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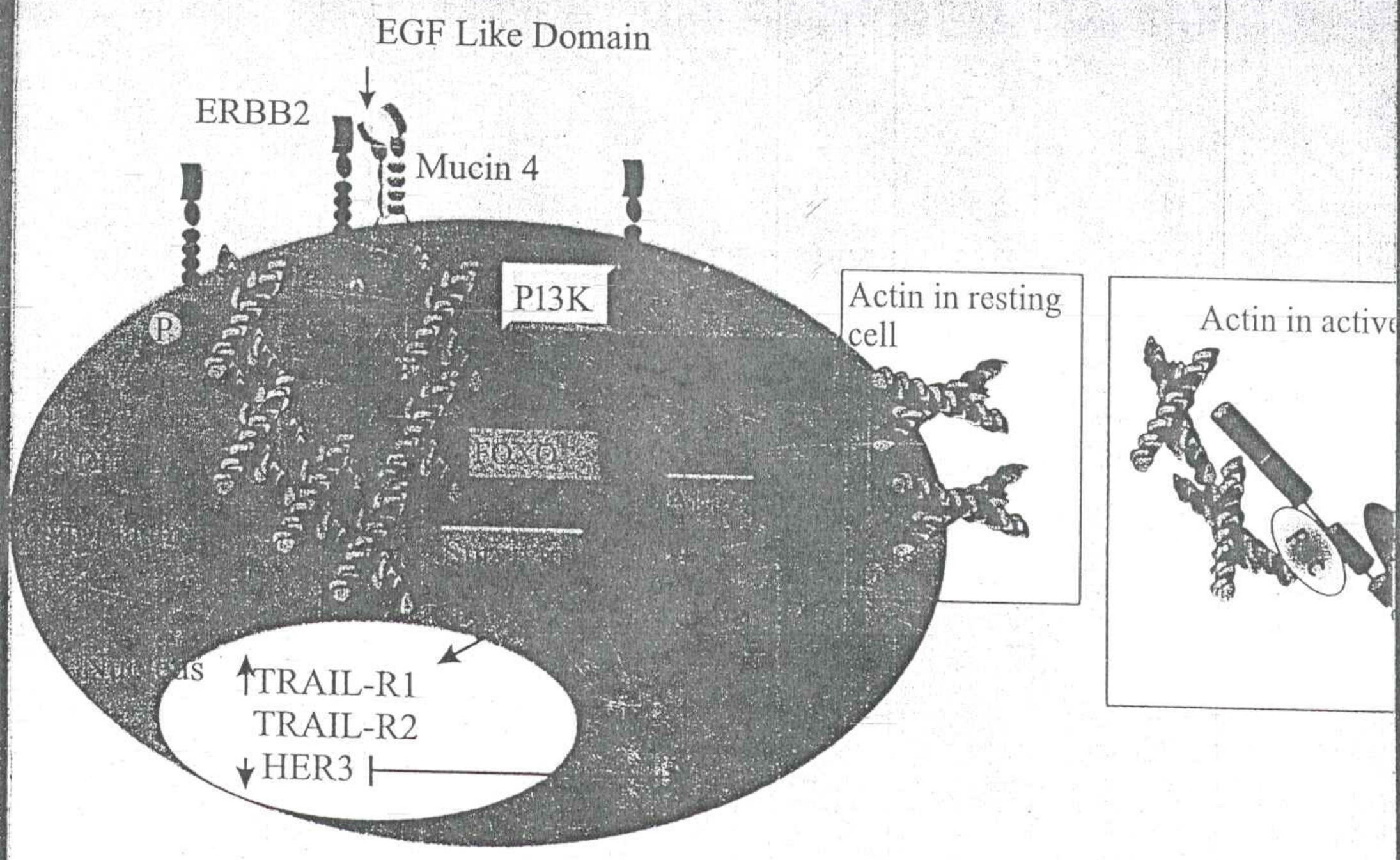

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Original Article

Disturbance of Carbohydrate Metabolism and Obesity Risk in Healthy Offspring of Diabetic Parents

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KEY WORDS:

Carbohydrate Metabolism, Obesity Risk, Diabetes

ABSTRACT

Objective: It is getting increasingly clear that obese phenotype results from alterations in numerous metabolic pathways involving several organs, as well as neuronal control of peripheral tissue and gene subsets underlying susceptibility to obesity. ***Materials and Methods:*** A total of 184 subjects (males & females) with and without family history of diabetes (FHD) were investigated to observe the early disturbance in the carbohydrate metabolism and the risk of overweight and obesity. Body weight, height, BMI, fasting blood glucose (FBG), 2hr oral glucose tolerance test (2hr OGTT) and HbA1C were determined. ***Results:*** It was observed that offspring of type 2 diabetic parents had significantly higher BMI, FBG, HbA1C and 2hr OGTT. There was higher prevalence of overweight, obesity, impaired fasting glucose (IFG) and impaired 2hr oral glucose tolerance test in subjects with FHD compared to those with no FHD. ***Conclusion:*** Offspring of type 2 diabetic parents has metabolic disturbances at an early age and are at higher risk of obesity. It is relevant to mention that initial reported associations with obesity are not verified in subsequent studies involving new patient materials. It is essential to study and integrate epidemiological and laboratory data of our local population for a better knowledge and relationships of different ethnic groups with different allele frequencies.

Introduction:

Research over the years has sequentially shown that the postmeal responses of insulin, glucagon, and glucose differ considerably between individuals with and without diabetes. It has been extensively evaluated in epidemiological studies that in a person without diabetes, the blood glucoses are tightly controlled. Postprandially, the synchronized rise in blood glucose and insulin results in suppression of hepatic glucose production by suppressing glycogenolysis and gluconeogenesis and increase in glucose uptake and utilization by the peripheral tissues particularly muscle and fat. Contrary to this, in diabetic patients, insulin release is deficient, paradoxical rise in glucagon contributes to postprandial hyperglycemia. Integration of different studies and re-interpretation of data obtained through basic and clinical research reveals that mechanistic link between obese parents and obese offspring and the relative role of genes, and a shared environment is incompletely defined. It is becoming progressively more understandable that congenital disorders of glycosylation (CDGs) are a rapidly emerging group of inherited disorders caused by defects in the synthesis and processing of the asparagines (ASN)-linked oligosaccharides of glycoproteins. More importantly, exceptionally wide clinical spectrum of CDG makes a broad screening for these disorders in children. There are direct pieces of evidence that suggest strong correlation between HbA1c and plasma glucose levels both at fasting and over postprandial periods[1,2]. It has lately been shown that alterations in the expression of some glycolysis-related genes suggest potential mechanisms involved in defective CHO metabolism[3].

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Materials and Methods:

The present study based on a total of 184 subjects (*male=84, females=100*) between the ages of 10-25 years, was approved by the Ethical Committee and the Research Board of the University of Health Sciences (UHS), Lahore. Written informed consent to participate in the study was obtained from each subject and/or his parents. All the subjects underwent a detailed general physical examination, had fasting blood glucose levels (FBG) <126mg/dl[4]. and no signs of acute or chronic illness. Subjects were asked to complete the questionnaire regarding their family history of diabetes and any other major disease such as cardiovascular and autoimmune diseases. Subjects with history of T1DM in either of the parents, with endocrinopathies (e.g. Cushing's syndrome, Down syndrome, Acromegaly, thyrotoxicosis, etc.) or any major illness since birth, were excluded from the study.

Study Design: Subjects were divided into the following 2 age-matched groups:

Group I: Children with family history of type 2 diabetes one or both parents (n=124; mean age: 22.52 yrs)

Group II: Children with no family history of type 2 diabetes (n=60; mean age: 21.28)

Physical Measurements and Blood Collection:

Body height was measured using a wall-mounted stadiometer and BW was measured using digital scale for all patients. Body mass index (BMI) was calculated according to the equation:

$BMI = BW (kg)/height (m)^2$

Four ml of venous blood was drawn from the cubital vein after overnight fasting of 12 h. Two ml of sample was added to a fluoride EDTA tube for glucose estimation whereas 2 ml of sample was added to an EDTA tube for HbA1-c measurements. Two hour-oral glucose tolerance test (2 h-OGTT) was carried out to evaluate the glucose tolerance status, according to the procedure as recommended by WHO[5]. All subjects were put on diet containing at least 150 gm of carbohydrates for 3 days prior to OGTT. The subjects were given 75 gm anhydrous glucose dissolved in plain water and the Two ml of blood samples were collected 2 h thereafter. The blood samples were centrifuged immediately and glucose levels were measured the same day.

Analytical Determinations:

All biochemical parameters were determined in duplicate using standard procedures. The diabetic condition or otherwise, of parents was reconfirmed by determining fasting blood glucose (FBG levels). Parents having FBG ≥ 126mg/dl were labeled as diabetic[4]. Serum glucose levels were determined by the glucose oxidase method using a commercial reagent kit (RANDOX Laboratories, Crumlin, UK). The estimations were made with a HumaStar 180 chemistry analyzer (Human, Weisbaden, Germany). HbA1-c was estimated by affinity liquid chromatography with a D-SI Glycomat (Provalis Diagnostics, Deeside, UK).

Results:

It was observed that offspring of type 2 diabetic parents had significantly higher BMI, FBG, HbA1C and 2hr OGTT. There was higher prevalence of overweight, obesity, impaired fasting glucose (IFG) and impaired 2hr oral glucose tolerance test in subjects with FHD compared to those with no FHD.

Table 1: Anthropometric & Metabolic Characteristics mean ± SEM of Children with Family History of Diabetic (FHD) and Healthy Parents (control)

Group	n	Body weight (kg)	Body height (m)	BMI (Kg/m^2)	Hb A1-c%	Glucose (mg/dl)	2h-OGTT (mg/dl)
FHD	124	64.82±1.9	1.66±0.01	25.10±0.68	5.51±0.05	97.76±1.16	119±2.94
Control	60	61.48±1.5[a]	1.68±0.01	21.49±0.42[a]	5.11±0.08[a]	84.34±1.19[a]	97.22±2.53[a]

[a] Significantly different from the appropriate group (P<0.05; student t-test): [a]FHD vs Control

Table 2: Percentages of Overweight, Obese, HbAIC, IFG and 2hr-OGTT in subjects with Family History of Diabetes (FHD) and Control Groups.

	FHD	Control
	n=124	n=60
Overweight BMI>25&<30	(16%)	(6.6%)
Obese BMI>30	(19%)	(3.3%)
HbA1c>5.5%	(41%)	(16%)
Impaired Fasting Glucose (FBG) ≥100mg/dl & <126mg/dl	(29%)	(5%)
Impaired 2hr oral Glucose Tolerance Test (2hr-OGTT) >140mg/dl	(22%)	(1.6%)

Body Weight and BMI

The Body weight and BMI were significantly high in patients with FHD compared to controls.

HBA1C

Data obtained from statistical analysis indicated that HBA1C was also significantly high in patients with FHD compared to the controls.

Fasting Blood Glucose (FBG) and 2hr OGTT

Frequently recorded cases displayed high FBG and 2hr OGTT in the group with FHD.

Discussion:

Accumulating evidence suggests that high fat diet (HFD) acts as a cellular stress and activates various proteins to counteract this stress. In accordance with this approach, it has lately been found that 8-Oxoguanine DNA Glycosylase (OGG1) suppresses HFD induced cellular stress. More prominently, in the absence of OGG1, a HFD led to accelerated development of several features of metabolic syndrome, including increased adiposity, hepatic lipid accumulation and impaired glucose tolerance upon high-fat feeding[6]. It has lately been reported that Tumor necrosis factor-α converting enzyme (TACE) promoted HFD-induced obesity, insulin resistance, in association with increased energy expenditure, suggesting an important role of TACE in the development of obesity-induced metabolic disorders[7]. It is surprising to note that Adipose triglyceride lipase-null mice are resistant to high-fat diet-induced insulin resistance[8]. Using transgenic mice it has been investigated that after 8 weeks of HFD feeding, Carnitine palmitoyltransferase-1 (CPT1) KO mice developed a phenotype of more severe insulin resistance than that in wild-type controls[9]. Our data clearly demonstrates that there are dysregulated metabolic activities in patients with FHD and on high fat diet.

We have previously shown that T2DM associated risk factors are more vigorously expressed in male offspring with a history of diabetes in both parents[10,11]. In this study we have shown that offspring of type 2 diabetic parents had significantly higher BMI, FBG, HbA1C and 2hr OGTT. There was higher prevalence of overweight, obesity, impaired fasting glucose (IFG) and impaired 2hr oral glucose tolerance test in subjects with FHD compared to those with no FHD. It was further confirmed by a contemporary study that indicated that glucose tolerance was interconnected with a family history of diabetes[12]. Additional proof of the concept was provided by different epidemiological studies that are line with the fact that FHD is positively linked to carbohydrate metabolism associated complications and obesity in offsprings[13, 14, 15, 16].

With the overwhelming advancements in human genome research, together with new tools such as dense whole genome maps of common polymorphisms and high-throughput genotyping platforms allowing complete analysis of genes in large population of patients and controls, we predict that a number of new susceptibility gene alleles for obesity will be established in the near future.

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