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Adiponectin and beta cell dysfunction in gestational diabetes: pathophysiological implications

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Abstract *Aims/hypothesis:* Gestational diabetes mellitus (GDM) identifies a population of young women at high risk of developing type 2 diabetes and thus provides an excellent model for studying early events in the natural history of this disease. Adiponectin, a novel adipocyte-derived protein with insulin-sensitising properties, has been proposed as a factor linking insulin resistance and beta cell dysfunction in the pathogenesis of type 2 diabetes. We conducted the current investigation to determine whether adiponectin is associated with beta cell dysfunction in GDM. *Methods:* We studied 180 women undergoing OGTT in late pregnancy. Based on the OGTT results, par-

ticipants were stratified into three groups: (1) NGT ($n=93$); (2) IGT ($n=39$); and (3) GDM ($n=48$). First-phase insulin secretion was determined using a validated index previously proposed by Stumvoll. Insulin sensitivity was assessed using the validated OGTT insulin sensitivity index of Matsuda and DeFronzo (IS_{OGTT}). *Results:* To evaluate beta cell function in relation to ambient insulin sensitivity, an insulin secretion-sensitivity index (ISSI) was derived from the product of the Stumvoll index and the IS_{OGTT} , based on the existence of the predicted hyperbolic relationship between these two measures. Mean ISSI was highest in the NGT group (6,731), followed by that in the IGT group (4,976) and then that in the GDM group (3,300) (overall $p<0.0001$), compatible with the notion of declining beta cell function across these glucose tolerance groups. Importantly, adiponectin was significantly correlated with ISSI ($r=0.34$, $p<0.0001$), with a stepwise increase in mean ISSI observed per tertile of adiponectin concentration (trend $p<0.0001$). In multivariate linear regression analysis, ISSI was positively correlated with adiponectin and negatively correlated with GDM, IGT and C-reactive protein ($r^2=0.54$). *Conclusions/interpretation:* Adiponectin concentration is an independent correlate of beta cell function in late pregnancy. As such, adiponectin may play a key role in mediating insulin resistance and beta cell dysfunction in the pathogenesis of diabetes.

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Abbreviations CRP: C-reactive protein · GDM: gestational diabetes mellitus · HOMA-B: homeostasis model of assessment for beta cell · HOMA-IR: homeostasis model of assessment for insulin resistance · IS_{OGTT} : OGTT insulin sensitivity index of Matsuda and DeFronzo · ISSI: insulin secretion-sensitivity index · NDDG: National Diabetes Data Group · QUICKI: quantitative insulin sensitivity check index · S_1 : insulin sensitivity index

Introduction

The pathophysiological hallmarks of type 2 diabetes mellitus are insulin resistance and beta cell dysfunction [1]. In healthy individuals, pancreatic insulin secretion is linked to peripheral insulin sensitivity through a postulated negative feedback loop that allows the beta cells to compensate for any change in whole-body insulin sensitivity by a proportionate and reciprocal change in insulin secretion. Accordingly, a hyperbolic relationship exists between insulin secretion and insulin sensitivity, such that the product of these two parameters, which has been referred to as the disposition index, is constant for a given degree of glucose tolerance [2, 3]. In the pathogenesis of type 2 diabetes, progressive deterioration of beta cell function leads to an inability to secrete sufficient insulin to compensate for insulin resistance, a process reflected by a concomitant decline in the disposition index [4, 5]. Given the requirement of both beta cell dysfunction and insulin resistance, a 'two-hit' model of the pathogenesis of type 2 diabetes has been suggested [6]. Alternatively, a so-called 'closed-loop' model has also been proposed, which postulates that diabetes may result from a failure of appropriate signalling between insulin-responsive peripheral tissues and insulin-secreting beta cells [4, 6]. In this context, understanding the molecular signals linking insulin sensitivity and insulin secretion would be of great interest.

Adipocyte-derived mediators such as NEFAs and TNF- α have been proposed as factors that may link insulin resistance and beta cell dysfunction in type 2 diabetes [7]. Another candidate is adiponectin, a novel adipocytokine with pleiotropic effects, including putative insulin-sensitising, anti-atherogenic and anti-inflammatory properties [8, 9]. Consistent with the low circulating levels of adiponectin observed in type 2 diabetes, adiponectin concentration is inversely related to both insulin resistance and central adiposity [10–13]. Moreover, low baseline adiponectin concentration can predict the future development of insulin resistance, while elevated baseline levels have been shown to be protective against the subsequent development of type 2 diabetes [14–18]. Importantly, however, while adiponectin has emerged as an apparent mediator of insulin resistance, its potential association with beta cell dysfunction has received limited attention.

Gestational diabetes mellitus (GDM) identifies a population of women at high risk of developing type 2 diabetes and thus potentially provides a model of early events in the natural history of type 2 diabetes [19]. GDM arises in a subset of young women in whom the considerable acquired insulin resistance of late pregnancy unmasks a previously unrecognised beta cell defect [20]. Accordingly, this population of women has been reported to exhibit a reduced mean disposition index both during and after pregnancy, when compared with normoglycaemic counterparts [20, 21]. In a cross-sectional study of 180 women in the third trimester, we recently demonstrated that women with GDM also exhibit hypoadiponectinaemia when compared with normoglycaemic controls, after adjustment for covariates including insulin resistance [22]. Given this

finding, we hypothesised that beta cell dysfunction may be related to reduced adiponectin concentration. Thus, the current analysis was undertaken to evaluate the relationship between adiponectin concentration and beta cell function in this cohort of women across different strata of glucose tolerance in late pregnancy.

Subjects and methods

The study design, protocol and laboratory methods have been fully described elsewhere [23]. The study protocol was approved by the Research Ethics Board at Mount Sinai Hospital and all subjects gave written informed consent.

Subjects Study participants were 180 pregnant women attending outpatient obstetrics clinics, who had been referred for a 100-g OGTT following an abnormal result on a screening 50-g glucose challenge test (plasma glucose ≥ 7.8 mmol/l 1 h post-challenge). Exclusion criteria were: (1) pre-existing chronic medical conditions that may affect acute-phase markers, including established diabetes mellitus, polycystic ovarian syndrome, collagen vascular diseases, inflammatory bowel disease and chronic inflammatory conditions; or (2) current use of corticosteroids. Participants were recruited prior to undergoing the 100-g OGTT.

Baseline evaluation On the day of the OGTT, demographic and historical information was collected by interviewer-administered questionnaire. Data collected were: (1) patient demographics; (2) information regarding current pregnancy including illnesses, infections and medications; (3) personal medical, obstetrical and smoking history; and (4) family history. Specific GDM risk factors were assessed including age, ethnicity, pre-pregnancy weight, weight gain during pregnancy, personal history of GDM, previous delivery of a macrosomic infant and a family history of GDM, macrosomic infant or type 2 diabetes. Anthropometric measurements of height (measured to nearest 0.5 cm) and weight (measured to nearest 0.1 kg) were obtained using a medical scale.

Laboratory measurements The 100-g OGTT was performed in the morning after an overnight fast. Venous blood samples were drawn at baseline and 60, 120 and 180 min after ingestion of a standard 100-g glucose load. Plasma adiponectin concentration was measured at 180 min (adiponectin level is not affected by food intake [13]) by radioimmunoassay (Linco Research, St. Charles, MO, USA) with a CV of 9.3% [12]. Fasting C-reactive protein (CRP) concentration was determined using the Behring BN100 and the N high-sensitivity C-reactive protein reagent (Dade-Behring, Mississauga, Ontario, Canada). Specific insulin was measured at each of the four time points of the OGTT using the Roche Elecsys 1010 immunoassay analyser and the electrochemiluminescence immunoassay kit. This assay shows 0.05% cross-reactivity to intact human proinsulin and the primary circulating split form des-31, 32 proinsulin.

Glycaemic status The OGTT stratified participants into three glycaemic tolerance groups: (1) GDM, as defined by the National Diabetes Data Group (NDDG) criteria (requires at least two of the following: [i] fasting glucose >5.8 mmol/l, [ii] 1-h post-challenge glucose >10.6 mmol/l, [iii] 2-h post-challenge glucose >9.2 mmol/l, or [iv] 3-h post-challenge glucose >8.1 mmol/l); (2) IGT, as defined by NDDG criteria (requires one of the above GDM criteria); and (3) NGT, defined as subjects not meeting any of the GDM or IGT criteria [24].

Insulin secretion and sensitivity indices Several models have been previously proposed for evaluation of insulin sensitivity and insulin secretion using measurements from the OGTT. In this study, we used the following models of insulin sensitivity: (1) the OGTT insulin sensitivity index of Matsuda and DeFronzo (IS_{OGTT}); (2) the QUICKI (quantitative insulin sensitivity check index) model; and (3) the homeostasis model of assessment for insulin resistance (HOMA-IR). The IS_{OGTT} model of Matsuda and DeFronzo for insulin sensitivity is defined by the following formula: $10,000/\sqrt{Gluc_0 \times Ins_0 \times \text{mean } Gluc \times \text{mean } Ins}$, where Ins_y and $Gluc_y$ represent plasma insulin and glucose values, respectively, at time y minutes during the OGTT [25]. Mean glucose and mean insulin were calculated using measurements at baseline and after 60, 120 and 180 min during the OGTT. The QUICKI model of insulin sensitivity is defined by the following formula: $1/(\log[Ins_0] + \log[Gluc_0])$ [26]. HOMA-IR is defined as follows: $(Gluc_0 \times Ins_0)/22.5$ [27]. The IS_{OGTT} , QUICKI and HOMA-IR indices have all been validated in pregnancy and in GDM [28]. In this validation study in pregnant patients, the IS_{OGTT} index showed better correlation with insulin sensitivity derived using the euglycaemic–hyperinsulinaemic clamp technique than either the QUICKI or the HOMA-IR model.

We used the following three measures of insulin secretion: (1) the Stumvoll first-phase measure of insulin secretion; (2) the Stumvoll second-phase measure of insulin secretion; and (3) the homeostasis model of assessment for beta cell (HOMA-B). The Stumvoll first-phase measure of insulin secretion is defined by the following formula: $1,194 + 4.724 \times Ins_0 - 117.0 \times Gluc_{60} + 1.414 \times Ins_{60}$ [29]. The Stumvoll second-phase measure of insulin secretion is defined as follows: $295 + 0.349 \times Ins_{60} - 25.72 \times Gluc_{60} + 1.107 \times Ins_0$ [29]. The Stumvoll first- and second-phase insulin secretion formulae were derived using multiple linear regression models to predict directly measured first- and second-phase insulin release during hyperglycaemic clamp studies [29, 30]. HOMA-B is defined by the following formula: $(20 \times Ins_0)/(Gluc_0 - 3.5)$ [27]. The HOMA-B formula was derived from a computer model of the interaction between fasting insulin and glucose [27]. Neither HOMA-B nor the Stumvoll indices have been validated in pregnancy. However, these measures have been validated in a number of other populations and have been shown to predict diabetes in prospective studies [30–33]. The incremental area under the insulin curve (AUC_{ins}) and the incremental area under the glucose curve (AUC_{glu}) were calculated using the trapezoidal rule.

Using Origin Version 6 (Microcal, Northampton, MA, USA), the relationship between the Stumvoll first-phase index and the IS_{OGTT} index of insulin sensitivity was approximated by the following rectangular hyperbolic function: $\text{Stumvoll first-phase index} = \text{constant}/IS_{OGTT}$. This relationship can be alternatively stated as $\text{Stumvoll first-phase index} \times IS_{OGTT} = \text{constant}$. To evaluate beta cell function in the context of ambient insulin resistance, an insulin secretion-sensitivity index (ISSI) was derived from the product of the Stumvoll first-phase index and IS_{OGTT} .

Statistical analyses All analyses were conducted using SAS Version 8.02 (SAS Institute, Cary, NC, USA). A p value of less than 0.05 was considered significant. Means and SDs or proportions were presented according to glucose tolerance group, and ANOVA and chi square tests were used to assess univariate differences between continuous and categorical variables respectively. The distributions of CRP, adiponectin, fasting insulin, HOMA-IR, IS_{OGTT} and all surrogate measures of insulin secretion were substantially skewed, and thus medians and interquartile ranges were presented for these variables (Table 1). In addition, the natural logarithmic transformations of CRP, adiponectin, fasting insulin, HOMA-IR, IS_{OGTT} and all surrogate measures of insulin secretion were used in univariate and multivariate analyses, with back-transformed results from multivariate analyses presented in tables and figures. Parity and smoking exposure were defined as indicated previously [22]. Univariate associations of adiponectin and CRP with ISSI were assessed by Spearman correlation analysis. Finally, multiple linear regression analysis was used to determine which factors were significantly and independently associated with variation in log ISSI. A forward selection approach was used, and the following independent variables were considered: age, ethnicity, pre-pregnancy BMI, previous GDM, family history of type 2 diabetes, adiponectin, CRP, IGT and GDM. The best-fit curves for ISSI in the entire dataset (Fig. 1), by glucose tolerance status (Fig. 2) and by adiponectin tertile (Fig. 3) were determined using Origin Version 6 (Microcal, Northampton, MA, USA).

Results

As described in an earlier report, there were no significant differences between the glycaemic tolerance groups in terms of age, weeks of gestation, pre-pregnancy BMI, weight gain during pregnancy, parity, smoking exposure, ethnicity or family history of type 2 diabetes or GDM (Table 1 and [22]). In the GDM group, 18.8% of subjects had a previous history of GDM or delivery of a macrosomic infant, compared with 10.3% of IGT subjects and 4.3% of NGT subjects (overall $p=0.0206$). CRP concentration was not significantly different across the three glycaemic tolerance strata, while median adiponectin concentration was highest in the NGT group (16.2 $\mu\text{g/ml}$), followed by

Table 1 Demographic and metabolic characteristics of study subjects

Characteristic	NGT (<i>n</i> =93)	IGT (<i>n</i> =39)	GDM (<i>n</i> =48)	<i>p</i> value
Age (years)	33.2 (4.5)	32.8 (4.7)	34.0 (4.3)	0.3980
Gestational age (weeks)	29.2 (2.7)	29.7 (1.9)	29.1 (2.2)	0.4268
Pre-pregnancy BMI (kg/m ²)	23.9 (4.5)	24.1 (4.2)	24.7 (5.1)	0.5977
CRP (mg/l)	5.2 (2.1–9.2)	4.4 (3.0–8.4)	5.5 (2.2–8.7)	0.7626
Adiponectin (µg/ml)	16.2 (12.4–19.3)	15.3 (11.7–19.8)	12.3 (7.9–16.6)	0.0004
Insulin sensitivity				
IS _{OGTT}	5.1 (3.6–7.2)	4.2 (3.0–5.7)	3.5 (2.3–4.2)	<0.0001
QUICKI	0.183 (0.017)	0.180 (0.019)	0.171 (0.016)	0.0006
Insulin resistance				
HOMA-IR	1.6 (1.1–2.3)	1.7 (1.3–2.5)	2.1 (1.6–3.3)	0.0002
Fasting insulin (pmol/l)	58.0 (39.5–77)	63.0 (47–81)	74.0 (53.5–104)	0.0036
Insulin secretion				
Stumvoll first-phase	1,288.3 (1,048.7–1,605.3)	1,200.6 (862.6–1,472.7)	1,161 (843.0–1,587.2)	0.0154
Stumvoll second-phase	339.8 (281.6–420.7)	324.9 (241.6–393.4)	310.5 (239.2–421.5)	0.0590
HOMA-B	180 (133.8–267.9)	172.8 (116.3–218.7)	154.6 (116.1–224.8)	0.2736

Age, gestational age, pre-pregnancy BMI and QUICKI are presented as mean followed by SD in parentheses. All other parameters are presented as median followed by interquartile range in parentheses. *p* values refer to overall differences across groups as derived from ANOVA.

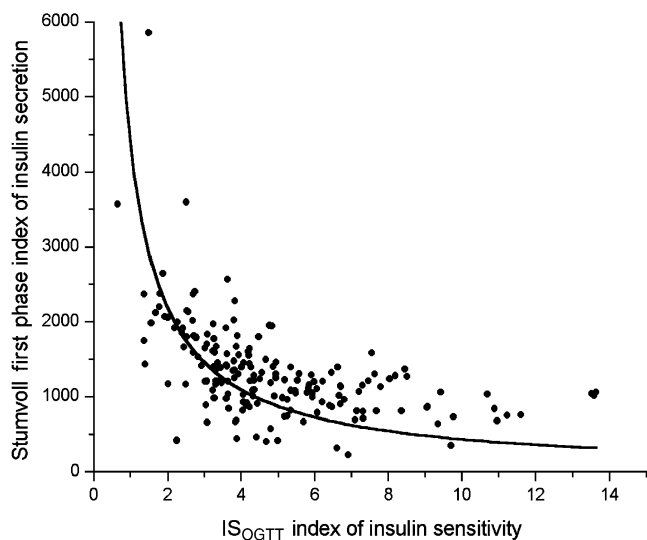


Fig. 1 Plot of Stumvoll first-phase index of insulin secretion vs IS_{OGTT} index of insulin sensitivity

that in the IGT group (15.3 µg/ml) and then that in the GDM group (12.3 µg/ml) (overall *p*=0.0004).

Metabolic characteristics pertaining to insulin sensitivity and secretion for the three glycaemic tolerance groups are presented in Table 1. Both measures of insulin sensitivity, IS_{OGTT} and QUICKI, showed the greatest insulin sensitivity in the NGT group, followed by that in the IGT group and then that in the GDM group (overall *p*<0.0001 and *p*=0.0006, respectively). Consistent with these observations, both measures of insulin resistance, HOMA-IR and fasting insulin, demonstrated that the GDM subjects had the highest insulin resistance, followed by the IGT patients and then the NGT subjects (overall *p*=0.0002 and *p*=0.0036, respectively).

Among measures of insulin secretion, the mean unadjusted Stumvoll first-phase index was highest in the NGT group (1,413.3), followed by that in the IGT group (1,255.1) and then that in the GDM group (1,218.2) (overall *p*=0.0154). The Stumvoll second-phase measure showed a similar pattern, though at borderline significance (overall *p*=0.0590). HOMA-B was not significantly different between the three groups.

Plotting the Stumvoll first-phase index vs IS_{OGTT} revealed the expected hyperbolic relationship between a measure of insulin secretion (Stumvoll first-phase) and a measure of insulin sensitivity (IS_{OGTT}) (Fig. 1). Thus, to evaluate beta cell function in the context of ambient insulin sensitivity, ISSI was derived from the product of the Stumvoll first-phase index and the IS_{OGTT}. When stratified according to glucose tolerance status, the ISSI hyperbolae showed a progressive shift towards the origin from NGT to IGT to GDM, indicative of poorer beta cell function with worsening glucose tolerance (Fig. 2). This pattern was further reflected in the trend of decreasing mean ISSI score from NGT (6731) to IGT (4976) to GDM (3300) (overall *p*<0.0001).

In univariate Spearman correlation analysis, ISSI was significantly correlated with adiponectin concentration (*r*=0.34, *p*<0.0001) and inversely related to CRP concentration (*r*=−0.17, *p*=0.022). When stratified according to tertile of adiponectin concentration, the ISSI hyperbolae displayed a progressive shift towards the origin associated with decreasing adiponectin tertile (trend *p*<0.0001), consistent with an association between declining beta cell function and reduced adiponectin concentration (Fig. 3).

To identify independent determinants of beta cell function, forward stepwise multiple linear regression analysis was performed with logarithmically transformed ISSI as the dependent variable. ISSI was negatively correlated with GDM, IGT and CRP, while adiponectin emerged as the sole

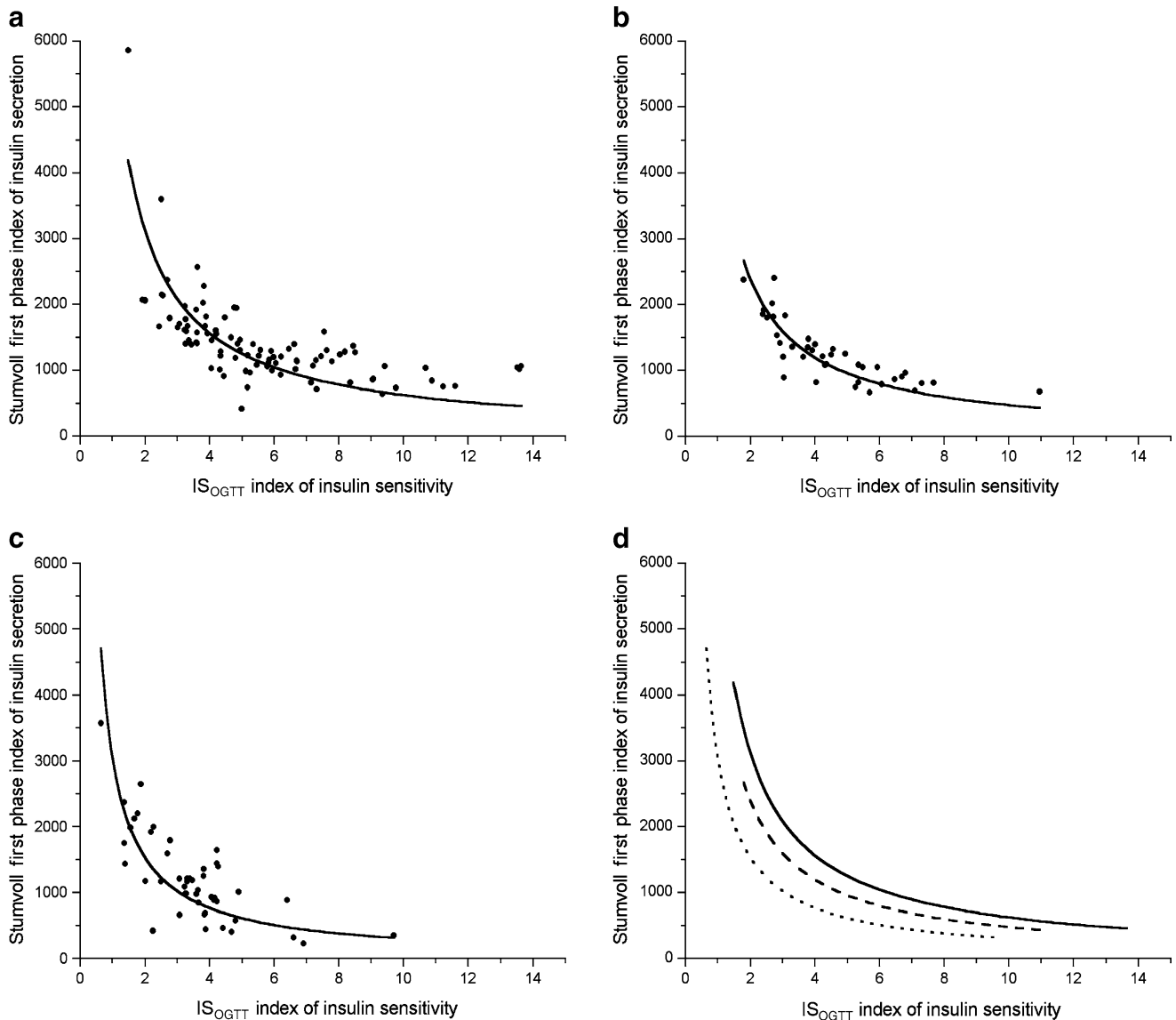


Fig. 2 Insulin secretion-sensitivity index (ISSI) curves according to glucose tolerance status. **a** NGT; **b** IGT; **c** GDM; and **d** composite graph showing all three curves (NGT, solid line; IGT, dashed line; GDM, dotted line) (trend $p < 0.0001$)

positive independent correlate of this index (Table 2). This model reconciled 54.01% of the variation in ISSI. Furthermore, adjustment for potential covariates, including age, ethnicity, pre-pregnancy BMI, previous GDM and family history of type 2 diabetes, did not significantly change the model, with GDM, IGT, CRP and adiponectin again emerging as independent predictors (data not shown).

The ratio of a measure of insulin secretion, the insulinogenic index, to a measure of insulin resistance (HOMA-IR) has previously been used to evaluate beta cell function [1, 32, 34]. The insulinogenic index (defined as the ratio of incremental change in insulin:incremental change in glucose over the first 30 min of an OGTT) is highly correlated to the ratio of the incremental area under the insulin curve (AUC_{ins}):incremental area under the glucose curve (AUC_{glu}) over the entire time course of the OGTT (S. E. Kahn, unpublished observation). Thus, the ratio of AUC_{ins}/AUC_{glu} :

HOMA-IR provides an alternate measure of beta cell function. As a measure of robustness of the findings reported here, multiple linear regression analysis was performed, using the logarithmic transformation of the ratio of AUC_{ins}/AUC_{glu} :HOMA-IR as the dependent variable. Consistent with the results of the ISSI multivariate analysis, adiponectin again emerged as an independent predictor variable (data not shown).

Discussion

In this study, we demonstrate that adiponectin concentration is an independent correlate of beta cell function in late pregnancy. Reduced adiponectin concentration is associated with beta cell dysfunction, as modelled by the insulin secretion-sensitivity index, a measure of beta cell respon-

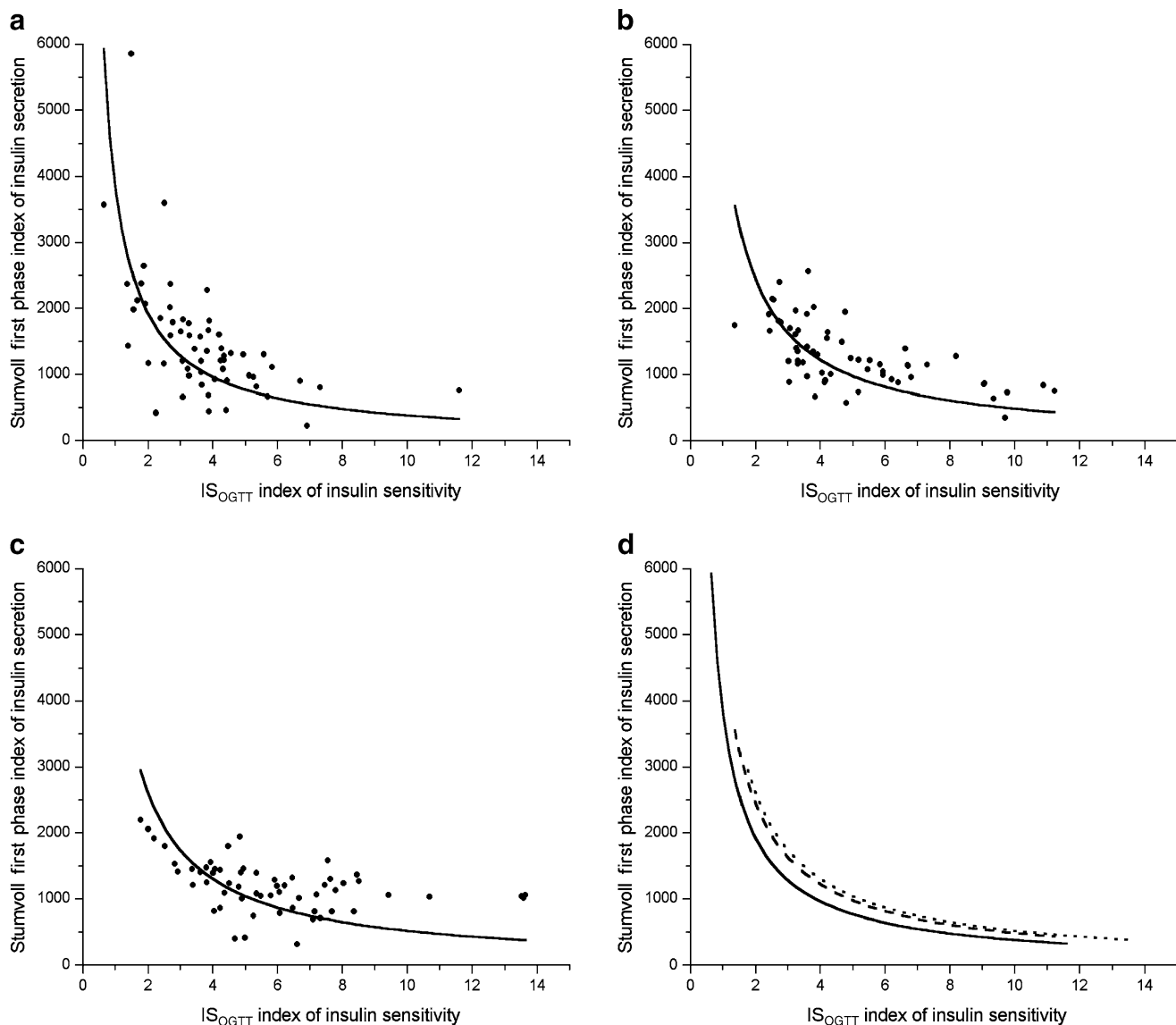


Fig. 3 Insulin secretion–sensitivity index (ISSI) curves according to adiponectin tertile. **a** Tertile 1 (4.1–12.3 µg/ml); **b** tertile 2 (12.4–17.0 µg/ml); **c** tertile 3 (17.2–39.4 µg/ml); and **d** composite graph

showing all three curves (tertile 1, *solid line*; tertile 2, *dashed line*; tertile 3, *dotted line*) (trend $p < 0.0001$)

siveness in the context of ambient insulin resistance. To date, hypoadiponectinaemia in both GDM and type 2 diabetes has been mainly characterised as a mediator of insulin resistance. The current study, however, raises the important possibility that adiponectin may be a factor link-

ing insulin resistance and beta cell dysfunction in the pathogenesis of diabetes.

The physiological feedback loop linking whole-body insulin sensitivity and beta cell responsiveness dictates that unbiased evaluation of beta cell function must take into account the impact of prevailing insulin sensitivity. Accordingly, the disposition index has been promoted as an important integrated measure of beta cell function in vivo. The disposition index is defined as the product of the acute insulin response to glucose (AIR_g) and the insulin sensitivity index (S_I), measures derived from the IVGTT [2, 3]. Given the requirement of the labour-intensive IVGTT, however, the disposition index has not been widely applicable to the clinical setting and has generally been reserved for small- to mid-sized research studies.

In the current study, ISSI was derived by applying the concept of the disposition index to measurements obtained

Table 2 Multiple linear regression analysis with dependent variable log insulin secretion–sensitivity index (log ISSI)

Variable	Parameter estimate	SE	F value	p value
GDM	-0.66006	0.05747	131.93	<0.0001
IGT	-0.31123	0.05917	27.66	<0.0001
Log adiponectin	0.19935	0.05835	11.67	0.0008
CRP	-0.01551	0.00480	10.44	0.0015

Model $r^2 = 0.5401$

during a standard OGTT. ISSI is defined as the product of the Stumvoll first-phase index of insulin secretion and the IS_{OGTT} index of insulin sensitivity. The Stumvoll first-phase model has been previously validated using the hyperglycaemic clamp technique [29]. Similarly, in validation studies in pregnant patients, the IS_{OGTT} index showed better correlation with insulin sensitivity derived using the euglycaemic–hyperinsulinaemic clamp technique than either the QUICKI or the HOMA-IR model [28]. Using these two validated indices, ISSI provides a simple and convenient approach for modelling beta cell function using the OGTT. Conceptually, the use of ISSI in this way is similar to the recent approach of evaluating beta cell function using the ratio of the insulinogenic index (a measure of insulin secretion):HOMA-IR [1, 32, 34]. Specifically, given the inverse relationship between insulin sensitivity and resistance, the product of a measure of insulin secretion and an index of insulin sensitivity (i.e. ISSI) would be expected to simulate the ratio of insulin secretion:insulin resistance. Furthermore, the use of ISSI to evaluate beta cell function is supported by the observed hyperbolic relationship between the Stumvoll first-phase index of insulin secretion and the IS_{OGTT} measure of insulin sensitivity. Finally, the biological validity of this approach is supported by the fact that, as shown in Fig. 2, ISSI can unmask the underlying differences in beta cell function associated with NGT, IGT and GDM, respectively, that were originally demonstrated using the disposition index. As such, we propose ISSI as a novel and convenient measure of beta cell function using the standard OGTT that may be useful both in a clinical setting and in large research studies. Further study in this regard is warranted.

In the current study, we have demonstrated an independent association between adiponectin concentration and ISSI. This finding is consistent with a previous report in which adiponectin and disposition index were studied concurrently. In a small longitudinal study of 13 obese women undergoing bariatric surgery, Guldstrand and colleagues demonstrated that adiponectin concentration is an independent determinant of the improvement in disposition index associated with significant weight reduction [35]. Although a recent study in post-partum women failed to detect an independent association between adiponectin and disposition index, the ability to address this question in that paper may have been undermined by the inclusion of both S_1 and disposition index as covariates in the multivariate analysis of adiponectin [36]. In a recent study of 49 adolescents, Bacha et al. demonstrated that adiponectin is an independent predictor of the proinsulin:insulin ratio, a marker of beta cell dysfunction [37]. The present study thus extends this intriguing association between adiponectin and beta cell function to a much larger patient population across different strata of glucose tolerance during pregnancy.

Previous studies have clearly established an association between hypoadiponectinaemia and insulin resistance in both GDM and type 2 diabetes [10, 22]. In this context, the current findings now raise the hypothesis that reduced adiponectin concentration may contribute to both insulin resistance and beta cell dysfunction in the pathogenesis of

type 2 diabetes. This idea is consistent with the findings of Yamauchi et al. in studies of transgenic mice overexpressing globular adiponectin in a leptin-deficient *ob/ob* background [38]. Interestingly, globular adiponectin overexpression afforded diabetes-prone *ob/ob* mice protection from diabetes that was accompanied by enhanced insulin sensitivity and (unexpectedly) increased insulin secretion, suggestive of improved beta cell function. It was thus speculated that adiponectin may have direct protective effects on beta cells. Indeed, the recent demonstration of marked expression of mRNA species encoding the adiponectin receptors AdipoR1 and AdipoR2 in human and rat beta cells lends further support to this idea [39]. Winzell et al. have suggested a dual action of adiponectin on insulin secretion in insulin-resistant mice [40]. In addition, recent preliminary findings suggest that, in vitro, adiponectin can increase insulin secretion through stimulation of insulin secretory granules in beta cells [41]. Taken together, these data support the possibility that adiponectin may have direct effects on beta cell function.

Although the molecular mechanisms by which adiponectin may exert protective or stimulatory effects on beta cell function are not clear, several potential models may be considered. One potential mechanism could involve the pro-inflammatory cytokine TNF- α , which has emerged as a potential mediator of beta cell dysfunction, possibly via disrupted insulin signalling or overproduction of the cytotoxic free radical nitric oxide [7, 42]. Since adiponectin appears to attenuate the effects of TNF- α in both adipose tissue and endothelium [8], adiponectin-mediated antagonism of TNF- α in islet cells may be a mechanism for beta cell protection. Secondly, considering the lipotoxicity theory for beta cell dysfunction, adiponectin may protect beta cells from ectopic fat deposition, as it has previously been shown to reduce intracellular lipid deposition in other tissues such as skeletal muscle [43]. Indeed, treatment with the globular domain of adiponectin has recently been shown to partially protect cultured beta cells from the deleterious effects of fatty acids, including insulin secretory dysfunction and apoptosis [44]. Finally, a third, less likely possibility involves insulin resistance at the level of the pancreas, which has been proposed as a potential factor in the development of beta cell dysfunction [45]. Given its insulin-sensitising effects on peripheral tissues such as muscle and liver, adiponectin could conceivably ameliorate insulin resistance in beta cells as well, leading to improved secretory function.

We recognise that the cross-sectional nature of this study precludes comment on causality in the association between adiponectin concentration and beta cell function. Indeed, chronic insulin resistance has been proposed as a potential cause of the beta cell defect in women with GDM [20]. In the context of this hypothesis, then, the association between hypoadiponectinaemia and beta cell dysfunction in our study may be a reflection of chronic insulin resistance. As such, despite supportive evidence suggesting that adiponectin may have direct effects on beta cells, we cannot exclude the possibility that the current observations reflect an indirect relationship mediated by chronic insulin resistance. Clearly, further study is warranted to address the physio-

logical basis underlying the observed association between adiponectin concentration and beta cell function.

A second potential limitation to consider is the possibility that auto-correlation between our measures of insulin secretion (e.g. Stumvoll first-phase index) and insulin sensitivity (e.g. IS_{OGTT}) may confound interpretation of their apparent hyperbolic relationship. However, if auto-correlation were underlying this relationship, one would not expect subjects with the same insulin sensitivity to exhibit different insulin secretion responses. In the current dataset, however, subjects with the same insulin sensitivity do indeed exhibit very different insulin secretion responses (e.g. depending on glucose tolerance status), as evidenced by the separate ISSI curves by glucose tolerance status shown in Fig. 2. This finding supports the contention that the hyperbolic relationship between the Stumvoll first-phase index and the IS_{OGTT} is not a spurious association on the basis of auto-correlation between the component measures and does indeed provide a measure of beta cell function.

In conclusion, we have introduced ISSI as a novel measure of beta cell function that can be derived from the standard OGTT and, using this index, have demonstrated that adiponectin concentration is an independent correlate of beta cell function in late pregnancy. Hypoadiponectinaemia is thus associated with both insulin resistance and beta cell dysfunction in GDM. As such, adiponectin emerges as an important factor potentially linking insulin resistance and beta cell dysfunction in the pathogenesis of type 2 diabetes.

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