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Adiponectin Is Present in Cord Blood but Is Unrelated to Birth Weight

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OBJECTIVE — In adults, adiponectin is reduced in association with excess adiposity, type 2 diabetes, and hyperinsulinemia. We assessed whether adiponectin was *1*) present in the fetal circulation, *2*) altered in the fetal circulation in the presence of maternal diabetes, and *3*) had relations to fetal cord blood insulin or adiposity.

RESEARCH DESIGN AND METHODS — We assessed adiponectin in cord blood in a large cohort of singleton offspring of diabetic mothers (ODM; $n = 134$) and control mothers ($n = 45$).

RESULTS — Adiponectin was present in cord blood and, in ODM, was higher in those delivered at later gestational ages (Spearman $r = 0.18$, $P = 0.03$). Adiponectin was slightly lower in ODM than control subjects (ODM 19.7 ± 6.1 vs. control 21.8 ± 5.3 μg/ml; $P = 0.04$), although this difference could potentially reflect different gestational ages in the two groups (ODM 37.6 ± 1.5 and control 40.1 ± 1.1 weeks). In contrast to adults, adiponectin levels in the fetus were unrelated to the degree of adiposity, blood insulin, or leptin in either control subjects or ODM.

CONCLUSIONS — Adiponectin is present in cord blood but does not show expected physiological relations with adiposity as observed in adults.

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Adipose tissue expresses a variety of secretory proteins of importance to metabolic and vascular disease. Recently, adiponectin, a 244–amino acid adipocyte-derived protein (1) has been described that is paradoxically reduced in obesity (2) and inversely related to leptin concentrations (3), despite being solely derived from adipose tissue in humans. Both type 2 diabetes and relative insulin resistance (in nondiabetic subjects) are associated with decreased adiponectin concentrations (4,5), while improvement of insulin sensitivity by either weight reduction (6) or administration of thiazolidinediones (7) is associated with increased adiponectin concentrations. Furthermore, in people matched for BMI, higher adiponectin concentrations are protective against later development of type 2 diabetes (8).

Exposure to maternal diabetes in utero is associated with increased adiposity at birth (9), as well as increases in fetal leptin (10) and insulin (11). Furthermore, the presence of maternal diabetes during pregnancy influences the long-term health of offspring with increases in future risk of obesity (12,13), type 2 diabetes (14), and impaired glucose tolerance (15–17).

Adiponectin has not been previously assessed in cord blood specimens. We wished to examine whether *1*) adiponectin was present in cord blood, *2*) relations to adiposity, sex, and circulating insulin and leptin observed in adults were also present in utero, and *3*) offspring of mothers with type 1 diabetes, a group at high risk of later development of metabolic disease, would have lower concentrations of adiponectin at birth.

RESEARCH DESIGN AND METHODS

Recruitment and clinical protocol

Recruitment, which began in January 1999 and ended in May 2001, took place in eight hospital-based antenatal centers in Scotland. A total of 250 women with type 1 diabetes consented to participate in the study (a 94% participation rate of those enrolled in and planning to deliver in the centers), and cord blood samples were obtained from 200 (80%). The 200 samples were further restricted to those in whom *1*) there was no evidence of hemolysis of cord blood (by visual inspection), *2*) cord blood had been collected within 20 min collection time for remaining samples: 2 min (1–7) [median (IQR)], and *3*) cord blood had been centrifuged and plasma frozen within 60 min [time from collection to freezing for remaining samples: 14 min (6–23)], as previously described (18). Of 151 offspring of type 1 diabetic mothers (ODM) potentially available after these restrictions, stored samples were available for adiponectin assay in 142. A total of 134 participants were included in the main analysis, and eight offspring who had been administered glucocorticoid in the 24 h before delivery were considered separately. A review of charts revealed that 27 mothers (20%) had been hospitalized during pregnancy due to hypertensive problems (9 for pregnancy-induced hypertension and 18 for preeclampsia). Twenty mothers (15%) had previously diagnosed thyroid

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Abbreviations: EDD, estimated date of delivery; IQR, interquartile range; LMP, last menstrual period; ODM, offspring of type 1 diabetic mothers.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

disease, 7 (5%) had asthma, and 1 had previously diagnosed epilepsy.

A convenience sample of control mothers, who had no history of obstetric or metabolic disease, and in which routine screening for gestational diabetes (using national guidelines: http://www.sign.ac.uk/guidelines/fulltext/55/section8.html) was negative were recruited from routine obstetric follow-up clinics after the 34th week of pregnancy in the same centers. Of the 145 women who gave initial consent, cord samples were attempted in 75 and obtained in 70. Forty-nine collections met the above restriction criteria, and samples were available for adiponectin assay in 46. One participant had received glucocorticoid in the 24 h before delivery and was not considered.

All clinics offer antenatal care delivered by a multidisciplinary team comprised of obstetricians, diabetologists, specialist midwives, diabetes specialist nurses, and dietetic support. Local management protocols for treatment of type 1 diabetes in pregnancy were followed. Data on clinical outcome, including cesarian section, intercurrent medical conditions, and hypertensive conditions of pregnancy were obtained by chart review. Gestational ages were calculated from estimated dates of delivery (EDDs) from chart review. EDD was derived from the date of last menstrual period (LMP) when available or by ultrasound when there was either a conflict with dates as assessed by LMP (>6 days) or when LMP was unavailable. HbA_{1c} was monitored at individual centers, as prescribed by local clinical protocols. Samples were sent in the first trimester, and 20 and 30 weeks of gestation were used for measurement using a single assay (BioRad Variant, nondiabetic reference range 4.4–5.7%; Bio-Rad, Hercules, CA) at a central reference laboratory (Western General Hospital, Edinburgh, U.K.).

Weight was measured at birth and, for offspring born between 33 and 42 weeks of gestation, further expressed as an SD score, as previously described (19). Individual birth weights are compared with mean (M_{CELL}) and SD (SD_{CELL}), which are derived from 26,000 nondiabetic deliveries in cells specific for sex, week of gestation, and parity (0 vs. ≥1). The *Z* score is calculated as ([birth weight − M_{CELL}]/SD_{CELL}). Skinfold thickness at subscapular and triceps was measured using Holtain calipers by pediatricians at each site, and a centrally agreed protocol that is available in writing at the time of measurement was followed. Skinfolds were not measured in all subjects. However, there were no significant differences in baseline demographic or biochemical measures between those with and without skinfold measurements in either control subjects or ODM (data not shown). All mothers gave informed consent. Protocols were approved by the local ethical committees.

Collections of cord bloods and assays

After delivery, 20 ml cord blood was collected from the umbilical vein, after cord clamping, and put into lithium heparin at ambient temperature. Depending on local circumstances, samples were then either transferred to local laboratories for centrifugation or centrifuged in situ before initial storage of plasma at −20°C and eventual central storage at −70°C (after a median [IQR] of 11[5–21] days). Previous analyses in this group have established that insulin is unstable when the collection of blood from umbilical vein is delayed for >20 min or freezing is delayed >60 min. By contrast, insulin propeptides are stable for at least 30 min after cord sampling and 24 h before freezing (18). For the purposes of this investigation, hormonal measures were only included if collected from cord within 20 min and frozen within 60 min.

Plasma insulin, 32-33 split proinsulin, leptin, and glucose were assayed as previously described (18). In two cases (both control subjects), insulin concentrations were below the detection limit of the assay (2 pmol/l). These data have been included with an assigned value of 1.9 pmol/l. These assays display low cross-reactivity with other insulin species.

Adiponectin was assayed with a radioimmunoassay kit specific for human adiponectin (HADP-61HK; Linco Research, St. Charles, MO) after 1:500 dilution. Samples were analyzed in two batches, with an intra-assay coefficient of variation (CV) 1.8–6.2% and interassay CV 6.9–9.3% for duplicates over a range of adiponectin concentrations.

Statistical analysis

Data were analyzed using standard software (SAS, Cary, NC). In several cases (insulin, proinsulin, and 32-33 split proinsulin) measures were not normally distributed; therefore, log-transformed values were used to approximate normal distributions. Differences between control women and women with type 1 diabetes were assessed by unpaired Student's *t* test or, where further predictor variables were included, by general linear models. The relation of adiponectin to other variables was examined by Spearman correlation and adjusted using partial correlation for sex and gestational age separately in ODM and control subjects. As we have previously demonstrated (18) that 32-33 split proinsulin concentrations are more stable than insulin in sampling conditions at birth, analysis of the relation of adiponectin to both 32-33 split proinsulin and insulin is included.

RESULTS

Anthropometric and hormonal measures in ODM versus control subjects

Mothers with type 1 diabetes were of similar age and parity as control mothers, while their offspring were heavier, more likely to be delivered by caesarian section, and delivered 2 weeks earlier on average than control subjects (Table 1). In keeping with this, SD scores for birth weight were dramatically higher in ODM, being on average almost 2 SD above that expected in the population and significantly greater than in control subjects (Table 1).

More detailed anthropometric measures were available in a subset (control subjects, $n = 18$ and ODM, $n = 55$). ODM were of similar length (crown-heel: ODM 50.9 ± 2.4 and control subjects 50.7 ± 2.2 cm; $P = 0.88$) but had increased subscapular (ODM 7.3 ± 2.2 vs. control 5.6 ± 2.0 cm; $P = 0.01$) and triceps (ODM 7.8 ± 3.1 vs. control 6.1 ± 2.47 cm; $P = 0.04$) skinfold thickness.

Relation of adiponectin to length of gestation, anthropometric, and hormonal measures

Adiponectin was present in cord blood, with concentrations ranging between 4.8 and 34.7 μg/ml. Values of adiponectin were normally distributed in both control subjects and ODM (Shapiro-Wilk statistic: 0.98 and 0.99, respectively) and were unrelated to delays in sample collection or freezing in either ODM or control subjects ($P > 0.5$ for all data not shown). In ODM, adiponectin concentrations were higher

Table 1—*Characteristics of mothers and offspring*

	Control mothers	Mothers with type 1 diabetes	*P**
n	45	134	
Age (years)	28.9 ± 6.1	29.7 ± 5.7	0.43
Duration of diabetes (years)	—	13.3 ± 7.4	—
Parity			
0	19 (42)	61 (45)	
1	20 (44)	53 (40)	0.84
>1	6 (13)	20 (15)	
Children (boys/girls)	21/24	66/68	0.76
Gestational age at delivery (weeks)	40.1 ± 1.1	37.6 ± 1.5	<0.001
Delivery			
Vaginal	30 (67)	41 (31)	
Elective caesarian	9 (20)	48 (36)	<0.001
Emergency caesarian	6 (13)	45 (34)	
Birth weight (kg)			
Boys	3.75 ± 0.51	3.81 ± 0.74	0.01†
Girls	3.36 ± 0.49	3.76 ± 0.64	<0.001†
Z weight of offspring‡	0.33 ± 1.10	1.94 ± 1.51§	<0.001
Cord insulin (pmol/l)	22.4 (15.0–39.6)	112 (58–218)	<0.001
Cord leptin (ng/ml)	8.7 (4.1–16.7)	32.0 (14.6–54.4)	<0.001
Cord adiponectin (μg/ml)	21.8 ± 5.3	19.7 ± 6.1	0.04

Data are means ± SD, *n*(%), or median (IQR). **P* value in unpaired *t*, Wilcoxon, or χ^2 test, as appropriate; †birth weights are unadjusted, and the *P* value for difference is dependent on maternal diabetes status and adjusted for gestational age at delivery; ‡*Z* weight is an SD score compared with standard values for gestational age, sex, and maternal parity; §*n* = 133, 1 child (gestation age at delivery, 29 weeks) was not included since a standardized birth weight was not available.

in those delivered at later gestational ages (Fig. 1 and Table 1). This was not apparent in control subjects, although the range of gestational ages at delivery was much narrower (Fig. 1 and Table 1).

In ODM, adiponectin concentrations were lower in boys than girls (means ± SE: boys 18.1 ± 0.8 vs. girls 21.1 ± 0.7 μg/ml; $P = 0.006$), a difference that remained significant after adjustment for gestational age (linear or linear and quadrilateral terms, $P = 0.005$ for effect of sex for both models). By contrast in control subjects, adiponectin concentrations tended to be higher in boys than girls, although this did not achieve significance (boys 23.3 ± 1.1 vs. girls 21.0 ± 1.1 μg/ml; $P = 0.14$).

In absolute terms, adiponectin concentrations were significantly lower in ODM (ODM 19.7 ± 6.1 vs. control subjects 21.8 ± 5.3 μg/ml; $P = 0.04$). This difference was confined to boys (ODM 18.2 ± 0.7 vs. control subjects 22.9 ± 0.7 μg/ml; $P = 0.001$), with no significant difference in girls (ODM 21.1 ± 0.7 vs. control subjects 20.8 ± 1.2 μg/ml; $P = 0.81$).

Adiponectin concentrations were unrelated to mode of delivery in both ODM (vaginal 19.0 ± 1.0, elective cesarian section 20.1 ± 0.9, and emergency cesarian section 19.8 ± 0.9 μg/ml; $P = 0.66$) and control subjects (vaginal 21.6 ± 1.0, elective cesarian section 22.6 ± 1.8, and emergency cesarian section 21.3 ± 2.2 μg/ml; $P = 0.85$), even after adjustment for gestational age at delivery and sex (ODM, $P = 0.56$ and control, $P = 0.82$).

There were no significant relations of adiponectin to anthropometric or hormonal measures at birth (Table 2). In particular, measures reflecting adiposity (*Z* score of birth weight, skinfold thicknesses, and cord leptin) did not show the negative relations with adiponectin that we hypothesized would be present. This was also the case in boys and girls considered separately (data not shown) and where correlations were not adjusted for gestational age at delivery (subscapular skin thickness in control subjects remained significant, $r = 0.52$; other relations were not significant). Adiponectin was unrelated to cord insulin or 32-33 split proinsulin (Table 2). In addition, in 114 women in whom HbA_{1c} measurements after the 26th week of pregnancy were available (6.9 ± 0.9%), there was no relation with cord adiponectin (Spearman $r = 0.05$, $P = 0.59$). By contrast, insulin, 32-33 split proinsulin, and leptin are significantly related to the *Z* score for weight in ODM in this group (Spearman $r = 0.55$, 0.42, and 0.43, respectively; $P < 0.0001$ for all). Adiponectin was unrelated to cortisol in cord blood and was no different in the small groups of ODM who had been administered glucocorticoid in the 24 h before delivery (ODM: 19.7 ± 6.1 μg/ml, $n = 134$ vs. ODM given glucocorticoids: 20.0 ± 7.1 μg/ml, $n = 8$).

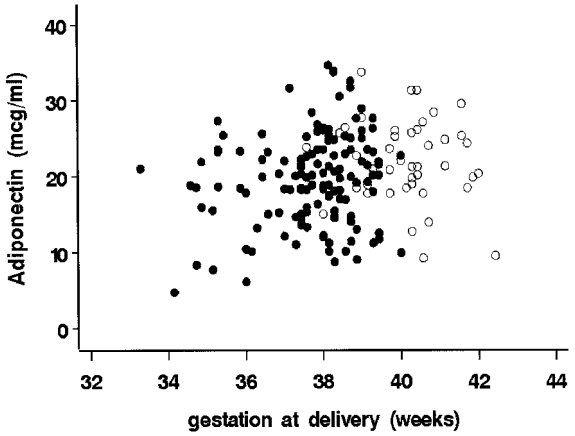

Figure 1—*Adiponectin concentrations in cord blood in ODM and control subjects. One ODM subject delivered at 29 weeks (adiponectin 12.0 mcg/ml, data not shown). Relation of gestational age to adiponectin: ODM, Spearman* r = *0.18,* P = *0.03; and control subjects,* r = *0.01,* P = *0.98.* ●*, ODM;* ○*, control subjects.*

CONCLUSIONS — Adiponectin is a novel product of adipocytes of potential importance to the later development of metabolic disease. We found that adiponectin is present in cord blood at relatively high levels—two- to threefold higher than that found in adults using the same assay (20,21). Notably, however, relations of adiponectin to adiposity found in adults largely appear to be absent at birth.

Table 2—*Correlation of adiponectin to anthropometric and hormonal measures*

	Control subjects	ODM
n	45	134
Z score of birth weight†	0.21	−0.14
Gestational age at delivery	−0.06	0.18*
Leptin	0.13	−0.02
Insulin	0.12	0.0
32-33 split proinsulin	0.20	−0.05
Cortisol	0.03	−0.05
Cord glucose	0.15	0.14
n	18	55
Crown-heel length	0.10	−0.09
Triceps skin thickness	0.18	0.05
Subscapular skin thickness	0.52*	0.08

Spearman correlation coefficients (*r*) of adiponectin versus anthropometric and hormonal measures in cord blood at birth. All analyses are adjusted for sex and gestational age at delivery except the *Z* score (no adjustment) and gestational age at delivery (sex-adjusted only). *$P < 0.05$; †birth weight *Z* score: SD score of birth weight in offspring grouped for gestational age, sex, and parity ($n = 133$).

Adiponectin concentrations have not been previously reported in cord blood. Given that there has been postulation as to the effects of adiponectin on insulin sensitivity (22–24), β-oxidation of fats (25), and inflammatory pathways (26), the presence of adiponectin in utero allows for potentially important effects on early growth and development. While it is likely that, at birth, adiponectin is largely derived from fetal adipose tissue, we do not have data to directly assess this. It is possible that adiponectin may be derived from maternal circulation or from other tissues, notably of the placenta, as is the case for leptin (27).

Adiponectin is solely derived from adipocytes in adults (2). Despite this, its presence is paradoxically reduced in obesity, and an inverse relation of adiponectin to measures of adiposity has been found in all adult studies (5,8,28–30). Unexpectedly, we found no inverse relation of adiponectin to a variety of measures that may reflect adiposity (adjusted birth weight, skinfolds, and cord leptin) in either ODM or control subjects. Adiponectin was positively related to subscapular skinfold measures in control subjects, although this result was not in accordance with other measures of adiposity. Some of the measures of adiposity might be criticized; several investigators were used at the various centers for measuring skinfolds, which likely reduced measurement precision. Additionally, we lack a direct measure of body composition. Nevertheless, it appears unlikely from our data that there is a strong relationship between adiposity and adiponectin at birth. By contrast and as we previously reported (18), other hormonal measures, such as insulin and 32-33 split proinsulin, are highly and significantly associated with adjusted birth weight and leptin in this group.

The mechanism by which increased adiposity results in lower adiponectin concentrations in adults is unknown. Adiponectin appears to be especially related to visceral fat mass in adults (20). We did not assess centrality of fat distribution, and it remains possible that a relationship with visceral fat exists at birth. Adiponectin is downregulated by glucocorticoids in vitro (31,32). In our study, although numbers were small, there was no evidence of modulation of adiponectin concentrations by glucocorticoids in vivo. Similarly, while vaginal delivery is associated with an increase in cord cortisol in this group (data not shown), no difference was seen in adiponectin by mode of delivery. We do not have detailed measures of other factors during delivery, such as the duration of intravenous infusions, and cannot exclude the effects of these on cord adiponectin.

Insulin probably does not directly influence adiponectin concentrations in adults. While in vitro studies have produced conflicting results (31,32), insulin administration in vivo to patients with type 1 diabetes does not seem to acutely modify adiponectin concentrations (33) and adiponectin is not altered in response to meals (4). The lack of relation between adiponectin and cord insulin suggests that, as in adults (33), circulating insulin may have little effect on adiponectin in utero. It should be noted, however, that in our study we did not measure maternal insulin antibodies, which are frequently present in cord blood (34) and allow passage of maternal insulin into the fetal circulation (35). The presence of antibodies could conceivably influence the relation of adiponectin to cord insulin; nevertheless, relations of insulin to birth weight and leptin were readily apparent in our study.

Adiponectin increased modestly with gestational age at birth in ODM but not in the control group. However, few participants in the control group were born at gestational ages <38 weeks. Thus, while we found differences in adiponectin concentration between male ODM and control subjects, we cannot exclude the possibility that this arises as a result of the difference in gestational age at delivery between the two groups.

Adiponectin level has also been found to be higher in adult women than men (29,30), although this sex difference is not present in all populations studied (5). Recently, downregulation of adiponectin by androgens has been demonstrated in animal models, forming a potential basis for these differences (36). Our data suggest that the sex difference in adiponectin is not normally present at birth in control subjects. By contrast, the expected sex difference was found in ODM. The reason for this is unclear. Boys have relatively higher lean mass than girls at birth (37). Though we lack detailed measures of body composition, the absence of a relation of adiponectin to adjusted birth weight and leptin makes it unlikely that subtle changes in body composition underpin the sex difference in ODM. At birth, androgen concentrations are higher in boys than girls (38) but do not appear to be influenced by the presence of maternal diabetes (39). We did not measure androgens directly, but it would appear unlikely that there is a major difference confined to the diabetic group.

Finally, current assays only measure monomeric adiponectin, and although the protein circulates in trimeric, hexameric, and larger forms, it has been suggested that altered states of oligomerization may have functional consequences (40). Adiponectin is also subject to glycosylation, which may have potential functional effects (41). It is possible that these properties of adiponectin are altered in ODM.

In summary, we found that adiponectin is present in human cord blood. The relations with adiposity found in adult studies do not appear to be present at birth and, despite marked differences in adiposity, insulin, and leptin at birth, there are at most modest changes in adiponectin of the offspring of mothers with type 1 diabetes compared with control subjects.

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