Does zygosity influence the metabolic profile of twins? A population based cross sectional study

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Abstract

Objective To study the influence of zygosity on the metabolic variables involved in the pathophysiology of type 2 diabetes.
Design Population based cross sectional study.
Setting Odense University Hospital, Denmark.
Participants 125 monozygotic twin pairs and 178 dizygotic twin pairs of the same sex born between 1921 and 1940.
Main outcome measures Clinical characteristics of monozygotic and dizygotic twins with or without a family history of type 2 diabetes.
Results Absolute prevalences of type 2 diabetes and impaired glucose tolerance according to the World Health Organisation criteria were similar in both the monozygotic and the dizygotic twins as were measurements of height, weight, body mass index, waist to hip ratio, and fasting plasma glucose and insulin concentrations. During the oral glucose tolerance test, monozygotic twins had a higher incremental plasma insulin area under the curve than dizygotic twins (10.05 (SD 0.68) *v* 9.89 (0.72) pmol/l×minutes, $P < 0.01$) indicating insulin resistance. In twins with normal glucose tolerance and without first degree relatives or co-twins with type 2 diabetes or impaired glucose tolerance, both the glucose and insulin areas under the curve were higher among monozygotic twins (glucose 214.4 (88.3) *v* 189.8 (78.4) mmol/l×minutes, $P < 0.05$; insulin 20 040 (14 865-32 554) *v* 17 625 (12 330-23 640) pmol/l×minutes, $P = 0.08$).
Conclusion Zygosity influences both plasma glucose and plasma insulin concentrations during an oral glucose tolerance test. This supports an intrauterine influence on glucose homeostasis and perhaps on insulin resistance in humans.

Introduction

Several epidemiological and metabolic studies have shown a strong association between low birth weight and the development of type 2 diabetes later in life.[1–4] Our finding of lower birth weights among monozygotic twins with type 2 diabetes compared with their genetically identical non-diabetic co-twins eliminates the possibility that the association is solely due to a putative genotype susceptibility to type 2 diabetes and a genetically determined low birth weight.[4–6] The association between type 2 diabetes and low birth weight may be due to an adverse intrauterine environment—for example, intrauterine malnutrition.

Intrauterine malnutrition is more likely to occur in twins because they share their uterine environment, and therefore they have lower birth weights than singletons.[7] Around two thirds of monozygotic twins are monochorionic—that is, they share a placenta. The sharing of the same nutritive source, and the development of vascular anastamoses between monochorionic twins, results in a different and possibly more adverse environment than that of dichorionic monozygotic and dizygotic twins—that is, twins having separate placentas.[7 8] According to the "thrifty phenotype hypothesis," sharing a placenta may influence metabolic variables permanently.[9] Monozygotic twins may therefore exhibit various metabolic abnormalities and have different prevalences of disease than dizygotic twins. The validity of twin studies investigating a possible genetic cause of a phenotype for which intrauterine factors are known has therefore been questioned.[10]

Participants and methods

Participants

We identified twins through the Danish twin register.[4 11–13] In November 1994, we sent a postal questionnaire to monozygotic twin pairs and dizygotic twin pairs of the same sex, who were alive according to the records of the civil registry. We included 3074 monozygotic and dizygotic twins (1537 pairs) born in Funen county, Denmark between 1931 and 1940 (aged 55 to 64 years) or born anywhere in Denmark between 1921 and 1930 (aged 65 to 74 years).

We asked the twins whether they had diabetes and, if so, we requested information on age at onset of the disease, use of insulin, and duration of insulin use. We asked each twin whether they were willing to participate in a study of diabetes using a standard oral glucose tolerance test and measurement of anthropometric factors.

Overall, 975 twin pairs responded to the questionnaire of which 303 twin pairs (31.1%) participated in the clinical examination; these were similar for age and self reported prevalence of diabetes to the group of twins who were not clinically examined.[13] We established zygosity with the similarity method by asking the twins about physical similarities and mistaken identity.[11 14] This method has been evaluated by comparison with serological zygosity testing, and it has a misclassification rate of less than 5%.[11] Overall, 125 twin pairs were monozygotic and 178 twin pairs were dizygotic.

Our study was approved by the regional ethics committees, and it was conducted according to the principles of the Helsinki Declaration.

Methods

The participants underwent a standardised oral glucose tolerance test with 75 g of glucose after an overnight fast for 10-12 hours. We took a sample of peripheral venous blood before the participants ingested the glucose then 30 minutes and 2 hours later. We analysed plasma glucose concentrations by the glucose dehydrogenase oxidation method, and we measured plasma insulin concentrations using a two site, two step, time resolved immunofluorimetric assay (DELFIA) as previously described.[15] We calculated

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incremental glucose and insulin areas under the curves with the trapezoidal method. Cross reactivities with proinsulin, C peptide, and Des(31,32)-split product in the insulin assay were all less than 0.4%. In the physiological ranges for plasma insulin, the intra-assay coefficients of variation were 3.6%-4.3% and the interassay coefficients of variation were 1.7%-3.4%. Waist circumference was measured midway between the lowest rib and the iliac crest with a tape measure in standing participants. Hip circumference was measured over the widest part of the gluteal region, and the waist to hip ratio was calculated.

Table 1 Prevalence (95% confidence interval) of type 2 diabetes and glucose tolerance among 250 monozygotic and 356 dizygotic twins

Twins	Type 2 diabetes	Impaired glucose tolerance	Normal glucose tolerance
Monozygotic	14.4 (10.1 to 18.7)	18.8 (13.8 to 23.7)	66.6 (60.7 to 72.5)
Dizygotic	12.1 (8.8 to 15.4)	23.0 (18.7 to 27.3)	64.9 (60.0 to 69.8)
Total	13.1 (10.4 to 15.8)	21.3 (18.0 to 24.6)	65.7 (62.0 to 69.4)

Table 2 Clinical characteristics and plasma glucose and insulin concentrations from oral glucose tolerance test in monozygotic and dizygotic twins. Values are mean (SD) unless stated otherwise

Variable	Monozygotic twins (n=250)	Dizygotic twins (n=356)	Difference of mean (95% CI)	P value
No of males	124	172		
Age (years)	67.0 (4.7)	66.3 (5.1)	0.8 (–0.03 to 1.6)	0.06
Height (cm)	165.6 (9.6)	166.5 (9.1)	–0.9 (–2.4 to 0.6)	0.26
Weight (kg)	71.6 (14.0)	72.0 (13.5)	–0.3 (–2.6 to 1.9)	0.77
Body mass index (kg/m^2)	26.0 (4.4)	25.9 (4.3)	0.1 (–0.6 to 0.8)	0.72
Weight to hip ratio	0.88 (0.08)	0.87 (0.09)	0.009 (–0.006 to 0.02)	0.23
Plasma glucose concentration (mmol/l):				
0 minutes	6.1 (1.6)	6.1 (1.7)	0.04 (–0.23 to 0.31)	0.78
30 minutes	9.9 (2.4)	9.6 (2.7)	0.29 (–0.12 to 0.71)	0.17
120 minutes	8.0 (4.3)	7.8 (4.3)	0.19 (–0.51 to 0.89)	0.59
Area under curve*	309.9 (175.3)	289.4 (194.8)	20.5 (–9.85 to 50.8)	0.16
Log of plasma insulin concentration (pmol/l):				
0 minutes	3.70 (0.55)	3.65 (0.53)	0.05 (–0.04 to 0.14)	0.27
30 minutes	5.57 (0.68)	5.43 (0.66)	0.14 (0.03 to 0.25)	<0.05
120 minutes	5.44 (0.80)	5.34 (0.81)	0.10 (–0.03 to 0.23)	0.14
Area under curve*	10.05 (0.68)	9.89 (0.72)	0.16 (0.04 to 0.27)	<0.01

*Minutes × concentration.

Table 3 Clinical characteristics and plasma glucose and insulin concentrations from oral glucose tolerance test in monozygotic and dizygotic twins with normal glucose tolerance. Values are mean (SD) unless stated otherwise

Variable	Monozygotic twins (n=134)	Dizygotic twins (n=162)	Difference of mean (95% CI)	P value
No of males	68	74		
Age (years)	65.9 (4.8)	65.2 (5.3)	0.7 (–0.5 to 1.8)	0.26
Height (cm)	167.5 (9.5)	167.1 (8.7)	0.5 (–1.6 to 2.6)	0.66
Weight (kg)	71.0 (13.1)	70.3 (12.6)	0.7 (–2.3 to 3.6)	0.65
Body mass index (kg/m^2)	25.2 (3.9)	25.1 (3.4)	0.15 (–0.69 to 0.98)	0.73
Weight to hip ratio	0.87 (0.08)	0.85 (0.09)	0.02 (0.0006 to 0.04)	<0.05
Plasma glucose concentration (mmol/l):				
0 minutes	5.6 (0.5)	5.5 (0.5)	0.07 (–0.04 to 0.19)	0.21
30 minutes	9.1 (1.6)	8.5 (1.4)	0.61 (0.27 to 0.94)	<0.001
120 minutes	5.8 (1.1)	5.8 (1.0)	–0.04 (–0.28 to 0.20)	0.73
Area under curve*	213.7 (88.8)	186.9 (80.3)	26.8 (7.5 to 46.2)	<0.01
Log of plasma insulin concentration (pmol/l):				
0 minutes	3.57 (0.49)	3.50 (0.45)	0.07 (–0.04 to 0.18)	0.21
30 minutes	5.65 (0.66)	5.4 (0.57)	0.24 (0.10 to 0.39)	<0.001
120 minutes	5.09 (0.72)	5.13 (0.71)	–0.04 (–0.21 to 0.12)	0.59
Area under curve*	9.97 (0.63)	9.81 (0.56)	0.16 (0.02 to 0.30)	<0.05

*Minutes × concentration.

Type 2 diabetes was defined as diabetes diagnosed after the age of 40 years and current treatment with antidiabetic drugs or diet, or both, according to WHO criteria[16]; a fasting venous plasma glucose concentration ⩾7.8 mmol/l or a venous plasma glucose concentration of ⩾11.1 mmol/l 2 hours after loading, or both. Impaired glucose tolerance was defined as a fasting venous plasma glucose concentration less than 7.8 mmol/l and a venous plasma glucose concentration between 7.8 mmol/l and 11.1 mmol/l 2 hours after loading. Participants with neither type 2 diabetes nor impaired glucose tolerance were considered to have normal glucose tolerance.

Statistical analysis

To reduce skewness we performed logarithmic transformations on the insulin data. The transformations yielded approximately normal distributions. We compared monozygotic and dizygotic twins by parametric analysis (t test) for unpaired data. All tests were two tailed, and $P \leqslant 0.05$ was considered significant.

Results

The prevalence of both type 2 diabetes and impaired glucose tolerance was similar in the 250 monozygotic twins and 356 dizygotic twins (table 1). No significant differences were found in height, weight, body mass index, or waist to hip ratio between both groups of twins (table 2). Fasting plasma insulin concentrations were similar in both groups. In the monozygotic twins, plasma glucose concentration at 30 minutes and incremental glucose area under the curve were non-significantly higher than in the dizygotic twins, and the monozygotic twins had higher plasma insulin concentrations at 30 minutes and 2 hours than dizygotic twins. Only the difference in plasma insulin concentration at 30 minutes reached statistical significance. The insulin area under the curve was significantly higher among monozygotic than dizygotic twins (10.05 (SD 0.68) v 9.89 (0.72), $P < 0.01$).

Twins concordant for normal glucose tolerance

We excluded 58 monozygotic twin pairs as one or both twins had either impaired glucose tolerance or type 2 diabetes. In the remaining 67 monozygotic twin pairs (134 individuals) both twins had normal glucose tolerance. We excluded 87 dizygotic twin pairs in which one or both twins had impaired glucose tolerance or type 2 diabetes, leaving 81 dizygotic twin pairs with normal glucose tolerance. Table 3 shows the characteristics of the monozygotic and dizygotic twins concordant for normal glucose tolerance. These twins had similar heights, weights, and body mass indices, but the monozygotic twins had a significantly higher waist to hip ratio and a higher plasma glucose concentration at 30 minutes (although similar at 0 and 2 hours) than the dizygotic twins. We found no difference in fasting plasma insulin concentrations between both groups of twins. The monozygotic twins had significantly higher plasma insulin concentrations at 30 minutes and significantly higher incremental glucose and insulin areas under the curves than dizygotic twins.

Twins without first degree relatives with diabetes

To avoid differences in genetic predisposition among the two groups of twins, we excluded 26 monozygotic

twins and 28 dizygotic twins with normal glucose tolerance and a first degree relative with diabetes. We compared the remaining 108 monozygotic and 134 dizygotic twins with normal glucose tolerance and without first degree relatives with diabetes (table 4). Both groups of twins had similar heights, weights, body mass indices, and waist to hip ratios. The monozygotic twins had significantly higher plasma glucose and insulin concentrations at 30 minutes than the dizygotic twins. Plasma glucose and insulin concentrations both at fasting and at 2 hours were similar in the two groups. The monozygotic twins had higher incremental glucose and insulin areas under the curve than the dizygotic twins.

Table 4 Clinical characteristics and plasma glucose and insulin concentrations from oral glucose tolerance test in monozygotic and dizygotic twins with normal glucose tolerance and no first degree diabetic relatives. Values are mean (SD) unless stated otherwise

Variable	Monozygotic twins (n=108)	Dizygotic twins (n=134)	Difference of mean (95% CI)	P value
No of males	54	66		
Age (years)	65.6 (5.0)	65.0 (5.3)	0.6 (–0.7 to 1.9)	0.38
Height (cm)	168.1 (9.5)	167.4 (8.6)	0.7 (–1.6 to 3.0)	0.55
Weight (kg)	71.3 (13.5)	70.3 (12.3)	1.1 (–2.2 to 4.3)	0.53
Body mass index (kg/m^2)	25.2 (4.1)	25.0 (3.4)	0.2 (–0.7 to 1.2)	0.67
Weight to hip ratio	0.86 (0.08)	0.85 (0.09)	0.01 (–0.007 to 0.036)	0.20
Plasma glucose concentration (mmol/l):				
0 minutes	5.6 (0.5)	5.6 (0.5)	0.02 (–0.11 to 0.14)	0.77
30 minutes	9.0 (1.5)	8.5 (1.3)	0.47 (0.11 to 0.83)	<0.02
120 minutes	5.8 (1.1)	5.8 (1.0)	–0.03 (–0.30 to 0.24)	0.81
Area under curve*	214.4 (88.3)	189.8 (78.4)	24.6 (3.45 to 45.7)	<0.05
Log of plasma insulin concentration (pmol/l):				
0 minutes	3.53 (0.51)	3.49 (0.47)	0.05 (–0.08 to 0.17)	0.47
30 minutes	5.60 (0.67)	5.37 (0.57)	0.23 (0.07 to 0.39)	<0.01
120 minutes	5.03 (0.64)	5.12 (0.72)	–0.08 (–0.26 to 0.09)	0.34
Area under curve*	9.92 (0.60)	9.79 (0.57)	0.13 (–0.02 to 0.28)	0.08

*Minutes × concentration.

Discussion

The differences we found between the monozygotic and dizygotic twins can not be explained by a larger prevalence of diabetes related genes among the monozygotic twins, as the differences persisted after exclusion of both twins with glucose intolerance and those with glucose tolerance with first degree diabetic relatives. Excluding a genetic cause of the observed differences between the two groups, and assuming a comparable postnatal environment, differences may be attributed to factors in the intrauterine environment. This agrees with findings of lower birth weights and higher perinatal mortality and morbidity among monozygotic than dizygotic twins.[7] Mothers of dizygotic twins are likely to be older than mothers of monozygotic twins, which might explain some of the differences between the groups. We are unaware of any evidence relating maternal age to the metabolic profile of twins during an oral glucose tolerance test.

Low birth weight

Several studies have proposed an association between low birth weight due to intrauterine malnutrition and the development of type 2 diabetes.[1–4] Associations have been shown between the pathophysiological mechanisms (low insulin secretion and peripheral insulin resistance) leading to type 2 diabetes and low birth weight in humans,[17–20] and rats experiencing protein deficiency in utero.[21–25] Monozygotic twins would, therefore, be expected to have a more abnormal insulin secretion or greater insulin resistance than dizygotic twins owing to exposure to a more adverse intrauterine environment. We were unable to show a lower insulin secretion (plasma insulin concentration 30 minutes after loading) among monozygotic than dizygotic twins. On the contrary, the monozygotic twins had higher plasma glucose and insulin concentrations in the oral glucose tolerance tests indicating insulin resistance. This supports reports of an association between an adverse intrauterine environment and the development of insulin resistance.[18–20 26] Our finding also agrees with studies showing an association between fetal growth retardation and low birth weight and plasma glucose concentration 30 minutes after loading.[26–29]

Twin studies

The classic twin model of concordances and heritabilty indices is used in the assessment of the effects of genetic and environmental factors on a given phenotype, because monozygotic twins are genetically identical whereas dizygotic twins have only 50% of their genes in common like singleton siblings. A greater similarity between monozygotic twin pairs has been interpreted as evidence of a genetic influence. The classic twin model is based on the assumption that environmental covariance both prenatally and postnatally is the same for both monozygotic and dizygotic twin pairs.

The differences we found between both groups of twins challenges the assumption of a similar intrauterine environment for both groups, and to some extent questions the validity of the classic twin approach, but only to the extent that the investigated phenotype has an intrauterine aetiological factor. Our results are primarily of importance for twin studies of diabetes and possibly insulin resistance and related disorders (the metabolic syndrome).

Despite the significant difference in the glucose area under the curve between the monozygotic and dizygotic twins—monozygotic twins being more hyperglycaemic—the prevalences of type 2 diabetes and impaired glucose tolerance were similar in both groups. The presence of type 2 diabetes and impaired glucose tolerance are, however, primarily based on plasma glucose concentrations at fasting and 2 hours after loading. Similar prevalences may be explained by the lack of significant differences in plasma glucose concentrations at these times between the two groups of twins. Also, the finding of similar plasma glucose and insulin concentrations at these times indirectly validates our previous conclusions of gene versus environment in studies of diabetes in monozygotic and dizygotic twins.[13]

Conclusion

Our findings support an intrauterine factor in the control of glucose homeostasis and perhaps the severity of insulin resistance in twins. Our findings may question the validity of the classic twin approach, where an equal environment is assumed for both monozygotic and dizygotic twins. Future studies are required to confirm

Key messages

- Zygosity affects glucose homeostasis and insulin resistance but has no influence on body weight and fat distribution
- Differences in glucose metabolism between monozygotic and dizygotic twins are independent of a family history of type 2 diabetes
- The validity of causal conclusions from classic twin studies may be questioned

the presence of a lower insulin action in monozygotic compared with dizygotic twins.

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One hundred years ago

The future of the woman physician

At the graduation exercises of the Women's Medical College of the New York Infirmary held recently, Dr. Frederick Peterson, clinical professor of insanity, delivered an address on the future of the woman physician to the ladies about to embark on the treacherous sea of medical practice. Although he referred to the sweet girl graduates with curious infelicity as "Amazons," he was most gallant in his estimate of their professional accomplishments and highly optimistic as to their prospects. He foretold that "with the gradual progress of civilisation, with the slow but sure evolution of society, the work of the woman physician must unfold and broaden to an extent undreamed of now." Although at present their professional work lies chiefly among women and children, he said, there are already indications of wider fields of labour. Among these indications may perhaps be counted the elaborate study of the effects of castration and excision of the vesiculae seminales and vas deferens for tuberculosis, published not long ago in the *Révue Médicale de la Suisse Romande* by the Princess Guedroytz de Béloséroff, an abstract of which appeared in the Epitome of the British Medical Journal of June 24th. But Dr. Peterson seems to be looking rather to laboratory research. To the delicate manipulations of this kind of work, he says, women can bring such deft and skilful fingers that a man's awkward hands seem like the flippers of a seal in comparison. Centuries of fine needlework, crocheting, and embroidery have, he adds, prepared those fingers for section cutting, staining, and the innumerable synthetical and analytical processes required by modern methods of scientific research. (*BMJ* 1899;ii:105)