Acta Genet Med Gemellol 33:467-474 (1984)

TWIN RESEARCH 4 - Part C: Clinical Studies
Proceedings of the Fourth International Congress on Twin Studies (London 1983)

Responses of Blood Glucose and Serum Insulin to Peroral Glucose Load in Normoglycemic Twins

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Abstract. Fasting blood glucose and serum immunoreactive insulin (IRI) and the responses of blood glucose and serum IRI to peroral glucose challenge were investigated in middle-aged normoglycemic male twins of 17 monozygotic (MZ) and 18 dizygotic (DZ) pairs recruited from the Finnish Twin Cohort Study. Also, the role of obesity and diet in the regulation of glucose and insulin metabolism was estimated. The fasting and 2 hr postprandial (PP) glucose showed higher pairwise correlations in MZ ($r = 0.78$ and 0.56) than DZ ($r = 0.08$ and -0.05) pairs whereas fasting and PP insulin levels and the areas under the PP glucose and insulin curves were weakly and similarly correlated in MZ and DZ twins. The pairwise correlations of the 1/2 hr and 1 hr, but not the fasting and 2 hr insulin/glucose ratios, were somewhat higher in MZ ($R = 0.51$ and 0.53) than DZ ($r = = 0.28$ and 0.30) pairs. In MZ twins, the intrapair differences in the body mass index were significantly correlated with those in the fasting and 2 hr PP glucose and insulin levels and those in the fasting and 1/2 hr insulin/glucose ratios (r from 0.47 to 0.76). Also, the intrapair differences in the dietary fat calories were correlated positively, but those in the calories derived from carbohydrates negatively, with the intrapair differences in several parameters of the glucose and insulin metabolism. These data suggest that the environmental contribution to the regulation of glucose and insulin metabolism in subjects within the normoglycemic range may be quite strong. Of the environmental factors studied, obesity and dietary fat consumption seem to have powerful regulatory roles, particularly in the response of insulin to the glucose load.

Key words: Glucose tolerance, Insulin sensitivity, Diabetes mellitus, Obesity, Diet, Twins

INTRODUCTION

Disturbances in the regulation of glucose and insulin metabolism outline the manifes-

tation of diabetes mellitus. Several metabolic processes involved with the development of diabetes mellitus, particularly the adult onset type, are apparently hereditary [4]. Previous twin studies on glucose and insulin metabolism, however, have generally been performed only in diabetic individuals or in unaffected cotwins of diabetics [3,4,10,11, 18-20,26,27]. In addition, deviations in the glucose and particularly insulin metabolism have been reported as risk factors for atherosclerosis and coronary heart disease also in the nondiabetic populations [7,16,21,24,25,29]. For these reasons, the present study was undertaken to estimate the relative contributions of genetic and some environmental factors in the regulation of glucose and insulin metabolism in normoglycemic monozygotic (MZ) and dizygotic (DZ) pairs of male twins.

METHODS

Subjects and Diets

A sample of 17 MZ and 18 DZ male twin pairs, aged 43 to 58 years and living in the vicinity of Helsinki University Central Hospital, was selected from the healthy individuals of the Finnish Cohort Study. Zygosity was established by mailed questionnaire as previously described [23]. Body weight ranged from 56 to 103 kg and the body mass index (weight/height^2 x 100) from 0.19 to 0.32. None of the subjects had diabetes mellitus or any detectable cardiovascular, thyroid, renal or gastrointestinal disease. All the subjects were studied as outpatients on their regular home diets. They were advised to go on with their normal dietary habits and to keep a food record for 9 days. The food consumption was determined from the written dietary histories by a modified food record method [6].

Glucose and Insulin Measurements

Fasting blood glucose and serum immunoreactive insulin (IRI) were determined in all subjects after an overnight fast. Thereafter, two hour oral glucose tolerance tests (1 g glucose/kg of body weight) were performed and blood for glucose and serum IRI taken at 1/2 hr, 1 hr and 2 hr after the glucose challenge. Blood glucose and serum IRI were determined according to the routine methods of our hospital laboratory.

Statistical Methods

The areas under the postprandial blood glucose and serum insulin curves (AUC) and the fasting and postprandial insulin/glucose ratios were calculated from the measured values. The MZ and DZ twin pairs were compared calculating pairwise intraclass correlations, and heritability estimates were determined according to Falconer [9] ($h^2 = 2\,(r_{MZ} - r_{DZ})$).

Also the role of some environmental factors in the regulation of glucose and insulin metabolism was estimated by the correlations between the intrapair differences of the environmental factors studied and the intrapair differences of the parameters of glucose and insulin metabolism. The blood glucose and serum insulin values were adjusted to body mass index (the values divided by the body mass index) except when the effect of the body mass index (obesity) was estimated. The correlation coefficients were calculated taking into account the observed log-normal distribution of the study parameters.

RESULTS

Table 1 shows the pairwise correlations for fasting and postprandial blood glucose and serum IRI in MZ and DZ twins. The fasting and 2 hr PP glucose showed higher pairwise correlations in MZ than DZ twins, whereas the 1/2 hr and 1 hr PP glucose and the areas under the PP glucose curves (AUC) did not differ between MZ and DZ pairs. The fasting and PP IRI levels and the AUC values for IRI showed quite low and similar pairwise

Table 1 - Correlation Coefficients for Fasting and Postprandial (PP) Blood Glucose and Serum Immunoreactive Insulin (IRI) in MZ Twins

Parameter	Correlation coefficients (r)	
	MZ pairs	DZ pairs
Blood glucose[a]		
Fasting	0.78*	0.08
1/2 hr PP	0.13	0.48*
1 hr PP	0.33	0.41
2hr PP	0.56*	−0.05
AUC[b]	0.32	0.44
Serum IRI[a]		
Fasting	0.21	0.35
1/2 hr PP	0.34	0.18
1 hr PP	0.24	0.24
2 hr PP	0.26	0.47*
AUC[b]	0.38	0.31
Insulin/glucose		
Fasting	0.25	0.31
1/2 hr PP	0.51*	0.28
1 hr PP	0.53*	0.30
2 hr PP	0.33	0.54*

[a] Adjusted to body mass index; log-normal distribution.
[b] Area under the postprandial curve.
* $P < 0.05$.

correlations in both types of twins. The pairwise correlations of the 1/2 hr and 1 hr PP insulin/glucose (I/G) ratios were significant in MZ but not in DZ twins, whereas the fasting and 2 hr I/G values did not reveal any major differences between MZ and DZ pairs. Generally, the pairwise correlation coefficients of MZ and DZ twins for the parameters of glucose and insulin metabolism showed considerable variation, and therefore, the heritability estimates were not calculated. These data suggest, however, that the contribution of environmental factors to glucose and particularly insulin metabolism may be quite strong in subjects within the normoglycemic range.

Since the MZ twins share the same genes and still show some intrapair differences in glucose and insulin metabolism, these differences must, of necessity, be due to environmental factors. The present study documented probably the most important of these factors in the regulation of glucose homeostasis, namely, obesity (body mass index) and diet. Table 2 shows the correlation coefficients between the intrapair differences of fasting and PP blood glucose and serum IRI and the intrapair differences of the body mass index and the dietary intakes of cholesterol, protein, fat, carbohydrates, alcohol and polyunsaturated/saturated (P/S) fat ratio in MZ twins. Significant positive correlations were observed between the intrapair differences in the body mass index and the fasting and 2 hr PP glucose and insulin, and the fasting and 1/2 hr PP insulin/glucose ratios. Thus, obesity seemed to explain the intrapair differences in glucose and insulin metabolism of these normoglycemic MZ twins to a considerable extent.

The intrapair differences in the percentage of dietary calories from fat showed strong positive correlations with the intrapair differences of 1/2 hr, 1 hr, 2 hr PP glucose and insulin, AUC-values for glucose and insulin and fasting, 1 hr and 2 hr PP insulin/glucose ratios in the MZ pairs. Particularly high correlation coefficients were observed between the AUC values for insulin and glucose and the dietary fat calories, so that 58% and 44% respectively of the intrapair differences of MZ twins in the insulin and glucose AUC values could be accounted for by the dietary fat intake. Similar, though not quite as strong negative correlations were observed between the intrapair differences in the percentage of dietary calories from carbohydrates and the parameters of glucose and insulin metabolism. The intrapair differences in the dietary cholesterol intake, the P/S ratios, both linked with fat intake, and the percentage of calories derived from protein and alcohol were only weakly correlated with the intrapair differences in the measured parameters of glucose and insulin metabolism, so that significant correlations were found only between the intrapair differences of dietary cholesterol intake and 1 hr PP insulin, AUC for insulin, 1 hr and 2 hr PP insulin/glucose ratios, and between the intrapair differences of the P/S ratio and the 1/2 hr PP glucose.

DISCUSSION

The pairwise correlations of the fasting and 2 hr PP glucose were strong in MZ but not DZ twins, suggesting a powerful genetic contribution to the regulation of glucose metabolism. However, the pairwise correlations of the 1/2 hr and 1 hr PP glucose and the AUC values for glucose were not different in MZ and DZ pairs, so that the overall genetic influence on glucose homeostasis was difficult to estimate. The individual variations in gastric emptying and intestinal absorption, however, have stronger effects on the 1/2 hr and 1 hr than 2 hr PP glucose values and, therefore, the fasting and 2 hr PP glucose values are probably the best indicators of glucose metabolism. Thus, the present data may still suggest that genetic factors have a considerable contribution to the regulation of glucose metabolism in subjects with normal blood glucose levels. In contrast to these findings, the pairwise correlations of the parameters in insulin metabolism were weak and similar in MZ and DZ twins. This suggests that environmental factors may contribute quite strongly to the regulation of insulin metabolism in normoglycemic subjects. This was also elucidated in the calculations of the insulin/glucose ratios that, with the exception of the 1/2 hr and 1 hr values, showed low and similar pairwise correlation coefficients for both MZ and DZ twins. However, these results may be due to the low number of pairs studied.

Several studies on MZ twin diabetics [3,4,10,11,18,19,20,26,27] have suggested that diabetes mellitus, particularly the adult-onset type, is strongly genetically determined. Barnett et al [4] found 48 concordant pairs out of 53 MZ pairs with non-insulin-dependent diabetes mellitus. Furthermore, in the five discordant pairs, the nondiabetic members showed marked metabolic abnormalities like high fasting and postprandial blood lactate, alanine, glycerol and lactate/pyruvate ratios. In the present study of normoglycemic twins, however, we did not find strong pairwise correlations in the regulation of glucose and particularly insulin metabolism. The different findings in diabetics and in our normoglycemic subjects are probably due to the population differences. It is possible that factors regulating glucose and insulin metabolism within the normoglycemic range are somewhat different from those important in the manifestation of diabetes mellitus. Also, the values of the parameters in the glucose and insulin metabolism of the normo-

Table 2 - Correlations Between the Intrapair Differences[a] of Blood Glucose and Serum Immunoreactive Insulin and the Intrapair Differences of Body Mass Index and Dietary Intakes in MZ twins

	Body mass index	Cholesterol (mg/kg/day)	Percentage of calories				P/S fat ratio
			Protein	Fat	Carbohydrates	Alcohol	
ΔB-Glucose							
Fasting	0.68*	0.17	−0.05	0.09	−0.11	0.04	0.44
1/2 hr PP	0.11	0.29	−0.06	0.61*	−0.44	−0.16	−0.51*
1 hr PP	0.34	0.36	0.04	0.58*	−0.66*	0.12	−0.12
2 hr PP	0.51*	0.02	0.09	0.47*	−0.18	−0.36	0.23
AUC[b]	0.38	0.33	0.02	0.66*	−0.59*	−0.05	−0.18
ΔS-IRI							
Fasting	0.76*	0.37	−0.02	0.43	−0.24	−0.20	0.29
1/2 hr PP	0.38	0.46	−0.05	0.49*	−0.30	−0.20	−0.14
1 hr PP	0.36	0.67*	0.29	0.78*	−0.70*	−0.14	−0.32
2 hr PP	0.54*	0.40	0.16	0.72*	−0.55*	−0.23	0.05
AUC[b]	0.35	0.68*	0.16	0.76*	−0.60*	−0.21	−0.36
ΔInsulin/glucose							
Fasting	0.72*	0.40	0.04	0.49*	−0.25	−0.26	0.26
1/2 hr PP	0.47*	0.37	−0.10	0.32	−0.09	−0.24	0.03
1 hr PP	0.34	0.69*	0.32	0.74*	−0.56*	−0.28	−0.39
2 hr PP	0.45	0.57*	0.04	0.74*	−0.58*	−0.17	−0.01

[a] Difference between cotwins calculated for each parameter.
[b] Area under the postprandial curve.
* $P < 0.05$.

glycemic subjects in the present study had a relatively small intrapair variation. It may therefore be more difficult to elucidate strong pairwise correlations in MZ twins in this experimental situation than if some had been diabetics.

The present data suggest that environmental factors may contribute considerably to glucose and particularly to insulin metabolism in normoglycemic subjects. In fact, the intrapair differences in obesity and in the percentage of dietary calories derived from fat were found to correlate strongly with the intrapair differences in glucose and insulin metabolism in MZ pairs. Obesity is recognized as a risk factor for glucose intolerance, insulin resistance and adult-onset diabetes mellitus [17,22,30,31]. However, there is also evidence that obesity is not always important in the etiology of non-insulin-dependent diabetes, since several MZ concordant pairs have been found even with considerably different weight and with neither twin overweight [4]. This may be true for diabetes mellitus, but the present study suggests that in subjects within the normoglycemic range obesity is strongly associated with the regulation of glucose and insulin metabolism.

The role of the diet in glucose and insulin metabolism has previously been studied both in normal subjects and in diabetics [2,5,14,15,28]. Our findings that the MZ intrapair differences in calories derived from fat are associated positively, but those of the calories from carbohydrates negatively, with the intrapair differences in the postprandial glucose and insulin levels are consistent with previous observations that a high carbohydrate diet will enhance insulin sensitivity in normal subjects and in patients with mild non-insulin-dependent diabetes [2,5,14,28]. In fact, the current trend in the treatment of diabetes is to increase the intake of complex carbohydrates at the expense of animal fat, so as to improve glucose utilization at a lower insulin level [1,12]. Furthermore, the diet low in fat and high in carbohydrates is probably advantageous both in normoglycemic subjects and in diabetics, since epidemiological evidence suggests that the incidence of atherosclerosis in the nondiabetic population, and possibly also in diabetics, is inversely correlated to the amount of carbohydrates in the diet [8,13]. The other dietary parameters considered – dietary intake of cholesterol, P/S ratio, and the percentage of calories derived from protein and alcohol – did not show any important influence on the regulation of the glucose and insulin metabolism.

Acknowledgment. *We thank Mrs. Leena Kaipiainen and Mrs. Marja Aarnio for expert technical and secretarial assistance.*

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