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ORIGINAL ARTICLE

# Raised plasma adiponectin levels in type 1 diabetic pregnancies

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## Summary

**Objectives** Adiponectin has antidiabetic properties. Our aim was to determine plasma adiponectin levels during pregnancy and postpartum (PP), in women with type 1 diabetic mellitus (T1DM) and nondiabetic (ND) women.

**Patients and Methods** Fasting plasma adiponectin and leptin levels were measured in 20 ND and 19 T1DM women, at 20 and 30 weeks' gestation, and 9 months' PP. Insulin measurements were made in ND women.

**Results** In both groups, after accounting for body mass index (BMI), leptin levels increased during pregnancy ($P < 0{\cdot}01$) and were significantly higher than PP ($P < 0{\cdot}001$). However, no significant differences in leptin levels were noted between both groups at any stage ($P = 0{\cdot}46$). Conversely, adiponectin levels were higher in T1DM at all stages of the study ($P < 0{\cdot}001$). A significant fall in adiponectin levels was seen between 20 and 30 weeks' gestation in both groups (ND: $P < 0{\cdot}001$; T1DM: $P < 0{\cdot}05$); however, this decrease was attenuated in the T1DM group. Adiponectin levels PP were significantly higher than at 30 weeks (ND: $P < 0{\cdot}001$; T1DM: $P < 0{\cdot}001$). Furthermore, in T1DM, adiponectin appeared to correlate negatively with leptin, but only reached significance PP ($r = -0{\cdot}46$, $P < 0{\cdot}001$). In the ND group, adiponectin correlated negatively with both leptin (PP: $r = -0{\cdot}56$, $P < 0{\cdot}0001$) and insulin ($P < 0{\cdot}005$).

**Conclusions** Higher adiponectin levels were noted in T1DM throughout gestation compared to ND pregnancies, with no difference in leptin levels. The significance of these findings needs to be determined.

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## Introduction

Pregnancy is associated with profound alterations in hormonal metabolism, directed towards supplying adequate nutrition for the foetus. Insulin action and sensitivity change over the course of pregnancy. During the first trimester, insulin sensitivity is slightly increased, but thereon declines, being lowest in the third trimester.[1] This relative insulin resistance leads to higher levels of glucose and free fatty acids that are in turn constrained by increased maternal insulin secretion. For the patient with type 1 diabetes, insulin requirements increase later in pregnancy. The time course for changes in insulin action suggests a hormonal cause for the insulin resistance. In the past, human placental growth hormone, progesterone, cortisol and prolactin have been implicated, but more recently focus has included adipocytokines.

Leptin, which is elevated during pregnancy, has been implicated in the increased insulin resistance in pregnancy.[2] Adiponectin, an adipocytokine with antiinflammatory and antiatherogenic properties,[3] unlike leptin, is implicated in increasing insulin sensitivity.[4] Moreover, in a recent study of nondiabetic (ND) women and women with gestational diabetes mellitus (GDM), Cseh *et al.* suggested a role for adiponectin in insulin resistance associated with pregnancy, women with GDM having lower adiponectin levels.[5] This has also recently been confirmed in other studies,[6,7] with the authors suggesting that decreased adiponectin concentration in GDM may not simply reflect maternal adiposity and the insulin-resistant state, but may contribute to the impaired glucose metabolism during pregnancy. These observations, together with the known antidiabetic effects of adiponectin,[4] may be particularly relevant to type 1 diabetic mellitus (T1DM) pregnancies, who are known to have offspring with a higher risk of developing impaired glucose tolerance and type 2 diabetes mellitus.[8,9] It is feasible that there is an alteration in insulin resistance *vs.* sensitivity in T1DM pregnancies that may programme foetal metabolism and that may be mediated through adiponectin. However, to date, there are no data on adiponectin levels in T1DM pregnancies. Therefore, in the present study, our aim was to compare adiponectin levels in T1 diabetic mothers and ND women, during pregnancy and postpartum.

## Methods

Having obtained local ethical approval (Local Research Ethics Committee, UK) and informed consent, we measured fasting

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**Table 1.** Characteristics of subjects

| | Normal ($n = 20$) | Type I diabetes ($n = 19$) |
|---|---|---|
| Age (years) | 30·1 ± 4·1 | 30·3 ± 4·9 |
| BMI (kg/m$^2$) | | |
| 20 weeks' gestation | 25·1 ± 3·3 | 25·9 ± 2·9 |
| 30 weeks' gestation | 27·1 ± 3·3 | 27·5 ± 2·7 |
| Postpartum | 23·6 ± 3·4 | 24·7 ± 2·7 |
| HbA1C (%) | | |
| 20 weeks' gestation | – | 6·2 ± 1·1 |
| 30 weeks' gestation | – | 6·3 ± 1·6 |
| Postpartum | – | 7·8 ± 2·1* |
| Fasting glucose (mmol/l) | | |
| 20 weeks' gestation | 3·8 ± 0·5§ | 6·6 ± 2·9 |
| 30 weeks' gestation | 4·0 ± 0·4§ | 5·8 ± 2·8 |
| Postpartum | 3·7 ± 0·6§ | 11·4 ± 4·4† |
| Foetal birthweight (kg) | 3·68 ± 0·35 | 3·31 ± 0·64‡ |
| Gestational age (weeks) | 39·1 ± 0·3 | 39·5 ± 0·6 |
| Gestational weight gain (kg) | 5·54 ± 1·63 | 4·68 ± 2·82 |
| Serum creatinine (μmol/l) | | |
| 20 weeks' gestation | 50 ± 5·5 | 52 ± 6·5 |
| Postpartum | 80 ± 9·5 | 78 ± 10·3 |
| Calculated GFR (ml/min) | | |
| 20 weeks' gestation | 156·2 ± 7·2 | 155·2 ± 9·8 |
| Postpartum | 94·8 ± 5·9¶ | 91·8 ± 7·8¶ |

Values are mean ± SD.

BMI, body mass index; HbA1C, haemoglobin A1C; GFR, glomerular filtration rate.

*Postpartum (PP) *vs.* 20 weeks, and 30 weeks, $P < 0·05$; †PP *vs.* 20 weeks, and 30 weeks, $P < 0·001$; ‡$P = 0·02$; §nondiabetic (ND) *vs.* type 1 diabetic mellitus (T1DM), $P < 0·01$; ¶PP *vs.* 20 weeks, $P < 0·01$.

(0800 h) plasma adiponectin and leptin in 20 ND women (tested with the oral glucose tolerance test) and 19 T1DM women (age of ND 30·1 ± 4·1 years; T1DM 30·3 ± 4·9 years; $P = 0·91$) at 20 and 30 weeks' gestation, and at 9 months PP after cessation of lactation. Consecutive T1DM patients were recruited from our joint diabetic and antenatal clinic. Control subjects were recruited from a general nondiabetic antenatal clinic at the same time. Serum insulin was measured in ND subjects. None of the study subjects was a smoker or had any evidence of renal disease or hypertension. There was no difference in blood pressure between the groups. Characteristics of the study group are presented in Table 1. All subjects had vaginal deliveries, which was unusual in the diabetic group, given that diabetic patients usually have a higher delivery rate by caesarean section and preterm delivery. All patients who enrolled completed the study.

For the diabetic patients, the mean duration of T1DM was 14·3 ± 9·2 years. The T1DM women maintained good glycaemic control during pregnancy; doses of insulin were adjusted according to the results of home glucose monitoring, where fasting glucose concentrations were targeted to be between 4 and 6 mmol/l and postprandial glucose levels (at 1 h) below 8 mmol/l.

### *Assays*

Insulin measurements were made in ND, using an enzyme-linked immunoassay (Dako Diagnostic Ltd). Commercially available assays were used to measure plasma adiponectin (Linco Research, MO, USA; intra- and interassay variation 3·4% and 7·5%, respectively) and leptin (Linco Research; intra- and interassay variation 3·2% and 7·8%, respectively).

### *Statistical analysis*

The design of this study, where multiple measurements were made within patients, created a hierarchical data structure. Hence, analysis of the data was performed by means of generalized linear mixed (fixed and random effect) hierarchical (patient and observation level) statistical models (Multilevel Models Project, Institute of Education, University of London, UK), by which total observed variation could be apportioned to that occurring between patients *vs.* within patients. Where appropriate, comparisons of patient characteristics between groups were accomplished using an unequal variance and paired *t*-test. In all analyses, statistical significance was considered achieved for $P < 0·05$.

## Results

As expected, body mass index (BMI) increased significantly from 20 to 30 weeks of gestation by an average of 1·83 kg/m$^2$ per individual ($P < 0·001$), with a significant PP fall to values lower than at 20 weeks' gestation ($P < 0·001$). No difference in BMI was noted between nondiabetic and T1DM women at any stage ($P = 0·61$): at 20 weeks' gestation (25·1 ± 3·3 *vs.* 25·9 ± 2·9 kg/m$^2$, $P$ = ns); at 30 weeks' gestation (27·1 ± 3·3 *vs.* 27·5 ± 2·7 kg/m$^2$, $P$ = ns); PP (23·6 ± 3·4 *vs.* 24·7 ± 2·7 kg/m$^2$, $P$ = ns). In addition, no difference in gestational weight gain from 20 to 30 weeks' gestation was noted between ND and T1DM (5·54 ± 1·63 *vs.* 4·68 ± 2·82 g, $P = 0·56$).

Fasting glucose levels (Table 1) were higher in the T1DM group than in the control group ($P < 0·01$). With the T1DM women requested to maintain good glycaemic control during pregnancy and with doses of insulin (at 20 weeks 13·1 ± 1·1 units; at 30 weeks 19·5 ± 3·0 units; PP 10·5 ± 3·8 units; 20 weeks *vs.* 30 weeks, $P = 0·008$; partum *vs.* PP, $P = 0·016$) adjusted according to the results of home glucose monitoring, glucose levels at 30 weeks were lower that at 20 weeks but just failed to reach significance ($P = 0·07$); glucose levels at 20 and 30 weeks were significantly lower than PP in T1DM women ($P < 0·001$). Serum creatinine did not differ between the two groups at any time point, but there was a significant increase in creatinine in both groups PP (Table 1; $P < 0·01$). Moreover, the calculated glomerular filtration rate (Cockcroft–Gault formula) was not significantly different between the groups at any time point (Table 1).

In both groups, leptin levels increased during pregnancy ($P < 0·01$) and were significantly higher than PP ($P < 0·001$) (Fig. 1a). However, no significant differences in leptin levels were noted between both groups of women at any stage (20 weeks, 30 weeks and PP, $P = 0·46$) (Fig. 1a). Conversely, adiponectin levels, corrected for haematocrit, were higher in T1DM at all stages of the

 

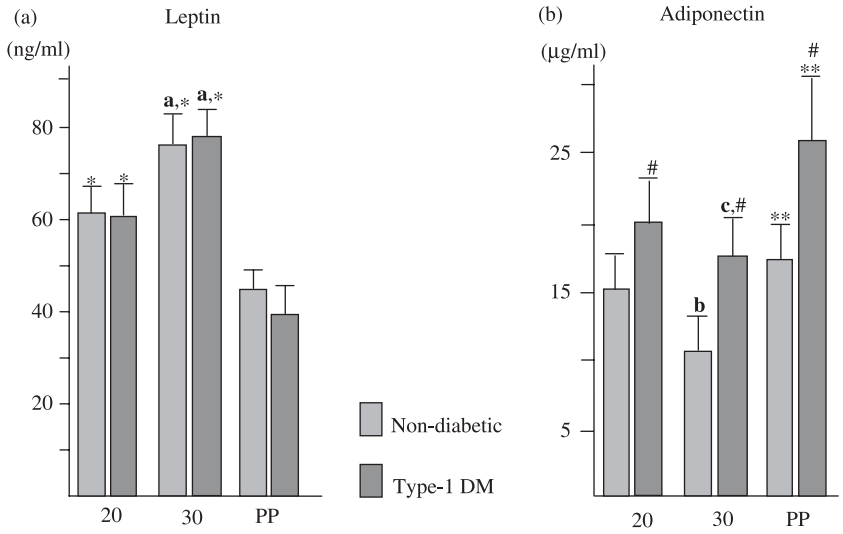


**Fig. 1** Plasma concentrations of (a) leptin (mean ± SEM), and (b) adiponectin (mean ± SD) in subjects with type 1 diabetes mellitus (T1DM) and nondiabetic (ND) subjects at 20 and 30 weeks' gestation and postpartum (PP). [a], $P < 0{\cdot}01$ *vs.* 20 weeks; *$P < 0{\cdot}001$ *vs.* PP; [b], $P < 0{\cdot}001$ *vs.* 20 weeks; [c], $P < 0{\cdot}05$ *vs.* 20 weeks; **$P < 0{\cdot}001$ *vs.* 30 weeks; #adiponectin levels higher in T1DM at all time points of study, $P < 0{\cdot}001$.

study ($P < 0{\cdot}001$) (Fig. 1b), even when BMI was included in the (hierarchical) modelling process. There was a significant fall in adiponectin (μg/ml) levels between 20 and 30 weeks, in both groups (ND: $15{\cdot}18 \pm 3{\cdot}0$ *vs.* $10{\cdot}58 \pm 3{\cdot}52$, $P < 0{\cdot}001$; T1DM: $20{\cdot}12 \pm 4{\cdot}1$ *vs.* $17{\cdot}38 \pm 3{\cdot}73$, $P < 0{\cdot}05$); however, this decrease was attenuated in the T1DM group (T1DM 13·6% decrease *vs.* ND 30·3%). Adiponectin levels PP were significantly higher than at 30 weeks (ND: $17{\cdot}12 \pm 3{\cdot}10$, $P < 0{\cdot}001$; T1DM: $25{\cdot}71 \pm 5{\cdot}8$, $P < 0{\cdot}001$), and than at 20 weeks (ND: $P = 0{\cdot}03$; T1DM: $P = 0{\cdot}02$). Adiponectin levels in T1DM women during the third trimester were similar to those observed in ND women PP ($17{\cdot}38 \pm 3{\cdot}73$ *vs.* $17{\cdot}12 \pm 3{\cdot}10$, respectively; $P = 0{\cdot}86$).

In T1DM, adiponectin levels correlated negatively with BMI throughout pregnancy (20 weeks: $r = -0{\cdot}65$, $P < 0{\cdot}0001$; 30 weeks: $r = -0{\cdot}51$, $P < 0{\cdot}001$; PP: $r = -0{\cdot}53$, $P < 0{\cdot}001$; Spearman's rank correlation test). Adiponectin also correlated negatively with leptin, but only reached significance PP (20 weeks: $r = -0{\cdot}13$, $P = 0{\cdot}65$; 30 weeks: $r = -0{\cdot}23$, $P = 0{\cdot}42$; PP: $r = -0{\cdot}46$, $P < 0{\cdot}001$). In the ND group, similar findings were noted in the correlation of adiponectin with BMI (20 weeks: $r = -0{\cdot}70$, $P < 0{\cdot}0001$; 30 weeks: $r = -0{\cdot}59$, $P < 0{\cdot}0001$; PP: $r = -0{\cdot}61$, $P < 0{\cdot}0001$). In these ND women, adiponectin correlated negatively with both leptin (20 weeks: $r = -0{\cdot}35$, $P = 0{\cdot}09$; 30 weeks: $r = -0{\cdot}42$, $P = 0{\cdot}005$; PP: $r = -0{\cdot}56$, $P < 0{\cdot}0001$) and insulin (20 weeks: $r = -0{\cdot}32$, $P = 0{\cdot}15$; 30 weeks: $r = -0{\cdot}60$, $P < 0{\cdot}0001$; PP: $r = -0{\cdot}23$, $P = 0{\cdot}42$). Foetal birthweight, after accounting for gestational age (T1DM delivered between 39 and 40 weeks, ND delivered between 39 and 41 weeks, gestational age being verified by first trimester ultrasound scan) and maternal parity, was lower in the T1DM group compared to ND ($3{\cdot}31 \pm 0{\cdot}64$ *vs.* $3{\cdot}68 \pm 0{\cdot}35$ kg; $P = 0{\cdot}03$). The sex of the cohort was not significantly different (T1DM: nine males, 10 females; controls: eight males, 12 females) and made no difference to the findings of the study. Using the generalized linear mixed (fixed and random effect) hierarchical (patient and observation level) statistical analysis, so that data were analysed over time, it was observed that plasma adiponectin levels did not correlate significantly with glucose in both groups, and no significant association was noted between maternal plasma adiponectin and haemoglobin A1C (HbA1C) or insulin dose in T1DM subjects. Moreover, maternal (gestational) plasma adiponectin levels were positively associated with birthweight in the ND group but failed to reach significance ($r = 0{\cdot}28$, $P = 0{\cdot}32$). In the T1DM group this association was found to be negative ($r = -0{\cdot}32$, $P = 0{\cdot}15$). Finally, adiponectin to leptin ratios were significantly higher in T1DM *vs.* ND throughout the study ($P < 0{\cdot}01$).

## Discussion

Pregnancy is associated with alterations in insulin resistance and sensitivity; adiponectin[5] and leptin[2] have been implicated in insulin resistance/sensitivity of pregnancy. Although we lack a direct measure of body composition, it is unlikely that any difference in adiposity between the two age-matched groups would explain our observations of significantly raised levels of the antidiabetic and antiinflammatory agent, adiponectin, in T1DM pregnancies, particularly given that both T1DM and ND showed no significant difference in BMI, gestational weight gain or leptin levels, at any stage. These differences in adiponectin remained significant PP.

The BMI in pregnancy is an indirect and very imprecise measure of the amount of body fat stores, and therefore may not be simply compared to the PP values. Therefore, the relationship of leptin and adiponectin to gestational weight and fat gain is unfortunately further complicated because the exact estimation of gestational fat gain remains difficult, as the calculated fat gain between different stages of pregnancy may vary as much as 50% depending on the method used.[10] We should note, however, that leptin levels in pregnancy were about 50% higher than those PP, and this rise is much higher than the average gestational fat gain, which, according to King *et al.*,[11] is usually around 25%.

Several factors have been suggested to regulate plasma and adipose tissue adiponectin levels.[12] The influence of insulin on adiponectin gene and protein synthesis is less clear. For example, chronic exposure of insulin decreased adiponectin mRNA expression in 3T3-L1 cells,[13] a murine cell line. However, others, using the same cell line[14] and human adipocytes,[15] have shown an increase in adiponectin expression with insulin. However, in the 'insulin-deficient' non-obese diabetic (NOD) mouse adiponectin levels did not change before or after the onset of diabetes, even though insulin levels fell dramatically.[16] A

recent study not only confirmed previous observations[17,18] of no change in adiponectin mRNA at 3 h but also showed that at 6 h there was an increase in adiponectin expression in insulin-sensitive but not insulin-resistant subjects.[19] Mannucci *et al.*[20] have also reported elevated levels of adiponectin in T1DM subjects compared to controls and T2DM subjects, with no correlation to HbA1c, as in our study. It is therefore apparent that the precise reason for the differences in plasma adiponectin seen in T1DM is unclear and may involve factors other than glucose and insulin.

With the aforementioned, it is unlikely that insulin therapy would entirely account for our findings. Although *in vitro* data have produced conflicting results, insulin administration *in vivo* to patients (nonpregnant) with T1DM did not change serum adiponectin levels.[21] Moreover, plasma adiponectin levels are significantly lower in women with GDM treated with insulin than in ND women, and insulin therapy did not alter this.[5] In a recent study by Morales *et al.*,[22] contrary to studies of adult T1DM,[21] adiponectin levels in paediatric T1DM subjects did not differ from those of healthy control subjects, although the adiponectin to leptin ratio was higher in the T1DM subjects. Our study also indicated a higher adiponectin to leptin ratio in T1DM.

Cseh *et al.* suggest a regulatory role of maternal adiponectin in neonatal development based on their observation of a significant positive correlation between adiponectin and neonatal body weight (NBW) in GDM and normal pregnancies.[5] However, in our longitudinal study, we found no significant association in either group. As the Cseh *et al.* study was a cross-sectional correlation, the issue of whether adiponectin is a regulator of neonatal development cannot be resolved. Cord blood adiponectin has been reported to correlate negatively (nonsignificant) with NBW in offspring of diabetics,[23] compared to the positive association noted in ND controls.[23,24]

The limitations of our study include mainly the fact that prospective assessment of microangiopathy was not performed in a consistent and reliable manner. Microangiopathy in T1DM is associated with increased plasma adiponectin levels.[25,26] However, Imagawa *et al.*[21] showed that, in type 1 diabetics, adiponectin levels were markedly elevated and that, from a cohort of 46, only two patients had retinopathy and two had microalbuminuria. This did not alter the significance of the elevated levels in T1DM.

In conclusion, our findings of higher adiponectin levels in T1DM throughout gestation compared to ND pregnancies, with no difference in leptin levels but higher adiponectin to leptin ratios, require further investigation. However, our study does not have measures of adiposity or glycaemia in the children, and any link of maternal adiponectin to foetal programming cannot therefore be drawn; future studies, with this question in mind, are needed.

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