Originals

Decreased stature in gestational diabetes mellitus

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Summary Short stature has been associated with various degrees of abnormal glucose tolerance in middle-aged people, where the effects of age and metabolic control would be difficult to exclude. We chose to examine body stature in women with gestational diabetes mellitus (GDM), a prediabetic state affecting a young group of people. A sample of 2772 Greek pregnant women, referred for GDM screening was examined. After a 100-g oral glucose tolerance test, 1787 women were classified as normal (N), 300 women were found with one abnormal glucose value (OAV) and 685 women with GDM. Basal insulin resistance was calculated in 640 women by homeostasis model assessment. In addition, 51 pregnant women with pre-existing Type II (non-insulin-dependent) diabetes mellitus and 109 with pre-existing Type I (insulin-dependent) diabetes mellitus were included in the study. There was a gradual decrease in mean height (cm) as glucose intolerance became more severe: N: 161.0 ± 6.2 , OAV: 160.2 ± 6.1 , GDM: $158.7 \pm$

6.3 , Type II diabetes 158.2 ± 7.0 ($p < 0.001$, analysis of variance]. Height in Type I diabetes (160.1 ± 5.9) did not differ from the normal group. The difference in height between the normal and GDM groups remained ($p < 0.001$) when body weight, age, birth before or after 1960 and educational status were also taken into account. An independent correlation was also found between height and insulin resistance ($n = 640$) adjusted for the above mentioned variables. In conclusion, short stature appears to be associated with glucose intolerance as an independent variable, even when this intolerance is both mild and temporary. The previously unrecognised independent association of stature with basal insulin resistance merits further investigation. [Diabetologia (1998) 41: 997–1001]

Keywords Diabetes, gestational, stature, insulin resistance, body mass index, socio-economic factors.

Adult height is determined by genetic and acquired factors. It has been reported that middle-aged patients with impaired glucose tolerance or Type II (non-insulin-dependent) diabetes mellitus are short compared with normal control subjects [1, 2]. In mid-

dle-aged diabetic patients it is, however, difficult to exclude the effect of ageing and long standing metabolic effects on height.

There is a lot of evidence that Type II diabetes and gestational diabetes mellitus (GDM) are both manifestations of the same pathophysiological process, which includes insulin resistance and impaired beta-cell function [3, 4]. Gestational diabetes mellitus is a heterogeneous disorder; it is characterised by hyperglycaemia or glucose intolerance with onset or first recognition during pregnancy. This is usually temporary and affects a younger group of people who have completed their skeletal growth and have not yet suffered age-related bone loss [5]. We considered that pregnant women with various degrees of glucose

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Abbreviations: GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; OAV, one abnormal value; HOMA, homeostasis model assessment; N, normal; LSD, least significant difference test.

Table 1. Anthropometric characteristics of the study groups

Groups	N	Age (years)	Prepregnancy weight (kg)	BMI (kg/m ²)	Height (cm)
N	1787	29.5 ± 5.6	64.2 ± 12.2	24.8 ± 4.5	161.0 ± 6.2
OAV	300	31.3 ± 5.5 ^a	66.5 ± 13.3 ^a	25.9 ± 4.8 ^a	160.2 ± 6.1 ^a
GDM	685	33.1 ± 5.5 ^a	68.7 ± 14.7 ^a	27.3 ± 5.7 ^a	158.7 ± 6.3 ^a
Type II	51	34.6 ± 6.0	78.7 ± 20.8 ^a	31.3 ± 7.5 ^a	158.2 ± 7.0
Type I	109	28 ± 5.4 ^b	62.7 ± 8.9	24.5 ± 3.4	160.1 ± 5.9

^a significance of difference from the preceding group ($p < 0.05$, LSD test).

^b significance of difference from normal ($p < 0.05$)

Data are expressed as means ± SD

intolerance (i.e. one abnormal value in the oral glucose tolerance test (OGTT), GDM or Type II diabetes), reflecting different degrees of insulin resistance or impaired insulin secretion or both would be a suitable model to evaluate possible differences in height compared with normal pregnant women. In addition, a group of pregnant women with pre-existing Type I diabetes (insulin-dependent) mellitus with long standing disturbances of glucose metabolism were included in the study.

Subjects and methods

This study was conducted on 2772 consecutive women who were referred to the Diabetes Centre of the Alexandra General Hospital of the University of Athens for screening for GDM during the years 1990 to 1996.

We included only women of Greek ethnic origin, born and brought up in Greece who were otherwise healthy. All women lived in the Athens metropolitan area, whose residents originate from all parts of the country. Exposure to sunshine is uniform in all parts of Greece (cloudiness range across the country 2.60–4.12 octas); therefore, vitamin D deficiency is not relevant for this age group in Greece. Age, height, educational status and pre-pregnancy weight were recorded for each pregnant woman; from these variables pre-pregnancy BMI was calculated. Height and weight were measured always in the morning by two experienced outpatient nurses using a portable stadiometer and weight scale (SECA, model 713 Hamburg, Germany) to the nearest centimetre.

On the same day a standard 100-g Oral Glucose Tolerance Test (OGTT) was performed at gestational age of 24–32 weeks. When more than one OGTTs were performed, the latest one was included in the analysis. HbA_{1c} measurements were used to identify women with pre-existing but unrecognised diabetes mellitus. Using the National Diabetes Data Group criteria [6] 1787 women were classified as normal (N), 300 women were found with one abnormal glucose value (OAV) and 685 women with GDM. Women who were first recognised as having Type I diabetes during pregnancy were excluded from the GDM group for the analysis. A further 51 pregnant women with pre-existing Type II diabetes and 109 with Type I diabetes were examined during the same period. During the OGTT insulin concentration was measured in 417 normal women, in 130 GDM and in 93 OAV women. All three subgroups were representative of their larger groups in respect of age, pre-pregnancy weight and height.

Plasma glucose concentration was measured with an auto-analyser using the hexokinase method. Serum insulin immu-

noreactivity was measured by ELISA (Boehringer Mannheim, Germany); the intra-assay and inter-assay coefficients of variation were 7.8% and 6.4%, respectively at 600 pmol/l; this method has a 40% cross-reactivity with human proinsulin. To evaluate basal insulin resistance and beta-cell function, we used the homeostasis model assessment (HOMA) [7] applying the following formulas: insulin resistance = $FI \times G/22.5$ and beta-cell function (%) = $20 \times FI/(G-3.5)$, where FI = fasting insulin (μU/ml) and G = fasting glucose (mmol/l).

Statistical analysis. Statistical analysis was performed using the *t* test when only two groups were compared and the analysis of variance test for comparison of more than two groups; the least significant difference test (LSD) was used to determine significant differences between any two of the groups. Multiple linear regression model was used to adjust for the effects of confounders and the 'B' value (which is the average change in the dependent variable when the corresponding independent variable increases by one unit and all the other independent variables remain constant) for variables.

Results

The mean values of the anthropometric characteristics of the various study groups are shown in Table 1. As expected, there was a gradual increase in mean age, mean pre-pregnancy weight and BMI in the OAV, GDM and Type II groups when compared to the normal group (analysis of variance, $p < 0.001$). On the other hand the Type I group was younger and did not differ from the normal group in pre-pregnancy weight and BMI.

The mean height of normal pregnant women was 161.0 ± 6.2 cm. The GDM and Type II groups were shorter than the normal group (N) and the OAV group had an intermediate mean height. The Type I group did not differ in height from the normal group (Table 1).

We further examined age, weight and socio-economic factors as possible confounding variables affecting height. There was no correlation between age and height in all the groups examined ($r = -0.1$). To exclude the effect of weight on height, we analysed the data separately for weight subgroups (Table 2). The differences remained even in the lean individuals.

Table 2. Mean height in the different weight subgroups

Body weight subgroup	40–59.9 kg	60–74.9 kg	> 75 kg
Height of Normal group (cm, X $\pm$ SD)	158.5 $\pm$ 5.4 (<i>n</i> = 690)	162.2 $\pm$ 5.9 (<i>n</i> = 806)	163.4 $\pm$ 6.6 (<i>n</i> = 291)
Height of GDM group (cm, X $\pm$ SD)	155.2 $\pm$ 0.71 (<i>n</i> = 57)	159.5 $\pm$ 6.2 (<i>n</i> = 274)	160.3 $\pm$ 5.9 (<i>n</i> = 213)
<i>p</i> value	< 0.001	< 0.001	< 0.001

Educational status, a reliable marker of socio-economic milieu, was considered separately for those who attended school for less than 12 years and those with higher education. Women with little education were indeed shorter compared with those with higher education ($p < 0.001$); however, the height differences between GDM and N groups remained: Group less than 12 years: N (*n* = 1054): 160.4 $\pm$ 6.3 compared with GDM (*n* = 403): 158.0 $\pm$ 6.5 cm, ($p < 0.001$) and group more than 12 years: N (*n* = 733): 161.8 $\pm$ 5.9 compared with GDM (*n* = 282): 159.6 $\pm$ 5.9 cm, ($p < 0.001$). Furthermore, to screen for a possible cohort effect, we analysed our data according to the date of birth separately for those born before and those born after the year 1960; birthdate 1945–1960: N group (*n* = 462) 160.1 $\pm$ 6.3 compared with GDM (*n* = 315) 158.1 $\pm$ 6.3 cm ($p < 0.001$); date of birth 1960–1980: N group (*n* = 1325) 161.3 $\pm$ 6.1 compared with GDM (*n* = 370) 159.2 $\pm$ 6.2 cm ($p < 0.001$). The difference in height between the GDM and the normal group remained in both periods, despite the fact that mean height was shorter in all women born before 1960 compared with those born after that date ($p < 0.001$).

When we included the above mentioned variables that influence the final height in the same regression model (Table 3), we found that GDM was the most important independent variable: a woman with gestational diabetes is predicted (**B**) to be 2.5 cm shorter compared with a woman with normal glucose tolerance.

In the group of 640 women, in whom insulin levels were also available, GDM women had significantly

higher basal insulin resistance matched for gestational age than normal pregnant women and the OAV group values were in between. In addition, beta-cell function (HOMA model) was decreased in GDM and OAV compared with normal women (Table 4). Furthermore, an inverse correlation was found between height and insulin resistance independently of age, weight and educational status (Table 5).

Discussion

As the Alexandra General Hospital is a referral centre for high-risk pregnancies for the whole Athens metropolitan area, we had the opportunity to study a large number of women with impaired glucose tolerance; in our series the per cent of GDM was 24.7 % and OAV was 10.8 %.

Our epidemiological data showed a short stature in young women with various degrees of glucose intolerance, who should be unaffected by osteoporosis. The mean height found in our normal group is identical to the mean height of adult women reported previously for the Greek population [8]. Interestingly, the gradual decrease in height paralleled the impairment of glucose tolerance, normal women being at one end and GDM and Type II women at the other. It can, therefore, be suggested that these two related disorders (GDM and Type II) also share another phenotypic feature, a slightly shorter than expected stature. Furthermore, the more insulin resistant GDM subjects had the greater decrease in adult height, resembling the Type II group. Our results thus agree with previous reports concerning Type II [1, 2]. It could be speculated that the subset of GDM who will eventually develop permanent Type II are found among those whose stature is shorter than expected.

Obesity is another important factor associated with the degree of glucose intolerance. However, shorter stature was found in lean as well as in obese women with GDM. It is to be noted that the mean height in the Type I group which has a totally different pathogenetic mechanism was not different from

Table 3. Association of height and glucose intolerance adjusting for age, weight and socio-economic status: results from multiple linear regression model

Variables	Partial Regression coefficients		statistical significance ^a <i>p</i>	95 % confidence intervals for B	
	B	Std Error		Lower Bound	Upper Bound
(constant)	151.97	0.83		150.34	153.59
OAV	−0.87	0.37	< 0.02	−1.59	−0.15
GDM	−2.52	0.27	< 10 ^{−4}	−3.06	−1.98
Age	−0.12	0.02	< 10 ^{−4}	−0.16	−0.08
Weight	−0.15	0.01	< 10 ^{−4}	0.13	0.17
Education	1.96	0.23	< 10 ^{−4}	1.51	2.42

^a two-tail

The “B” value denotes the average change in the dependent variable when the corresponding independent variable increases by one unit and all the other independent variables remain constant

Table 4. Insulin concentrations measured during the OGTT and insulin resistance and beta-cell function calculated using the HOMA model

	Normal group <i>n</i> = 417	OAV group <i>n</i> = 93	GDM group (<i>n</i> = 130)
Fasting insulin (pmol/l)	90 ± 42	96 ± 42 ^a	108 ± 54 ^{ab}
Insulin 60 (pmol/l)	546 ± 300	606 ± 234	564 ± 288
Insulin 120 (pmol/l)	498 ± 306	696 ± 354 ^b	816 ± 390 ^{ab}
Insulin 180 (pmol/l)	366 ± 264	486 ± 300 ^b	624 ± 354 ^{ab}
Insulin Resistance (x ± SE)	2.98 ± 0.7	3.63 ± 1.8 ^{ab}	4.18 ± 0.22 ^{ab}
% beta-cell function (x ± SE)	3.4 ± 0.18	2.65 ± 1.3 ^a	2.3 ± 0.12 ^b

^a significant difference from previous group ($p < 0.05$, LSD test)

^b significant difference from normal group ($p < 0.01$, LSD test)

Table 5. Multiple linear regression of height as dependent variable with IR (HOMA model), age, weight and socio-economic status

Variables	Partial Regression coefficients		statistical significance ^a <i>p</i>	95 % confidence intervals for B	
	B	Std Error		Lower Bound	Upper Bound
(constant)	154.25	1.74		150.84	157.66
IR	-0.49	0.13	< 10 ⁻⁴	-0.76	-0.23
Age	0.16	0.02	< 10 ⁻⁴	0.12	0.19
Weight	-0.17	0.04	< 10 ⁻⁴	-0.26	-0.09
Education	1.27	0.24	< 10 ⁻⁴	0.81	1.7

^a two-tail

that of the normal group, as has already been reported [9].

Height is mainly determined by genetic and hormonal factors; however, socio-economic factors may also influence adult height. Up to the late 50s socio-economic conditions in Greece were influenced by the aftermath of the war and civil war, while after 1960 the standard of living greatly improved [10]. Thus, we were able to analyse for a possible cohort effect. Both whether birth was before or after 1960 as well as the educational status were found to influence the final height, however the difference between GDM and the normal group remained.

A few studies have examined the association between height and established glucose intolerance [1, 2, 11–15]. These data taken together with our results suggest that, at least in females in various ethnic groups, there is a negative association between height and glucose tolerance. Interestingly, this association is already obvious in a prediabetic state such as gestational diabetes mellitus. We cannot draw any conclusions as to the pathophysiological mechanisms responsible for this difference in height. However, it is interesting that according to our results insulin resis-

tance is an independent predictor of height in these women, a finding not reported previously. As it is known that insulin is important for normal growth, both directly and indirectly through its effect on the GH/IGF1 axis [16], it can be speculated that impairment in insulin secretion or action or both before the completion of puberty could have a detrimental influence on adult height. Another possible mechanism could be reduced fetal growth which has been reported to be associated with insulin resistance as well as with GDM and the future development of Type II diabetes [17–19]. Unfortunately this information was not available in our study. Finally, it is possible that the gene(s) which define height are associated with certain of the – so far elusive – genes which confer susceptibility to glucose intolerance.

It seems that height has so far been overlooked as an independent variable in epidemiological studies dealing with various forms of glucose intolerance. This was either because interest was focused on obesity, where BMI was normally used, or because height was taken only as an index of socio-economic status. Further studies are needed to investigate the mechanisms through which decreased final stature is associated with glucose intolerance or insulin resistance or both.

We conclude that short stature is associated with various degrees of abnormal glucose tolerance in pregnant women. We found a significant gradual decrease in mean height as glucose intolerance and insulin resistance became more severe. This relationship was independent of obesity, age and socio-economic factors. Furthermore, we showed an independent relationship between height and basal insulin resistance, a previously unrecognised finding, which needs to be elucidated. Finally, it could be argued that Type II and GDM share another phenotypic feature, decreased stature, which provides further evidence that they are both part of the same broader disorder.

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References

1. Brown DC, Byrne CD, Clark PMS et al. (1991) Height and glucose tolerance in adult subjects. *Diabetologia* 34: 531–533
2. Williams DRR, Wareham NJ, Brown DC et al. (1995) Undiagnosed Glucose Intolerance in the Community: the Isle of Ely Diabetes Project. *Diabet Med* 12: 30–35
3. Pendegross M, Fazoni E, DeFronzo R (1995) NIDDM and GDM: same disease, another name? *Diabetes Rev* 3: 566–583
4. Buchanan T, Catalano P (1995) The pathogenesis of GDM: implication for diabetes after pregnancy. *Diabetes Rev* 3: 584–601

5. Compston JE (1990) Osteoporosis. *Clin Endocrinol (Oxf)* 33: 653–682
6. National Diabetes Data Group (1979) Classification and diagnosis of diabetes and other categories of glucose intolerance. *Diabetes* 18: 1039–1057
7. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC (1985) Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28: 412–419
8. Alevizaki CC, Velentzas Ch, Ikkos DG et al. (1982) Height and weight of healthy Greek children aged 5–18 years. *Materna Medica Greca* 10 (4):371–383
9. Holl RW, Heinze E, Seifert M, Grabert M, Teller WM (1994) Longitudinal analysis of somatic development in paediatric patients with IDDM: genetic influences on height and weight. *Diabetologia* 37: 925–929
10. Drakatos KC (1997) The grand cycle of the Greek economy 1945–1995. Papazisis Publications, Athens
11. Quatrato A, Minei A, De Rosa N, Giugliano D (1992) Height and glucose tolerance. *Diabetologia* 35: 698 (Letter)
12. Ohlson LO, Larsson B, Eriksson H, Svärdsudd K, Welin L, Tibblin G (1987) Diabetes mellitus in Swedish middle-aged men; the study of men born in 1913 and 1923. *Diabetologia* 30: 386–393
13. McKeigue PM (1991) Impaired glucose tolerance and height. *BMJ* 303: 365 (Letter)
14. Swai AB, Kitange HM, Masuki G, Kilima PM, Alberti KG MM, McLarty DG (1992) Is diabetes mellitus related to undernutrition in rural Tanzania? *BMJ* 305: 1057–1062
15. Jang H, Cho N, Jung H, Han I, Min H, Metzger B (1995) Short stature in Korean Women: a contribution to the multifactorial predisposition to gestational diabetes mellitus (GDM). *Diabetes* 44: 94A (Abstract)
16. Menon RK, Sperling MA (1996) Insulin as a growth factor. *Endocrinol Metab Clin North Am* 25: 633–647
17. Phillips, DIW, Barker DJP, Hales CN, Hirst, S, Osmond C (1994) Thinness at birth and insulin resistance in adult life. *Diabetologia* 37: 150–154
18. Olah KS (1996) Low maternal birth weight – An association with impaired glucose tolerance in pregnancy. *J Obstet Gynecol Neonatal Nurs* 16: 5–8
19. Hales CN, Barker DJP, Clark PMS et al. (1991) Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ* 303: 1019–1022