, obesity, weight gain), different screening and diagnostic criteria for GDM, and variation in assay methods and reporting.¹

Therefore, we aimed to investigate the association of adipocytokines and other inflammatory biomarkers with development of GDM using biobanked serum samples from an established randomised controlled trial (RCT).²⁰ We also explore these associations after adjustment for age, BMI and past history of GDM.

Materials and Methods

Study design and population

The study population included 103 women with biobanked serum samples from the control group of a large RCT of healthy lifestyle in high risk pregnancy, aiming for prevention of excess gestational weight gain (GWG).²⁰ Recruitment was at 3 large tertiary teaching hospitals in Melbourne, Australia (2008-2010) and study participants were identified as being high risk for GDM based on a validated risk prediction tool.²¹ This captured women with singleton pregnancies <15 weeks gestation if overweight (BMI>25kg/m² or >23 kg/m² if high risk ethnicity) or obese (BMI≥30 kg/m²) with an increased risk of GDM (score ≥3 from the risk prediction tool). Patient data including demographics, antenatal characteristics, and longitudinal evaluation of maternal, neonatal and obstetric outcomes were recorded. The

study was approved by the Monash Health Research Advisory and Ethics Committee and all participants gave written informed consent.

Blood samples and assays

Fasting venous blood was drawn between 12-15 weeks gestation for all women. Serum was stored in multiple aliquots under sterile conditions at -80°C. Sandwich-type enzyme linked immunosorbent assays (ELISA) were used. Samples were thawed immediately prior to use and all assays were performed in duplicate on 96 well plates according to manufacturers' instructions. Pilot studies were performed to calculate dilutions and ensure concentrations fit within the standard curve for each assay. Analyte concentrations were calculated from best-fit standard curves, multiplied by the dilution factor to determine target protein concentrations. Intrassay and interassay coefficients of variation were all <10%.

HMW adiponectin was measured using the ALPCO ELISA (Cat no. 47-ADPHU-E01), which required pretreatment with Protease II to selectively digest low and middle molecular weight adiponectin. The assay has a sensitivity of 0.019ng/mL. IL-6 was measured using the Abcam high sensitivity ELISA (ab46042) with sensitivity 0.81pg/mL. Visfatin was measured using the BioVendor ELISA (RAG004R) with a sensitivity of 30pg/mL. Omentin-1 was measured using the Millipore ELISA (EZH0MNTN1-29K) with a sensitivity of 0.23ng/mL. Type 1 PAI-1 was measured using the Abcam ELISA (ab108891) with a sensitivity of ~0.05ng/mL. SHBG was measured using the Demeditec Diagnostics ELISA (DE2996) with a sensitivity of 0.77nmol/L. The MCP-1 Picokine ELISA (EK0441) had a sensitivity <1pg/mL. ADMA was measured using the Elabscience ELISA (E-EL-0042) with a sensitivity of 9.38ng/mL.

Variables and outcomes

Demographic characteristics were collected using a questionnaire. Body mass index (BMI) was calculated at 12-15 weeks gestation by an anthropometric nurse independent to the research staff. Maternal, neonatal and obstetric outcomes at delivery and discharge from hospital were obtained from Birthing Outcomes System database. This includes standardised information for routine reporting of perinatal data in Victoria.

Development of GDM was the primary study outcome. Ninety (87%) women in the control group completed GDM screening at 26-28 weeks gestation with an oral glucose tolerance test (OGTT). Thirteen (13%) were misdirected to have a screening non-fasting 50g glucose challenge test (GCT) as per standard practice at the time and did not progress to OGTT as the results were normal. GDM was diagnosed based on Australasian Diabetes in Pregnancy Society (ADIPS 1998) criteria (fasting ≥ 5.5 mmol/L and/or 2hr ≥ 8.0 mmol/L).²²

Statistical analysis

Study power was met for each biomarker (power 80%, α 0.05) based on calculations performed a priori using previous literature comparing women with normal glucose tolerance (NGT) and GDM. Maternal characteristics and biomarkers were compared between study groups using the Student's t-test or Mann-Whitney U-test for continuous variables and chi squared tests for categorical variables. Biomarker distribution was examined using the Shapiro-Wilk test and correlations were performed using Spearman's correlation test. Outlying biomarker results were carefully examined graphically, and analyses were repeated after exclusion of influential points lying 3 standard deviations above or below the mean. The association between each biomarker quartile and development of GDM was evaluated using

univariable and multivariable logistic regression analysis and reported as crude and adjusted odds ratios (OR) with 95% confidence intervals (CI). ORs are reported per 1 unit increase in each biomarker. The relationship between significant biomarkers and development of GDM was also evaluated in a categorical analysis using quartiles for each biomarker. Maternal characteristics associated with risk of GDM were tested as covariates in multivariable models, including age, BMI, smoking status, parity, country of birth, past history of GDM, and family history of diabetes. Age, BMI and past history of GDM were the significant covariates used in final models. The analysis was performed using STATA 14 (StataCorp, Texas, USA) and two-sided p-values were significant at $p < 0.05$.

Results

Maternal and neonatal characteristics

There was no statistically significant difference in maternal age, parity, country of birth, smoking, BMI or family history of diabetes in women with NGT ($n=78$) and women who developed GDM ($n=25$). Women who developed GDM were more likely to have a past history of GDM with their previous births ($p=0.004$). Women with GDM delivered their babies earlier ($p=0.035$). (Table 1)

Adipocytokines and inflammatory biomarkers

Women with GDM had lower HMW adiponectin ($p=0.0001$) and omentin-1 ($p=0.0172$) compared to women with NGT. There was no significant difference between groups for the other biomarkers. (Table 2)

HMW adiponectin was negatively correlated with FPG, 1hr and 2hr glucose during the OGTT ($r=-0.2143$, -0.3606 , -0.3829 , all $p<0.05$ respectively), but was not significantly associated with BMI. Omentin-1 was negatively correlated with 1hr and 2hr glucose ($r=-0.226$, -0.210 , all $p<0.05$). SHBG was negatively correlated with FPG, 1hr and 2hr glucose during the OGTT ($r=-0.2461$, -0.2335 , -0.3137 , all $p<0.05$). IL-6 and ADMA were correlated with BMI.

In multivariable regression, the risk of GDM associated with a $1\mu\text{g/mL}$ increase in HMW adiponectin was OR 0.37 (95% CI 0.19-0.74). For a 1ng/mL increase in omentin-1 the risk was 0.97 (0.94-0.99), and for a 1pg/mL increase in IL-6 the risk of GDM was 1.87 (1.03-3.37). Results for the remainder of the biomarkers were non-significant. When examined in quartiles, HMW adiponectin $<25^{\text{th}}$ percentile ($<1.53\mu\text{g/mL}$) was associated with increased risk of GDM (10.92 [3.41-34.91]) compared to $\geq 25^{\text{th}}$ percentile; omentin-1 $<25^{\text{th}}$ percentile ($<38.36\text{ng/mL}$) was associated with increased risk of GDM (3.93 [1.26-12.22]) compared to $\geq 25^{\text{th}}$ percentile, and IL-6 $>75^{\text{th}}$ percentile ($>2.58\text{pg/mL}$) was associated with increased risk of GDM (3.44 [1.01-11.69]) compared to $\leq 75^{\text{th}}$ percentile. (Table 3)

Discussion

Risk stratification of women at risk of GDM may facilitate streamlined antenatal care, targeted interventions to potentially reduce GDM and related risks, and prompt GDM screening and management.^{4,23} Clinical screening tools in women at high risk of GDM may be improved by addition of biomarkers reflecting early inflammation and insulin

resistance.^{15,24} We used commercially available ELISA assays to measure novel serum adipocytokines and inflammatory biomarkers at 12-15 weeks in women identified at high risk for GDM based on a validated risk prediction tool.²¹ We determine their association with development of GDM in this context. We found that HMW adiponectin, omentin-1 and IL-6 were associated with development of GDM when adjusted for maternal risk factors. SHBG was negatively correlated with OGTT measures, but was not associated with development of GDM.

Adiponectin is the most abundant adipose-specific protein with anti-inflammatory and insulin-sensitizing properties.²⁵ Maternal secretion declines during pregnancy. Levels are negatively correlated with BMI and adiposity, and insulin resistance, and downregulation may predict GDM before clinical diagnosis.¹ However, studies have had conflicting results with increased risk of GDM in some^{24,25-27} and no association in others.^{28,29} These contradictory results arise due to different study designs, assay methods, and varied approaches to confounding factors such as obesity and insulin sensitivity. A prospective study of 38 women who developed GDM found that adiponectin at 6-13 weeks gestation was associated with risk of developing GDM after adjustment for BMI and first trimester HbA1c (OR 1.12 per 1µg/mL decrease in adiponectin, p=0.02).⁶ Bao et al. (2015) performed a meta-analysis of 9 prospective studies and found that first or early second trimester adiponectin levels were lower in women who later developed GDM.³⁰ Nanda et al. (2011) showed that adiponectin was significantly lower in women who developed GDM and may improve detection rates for GDM in a risk prediction tool.²⁷

Total adiponectin circulates in the serum as multimers – a lower molecular weight trimer, a

mid-molecular weight hexamer and a high-molecular weight complex.³¹ The high molecular weight (HMW) isoform is the most active, accounting for most of its peripheral metabolic effects including insulin-sensitizing and anti-atherogenic effects.^{31,32,33} Hedderston et al. (2013) found that low pre-pregnancy adiponectin concentrations, both total and HMW adiponectin, may identify women at risk of GDM.³¹ HMW adiponectin is thought to decrease significantly in normal pregnancy,³⁴ however no studies have specifically examined HMW adiponectin during pregnancy in women who developed GDM. We hypothesized that HMW adiponectin may be a more specific early marker for GDM. Here, we found a 63% decreased risk of GDM associated with a 1µg/mL increase in HMW adiponectin adjusted for maternal factors, when measured at 12-15 weeks gestation. When examined in quartiles, HMW adiponectin levels lower than 1.53µg/mL was associated with an 11-fold increased risk of GDM adjusted for maternal factors.

Omentin-1 is a novel adipocytokine recently linked to susceptibility to type 2 diabetes.¹ It has insulin-sensitizing effects that may play a role in the metabolic adaptations of normal gestation.³⁵ Barker et al. (2012) found that maternal omentin-1 was significantly lower in non-obese women with GDM compared to NGT at the time of elective caesarean section, however there was no difference in obese groups.¹⁴ Our paper is the first longitudinal study in pregnancy focused on GDM. Here we found that increasing omentin-1 at 12-15 weeks gestation was associated with decreased risk of GDM, corrected for maternal factors including BMI. Omentin-1 less than 38.36ng/mL was associated with a 4-fold increased risk of GDM.

Interleukin-6 (IL-6) rises in pregnancy,¹⁰ is correlated with adiposity, and is an important mediator of insulin resistance.²⁵ Our study confirmed a correlation between IL-6 and BMI in pregnancy, and showed that increasing IL-6 at 12-15 weeks was associated with development of GDM adjusted for maternal factors. IL-6 >75th percentile or above 2.58pg/mL was associated with a 3.5-fold increased risk of GDM. Case-control studies have had variable results. Hassiakos et al. (2015) found that first trimester levels of IL-6 may be a predictor of GDM in a low risk population, combined with maternal weight and age.¹⁰ Georgiou (2008) found that IL-6 levels at 11 and 28 weeks gestation did not significantly differ in women who developed GDM in a small (n=28) matched case control study.²⁴ Lain et al (2008) also found a lack of difference in IL-6 concentrations in early pregnancy (mean 9.3±2.6 weeks).²⁵ Relatively small changes in insulin resistance in early pregnancy may be insufficient to alter IL-6,²⁵ and larger studies are required to determine its use as an early predictor of GDM.

SHBG may be a good candidate for first trimester prediction of GDM.¹⁵ Caglar et al. (2012) reported lower first trimester (13-16 weeks) SHBG in women who developed GDM (n=30 GDM, n=63 NGT) and in those who needed insulin therapy (n=15).¹⁶ Nanda (2011) found a small improvement in GDM screening ability at 11-13 weeks by combining SHBG (AUC 0.842) to adiponectin and maternal factors (AUC 0.831).²⁷ Here, we found a negative association with SHBG and glucose measures on the OGTT, but did not find an independent association with development of GDM. Similarly, Rasanen et al. (2013) found no association between SHBG at 5-13 weeks and GDM.³⁶ Again, early pregnancy may be too premature to sensitively detect serum changes in SHBG associated with GDM.

The remaining markers studied were novel in their associations with GDM.¹ Whilst the markers visfatin, MCP-1, PAI-1 and ADMA may be altered in pregnancy and in GDM, we found no association between first trimester levels and development of GDM. Ferreira et al. (2011) found increased visfatin levels at 11-13 weeks in women who developed GDM (n=100) compared to non-diabetic controls (n=300), however visfatin did not improve screening ability for GDM.¹³ Georgiou et al. (2008) also did not find any difference in MCP-1 at 11 or 28 weeks in women who developed GDM.²⁴ Our current data suggests that early pregnancy levels of these markers may not be associated with development of GDM.

In this study, we have examined inflammatory biomarkers as early predictors of GDM. To the best of our knowledge, current literature is limited by variable adjustment for confounders, small sample size, and differences in assay methodology and standardization. Here we used accurate, commercially available ELISA assays to measure biomarkers at 12-15 weeks in a well-characterised cohort embedded within an RCT of women identified at high risk of GDM based on a validated risk prediction tool. We were able to explore contribution of clinical risk factors for GDM such as age, BMI, past history of GDM, and country of birth. Our next step is to combine these significant biomarkers with our validated risk prediction tool,⁴ to determine their additional predictive ability in early identification of women at risk of GDM.

Limitations include that the study population is already identified as high risk of GDM, which may decrease differences in inflammatory markers between groups. Women in our study were all overweight or obese, and further studies are required to examine prediction in non-obese women. Thirteen women had a negative glucose challenge test for GDM screening

and did not proceed to OGTT, however results were also examined in only women who had an OGTT and were not significantly different. Of note, IL-6 and omentin-1 were not significantly associated with GDM on univariable regression analysis in our cohort ($p=0.15$ and $p=0.06$ respectively). Here, past history of GDM was a strong predictor of GDM development in this cohort (OR 7.2) and its inclusion in the multivariable models resulted in a significant relationship (both $p=0.04$). Studies of larger sample size are needed to further evaluate these findings. Lastly, we used research grade commercially available ELISA kits for analysis. Further research is required in large validation studies to confirm these results.

Pregnancy is a unique physiologic state associated with alterations in metabolic and hormonal function to nourish the growing fetus. Here we show that the adipocytokines HMW adiponectin, IL-6 and omentin-1 are altered in early pregnancy in women who develop GDM. These biomarkers may improve sensitivity and specificity of clinical risk prediction algorithms in women at high risk of GDM. Prospective long term studies of greater sample size are needed to confirm our findings, including feasibility of utilising biomarkers in routine antenatal care, and any potential cost-saving implication of biomarker screening.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

SKA, SS, BdC, NS, CH and HJT planned and designed the study. SKA, SS, DH and AMA performed laboratory biomarker analysis. SKA and HJT drafted the manuscript and SKA performed the data analysis. All authors provided significant intellectual contribution in

interpreting data and critical review of the manuscript. All authors approved the final version of the manuscript.

HJT is the guarantor of this work and, as such, had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

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Table 1. Maternal and neonatal characteristics of women with and without GDM

Characteristic	NGT (n=78)	GDM (n=25)	p-value
Maternal age (years), median (IQR)	31.0 (28.0-35.4)	32.7 (30.2-33.6)	0.194
Parity, n (%) Primiparous Parous	27/66 (40.9)* 39/66 (59.1)*	8/24 (33.3)* 16/24 (66.7)*	0.627
BMI (kg/m²), median (IQR)	29.5 (25.5-34.0)	28.0 (26.0-31.0)	0.577
Country of Birth, n (%) Australia South East and North East Asia Southern and Central Asia Other (Africa, Europe, Polynesia)	36 (46.2) 8 (10.3) 26 (33.3) 8 (10.2)	6 (24.0) 7 (28.0) 9 (36.0) 3 (12.0)	0.099
Current Smoker, n (%)	6 (7.7)	1 (4.0)	1.000
Past history of GDM, n (%)	4 (5.1)	7 (28.0)	0.004 [†]
Family history of diabetes, n (%)	32/59 (54.2)*	15/20 (75.0)*	0.102
Gestation (wks), median (IQR)	40.0 (38.4-40.5)	39.1 (38.4-39.5)	0.035 [†]

Abbreviations: NGT=normal glucose tolerance; GDM=gestational diabetes mellitus;

IQR=interquartile range; BMI=body mass index at baseline

*Numbers are shown as a proportion of total with data available

[†] statistically significant with p-value <0.05

Table 2. Serum levels of inflammatory markers according to GDM status

Biomarker	NGT (n=78)	GDM (n=25)	p-value
HMW adiponectin µg/mL	2.59 (1.75-3.38)	1.43 (1.30-2.14)	<0.001 [†]
IL-6 pg/mL	1.92 (1.57-2.56)	2.03 (1.67-2.90)	0.428
Visfatin ng/mL	0.13 (0.08-0.22)	0.12 (0.06-0.19)	0.772
Omentin-1 ng/mL	52.01 (41.09-69.91)	40.48 (31.58-56.93)	0.017 [†]
PAI-1 ng/mL	33.90 (11.51)	32.27 (10.71)	0.533
SHBG nmol/L	355.67 (236.42-435.61)	329.98 (241.43-408.54)	0.228
MCP-1 pg/mL	91.98 (43.97-135.03)	60.74 (34.66-119.75)	0.162
ADMA µmol/L	6.25 (4.69-8.58)	6.43 (5.34-7.46)	0.959

Abbreviations: NGT=normal glucose tolerance, GDM=gestational diabetes mellitus

All results reported are median (IQR) except PAI-1 is mean (SD).

Outliers were excluded for IL-6 (n=1), SHBG (n=2) and omentin (n=1).

[†] statistically significant with p-value <0.05

Table 3. Univariable and multivariable regression analysis for GDM

	Unadjusted model		Maternal factors and biomarker*	
Biomarker	OR (95% CI)	p-value	OR (95% CI)	p-value
HMW adiponectin $\mu\text{g/mL}$ 1 $\mu\text{g/mL}$ increase <25 th percentile (1.53 $\mu\text{g/mL}$)	0.40 (0.22-0.71) 11.17 (3.87-32.24)	0.002 [†] <0.001 [†]	0.37 (0.19-0.74) 10.92 (3.41-34.91)	0.005 [†] <0.001 [†]
IL-6 pg/mL 1 pg/mL increase >75 th percentile (2.58 pg/mL)	1.45 (0.97-2.43) 2.07 (0.77-5.56)	0.149 0.147	1.87 (1.03-3.37) 3.44 (1.01-11.69)	0.036 [†] 0.048 [†]
Visfatin ng/mL 1 ng/mL increase	1.90 (0.34-10.44)	0.463	1.48 (0.19-11.27)	0.704
Omentin-1 ng/mL 1 ng/mL increase <25 th percentile (38.36 ng/mL)	0.98 (0.95-1.00) 3.44 (1.25-9.47)	0.063 0.017 [†]	0.97 (0.94-0.99) 3.93 (1.26-12.22)	0.044 [†] 0.018 [†]
PAI-1 ng/mL 1 ng/mL increase	0.99 (0.95-1.03)	0.529	0.97 (0.92-1.02)	0.193
SHBG nmol/L 1 nmol/L increase	1.00 (0.99-1.00)	0.313	1.00 (0.99-1.00)	0.616
MCP-1 pg/mL 1 pg/mL increase	0.99 (0.98-1.00)	0.121	0.99 (0.96-1.00)	0.152
ADMA $\mu\text{mol/L}$ 1 $\mu\text{mol/L}$ increase	0.96 (0.83-1.12)	0.630	0.94 (0.79-1.11)	0.465

Table 3 contains results for logistic regression analysis analyzing risk of GDM according to each biomarker studied. The unadjusted models on the left of the table examine the risk of GDM (odds ratio OR [95% confidence interval CI]) per 1 unit increase in each biomarker studied in univariable regression analysis. The adjusted models on the right side of the table examine the risk of GDM (OR [95% CI]) per 1 unit increase in each biomarker studied, adjusted for maternal factors age, BMI and past history of GDM in multivariable regression analysis. Significant results were then also examined in quartiles.

Outliers were excluded for IL-6 (n=1), SHBG (n=2) and omentin (n=1).

*Adjusted for age, BMI, and past history of GDM

[†]statistically significant with p-value <0.05

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