Phosphoglucomutase Genetic Polymorphism and Body Mass

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ABSTRACT: *Background:* We have searched for a possible association of the genetic polymorphism of Phosphoglucomutase locus 1 (PGM_1), a key enzyme in carbohydrate metabolism, with body mass. *Methods:* Adults (n = 257) with type 2 diabetes, 74 children referred for "obesity," and 740 consecutive healthy newborn infants were studied. Body mass index, body weight, birth weight, and PGM_1 phenotype were determined. Sexes were analyzed separately. *Results:* In type 2 diabetes, females carrying the PGM_1*2 allele are less represented among subjects with extreme body mass index deviation as compared with other classes of subjects. Among children referred for "obesity," females carrying the PGM_1*2 allele are less represented among children with extreme body weight deviation. Among consecutive infants, in both sexes the proportion of those showing a birth weight higher than the 3rd quartile is lower in homozygous $PGM_1$2/2 subjects than in other PGM_1 phenotypes. *Conclusions:* The data suggest that during extrauterine life, females carrying the PGM_1*2 allele are relatively protected from extreme body mass increase. During intrauterine life, $PGM_1$2/2 homozygotes show a tendency to low body mass increase. Because PGM_1 enzymatic activity depends on its phosphorylation status by the kinase Pak1, both structural differences of the PGM_1 allelic product and different rates of activation by Pak between sexes might be responsible for the pattern observed. At present, the effect of other genes near PGM_1 and in linkage disequilibrium with it cannot be ruled out. **KEY INDEXING TERMS:** PGM_1; Genetic polymorphism; Body mass index; Birth weight; Overweight. **[Am J Med Sci 2007;334(6):421–425.]**

Obesity is a heterogeneous group of disorders having in common energy balance disturbances and fat cell increase. Besides excess caloric intake and a sedentary lifestyle, genetic factors are also of importance in the development of obesity. Moreover variation in energy intake and participation in physical activity are not independent from genetic factors[1,2]. At present, more than 400 chromosomal regions have been identified as candidate genes.[3–7] Moreover, obesity shows different patterns in males and females, suggesting that sex hormones may modify the effect of genes involved in the development of obesity disorders.

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Phosphoglucomutase (PGM) is a highly polymorphic enzyme that plays a key role in glycide metabolism. Associations with birth weight have been observed both in normal and diabetic pregnancy,[8,9] suggesting that its genetic variability may be important for body mass development. Differences between males and females concerning the effect of PGM_1 on birth weight have been also reported.[10]

Phosphoglucomutase Polymorphism

Phosphoglucomutase is an enzyme widely distributed in nature that catalyzes the reversible reaction: glucose-1-phosphate <—> glucose-6-phosphate, an essential step in carbohydrate metabolism. Four separate loci determine distinct sets of PGM isozymes: PGM_1, PGM_2, PGM_3, and PGM_4.[11–14] About 85% to 95% of total PGM activity is determined by the PGM_1 locus, that shows an electrophoretic polymorphism determined by the occurrence of 2 codominant alleles: $PGM_{1*}1$ and PGM_1*2 at a locus on the short arm of chromosome No. 1). *In vitro* the activity associated with PGM_1*2 is higher than that associated with PGM_1*1.[15] Recent studies have shown that Pak1 (p-21 activated kinase) binds to, phosphorylates, and enhances the enzymatic activity of PGM_1.[16] Differences in activation between the 2 allelic products of PGM_1

are likely but have not yet been investigated. Thus, *in vivo*, differences in enzymatic activity between PGM_1 phenotypes could be more marked relative to those observed *in vitro*.

Isoelectrofocusing[17–19] and heat denaturation[20] studies have revealed a greater variability within the PGM_1 locus leading to the identification of 8 different PGM_1 alleles. Recent evidence indicates that intragenic recombination has an important role in generating PGM_1 variability.[21–25]

The central role in glycide metabolism, the organ specificity of some sets of PGM isozymes (the PGM_4 locus is active only during lactation and its isozymes are present only in milk[14]), the variable proportion of different sets of isozymes between different tissues and within a given tissue,[13] and the presence of genetic polymorphism in all human populations strongly suggest that genetic variability of PGM is adapted to specific functions of tissue and organs and may have importance in energy expenditure and physical activity.

In the present study, we searched for a possible association of the PGM_1 phenotype with body mass in adults and children and with birth weight in newborns from normal pregnancy. Sexes have been analyzed separately.

Materials and Methods

Samples Studied

Adults With Type 2 Diabetes. Adults (n = 257) with type 2 diabetes from the Caucasian population of Penne, a small rural town in southeastern Italy, were studied. The sample was chosen randomly from a population of about 2000 subjects under care at the Center of Diabetology of the local hospital. Samples were collected over a period of about 18 months from patients scheduled for metabolic control on a previously fixed day of the week. The sample includes male and female patients (mean age, 66.3 years; SD, 9.8).

Children Referred for 'Obesity'. Caucasian children (n = 74; ages between 3 and 14 years), referred for "obesity" to the out-patient Department of our Pediatric Clinic, were studied. Children were considered obese if their weight exceeded more than 20% the mean weight for their age, height, and sex. All children were above median height. The cutoff point between "moderate" and "severe" deviations of body mass was fixed on 4 standard deviations above the mean. Cases considered for our analysis were not associated with known disease and did not show abnormalities of the following parameters: glycemia, triglyceridemia, cholesterolemia, and urinalysis with determination of free cortisol in the urine.

Newborns From Healthy Women. Consecutive healthy newborn infants (n = 740) collected from the Caucasian populations of Rome and Penne were studied. No significant differences in PGM_1 distribution, birth weight, and gestational age were observed between the sample of Rome and that of Penne. Birth weight percentile was evaluated for each class of gestational age according to tables for the population of Florence.[25] Gestational length was estimated from the date of the last menstrual period and checked with Dubowitz score as an additional index of neonatal maturity.

Blood samples in adults and children were obtained by vasopuncture. Newborn blood samples were collected from the placental side of umbilical cord after its section. The investigation was approved by the Department of Biopathology and Imaging Diagnostics, and patients or parents of children gave informed consent to be included or include their children in this investigation.

Laboratory and Statistical Methods

PGM_1 phenotype was determined in all subjects by starch gel electrophoresis according to the method of Spencer et al.[11] The χ^2 test of independence was performed, using SPSS programs.[26] Three-way contingency tables were analyzed, using a log-linear model according to Sokal and Rohlf.[27] Combined probabilities were evaluated according to Sokal and Rohlf.[27]

Results

Table 1 shows the proportion of subjects with extreme body mass distribution (body mass index

Table 1. Percent Proportion of Subjects With Severe Body Mass in Adults With Type 2 Diabetes and of Children Referred for Obesity in Relation to PGM1 Phenotype and Gender

Adult Subjects With Type 2 Diabetes				
	Males		Females	
	$PGM_1$1/1 Phenotype	PGM_1*2 Carriers	$PGM_1$1/1 Phenotype	PGM_1*2 Carriers
Proportion of subjects with BMI >35	9.2%	16.1%	15.5%	6.1%
No. of subjects	65	56	71	65

Three-way contingency table analysis by log linear model x = PGM_1; y = BMI; z = sex; xyz interaction $P = 0.045$
Independence between BMI and gender: in $PGM_1$1/1 P = 0.300: in carriers of PGM_1*2 allele $P = 0.070$

Children Referred for "Obesity"				
	Males		Females	
	$PGM_1$1/1 Phenotype	PGM_1*2 Carriers	$PGM_1$1/1 Phenotype	PGM_1*2 Carriers
Proportion of children with weight >4 SD	33.3%	27.8%	34.6%	6.7%
N° of children	15	18	26	15

Three way contingency table analysis by log linear model x = PGM_1; y = BMI; z = sex; xyz interaction $P = 0.150$
Independence between BMI and gender: in $PGM_1$1/1 $P = 0.980$: in carriers of PGM_1*2 allele $P = 0.024$
Combining probabilities: for interaction $P = 0.040$; for independence between body mass and gender in carriers of PGM_1*2 allele $P = 0.013$