

KETOSIS RESISTANT DIABETES OF THE YOUNG : A PROFILE OF ITS EXOCRINE AND ENDOCRINE PANCREATIC DYSFUNCTION

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(Received on November 10, 1993)

Abstract: A subset of insulin requiring diabetes in the young (IRDY) is ketosis resistant. Its pathogenesis and pathophysiology remain ill defined. The current study was done to evaluate the exocrine and endocrine dysfunction in ketosis resistant young diabetics. Faecal chymotrypsin (unit/G), basal & stimulated c-peptide levels (pmol/ml) and sonographic evaluation of the pancreas were done in 59 IRDY patients : 34 ketosis resistant (KR) and 24 ketosis prone (KP). Faecal chymotrypsin levels in KR (11.1 ± 3.4) and KP (10.3 ± 5.1) were lower than in controls (22.4 ± 7.3) ($P < 0.01$). KR subjects had better endogenous insulin reserves than KP subjects : the basal and stimulated c-peptide levels in KR patients (0.12 & 0.17) were higher than in KP subjects (0.06 and 0.07) ($P < 0.05$). A strong correlation was noted between the exocrine and beta cell dysfunction in KR subjects ($r = 0.7$, $P < 0.05$). Pancreas was smaller in KR and KP patients than in controls ($P < 0.05$) on sonography. Thus the resistance to ketosis is a reflection of the better preserved beta cell reserves in the KR patients. Loss of the trophic effect of insulin and associated malnutrition is responsible for their exocrine dysfunction.

Key words: protein deficiency diabetes mellitus faecal chymotrypsin
insulin dependent diabetes mellitus exocrine pancreatic dysfunction
sonography of the pancreas c-peptide islet B cell dysfunction

INTRODUCTION

In tropical countries like India 65-98% of diabetics with childhood onset (<20 yrs) require insulin. Although the majority of them are ketosis prone (KP) which is characteristic of IDDM, a minority of them have been observed to be ketosis resistant (KR). This latter subset of insulin requiring ketosis resistant young diabetics are indigent subjects who discontinue insulin for reasons of sheer unaffordability, yet survive for months or years. Impressed by their resistance to ketosis, WHO has proposed to name this ailment as

Protein Deficiency Diabetes Mellitus (PDDM), WHO (1). Precise clinical definition of this subgroup is difficult and even impossible. There is scanty and controversial information on the exocrine pancreatic dysfunction in the KR subjects (2, 11). On the other hand, subclinical exocrine insufficiency has been well documented in IDDM (3, 4).

AIM OF THE STUDY

To identify the degree of exocrine and endocrine pancreatic dysfunction in KR young diabetics.

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METHODS

A total of 58 young diabetic subjects with age at onset of diabetes at < 30 years were studied. These subjects were stratified into two subgroups: (a) Ketosis prone (KP) i.e. classical IDDM, and (b) Ketosis resistant (KR). The latter did not develop ketoacidosis *on abstinence from insulin (against medical advice or for socio-economic reasons)* for a period of 5 to 998 (mean 166.65) days. A careful clinical history was supplemented by a complete physical examination including measurement of Body Mass Index (BMI). There were 10 age and sex matched healthy nondiabetic controls.

The degree of exocrine pancreatic insufficiency was measured by means of a faecal chymotrypsin (FCT) photometric assay (units/gram of stool) (5). The clinical decision levels for this assay are : >5 μ /g= normal, 3-5 μ /g borderline, <3 μ /g = low.

On ultrasonography, the maximum diameter of the head, body and the main pancreatic duct was recorded. The echotexture of the gland was noted and calcification looked for. Calcification was also checked on a plain film of the abdomen. (No case of fibrocalcific pancreatic diabetes was included in this study).

Islet B cell function was assessed by a measurement of C-peptide (pmol/ml - basal and 6

minutes post IV glucagon stimulation (6). The C-peptide level was measured by a radioimmunoassay method using a kit from Novo-Nordisk, Bagsvaerd, Denmark.

Student's 't' test, Mann-Whitney U test and Chi-square test were used for statistical analysis. Correlation was tested using Spearman's rank correlation coefficient.

RESULTS

Clinical and biochemical features : The KR subjects could abstain from insulin without developing ketosis for a much longer duration than KP patients ($P < 0.0001$) (Table I). In other words, a much shorter abstinence resulted in ketosis/diabetic ketoacidotic coma in KP patients as compared with KR patients. KR subjects had a later onset ($P < 0.05$) and an apparently shorter duration of diabetes as compared with KP patients. A past history of malnutrition with failure to thrive and clinical signs of PCM and avitaminosis were somewhat commoner in KR as compared with KP patients. However, the difference did not achieve statistical significance. None of the subjects gave a history of steatorrhoea. The BMI of KR subjects was lower than that of KP patients and controls ($P < 0.01$). Blood glucose levels and insulin requirements between KR and KP patients were similar ($P = NS$).

TABLE I : Clinical parameters of insulin requiring/dependent diabetics : Ketosis resistant (KR) and Ketosis prone (KP).

Clinical parameters	KR (n=34)	KP (n=24)	Controls (n=10)
Sex Ratio (M : F)	21 : 13	13 : 11	6 : 4
Age in yrs at sampling mean (SD)	22.6 (7.5)	20.5 (7.56)	23.4 (4.7)
Age in yrs at DM onset mean (SD)	18.99 (6.19) *	15.13 (6.17)	-
Duration in yrs of DM mean (SD)	3.9 (2.9)	5.53 (6.41)	-
Insulin abstinence in days; mean (SD)	166.65 (258.5) ****	44.12 (78.9)	-
BMI, kg/m ² ; mean (SD)	17 (3.03) ***	19.18 (3.3)	19.7 (2.5) **
Blood glucose, mg/dl mean (SD)	521.3 (137.2)	475.3 (184)	-
Insulin requirements μ /d mean (SD)	62.4 (26.4)	51 (21.7)	-

* $P < 0.05$ KR compared to KP
 ** $P = 0.01$ Controls compared to KR
 *** $P < 0.01$ KR compared to KP
 **** $P < 0.0001$ KR compared to KP

Exocrine pancreatic insufficiency : KR and KP patients had similar FCT levels (11.1 ± 3.4 vs 10.3 ± 5.1 , respectively) which were however lower than those of controls (22.4 ± 7.3 ; $P < 0.01$) (Fig.1).

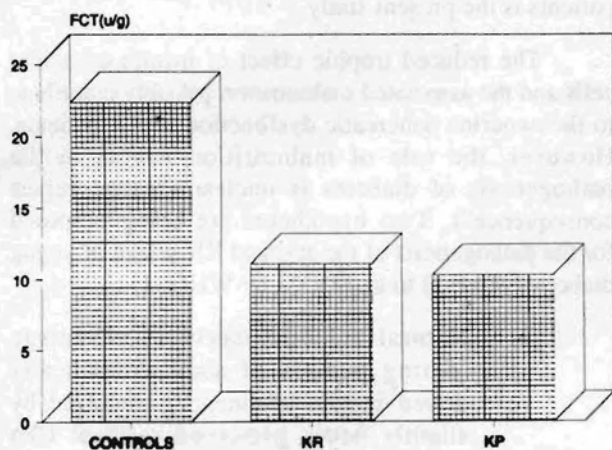


Fig.1 : Fecal chymotrypsin in insulin requiring young diabetics : ketosis resistant (KR) and ketosis prone (KP).

Ultrasonography of the pancreas : Pancreatic dimensions were similar among KR and KP patients, but smaller as compared with controls ($P < 0.05$) (Fig.2). No ductal dilation, abnormal echotexture or calcification was recorded in any of these subjects.

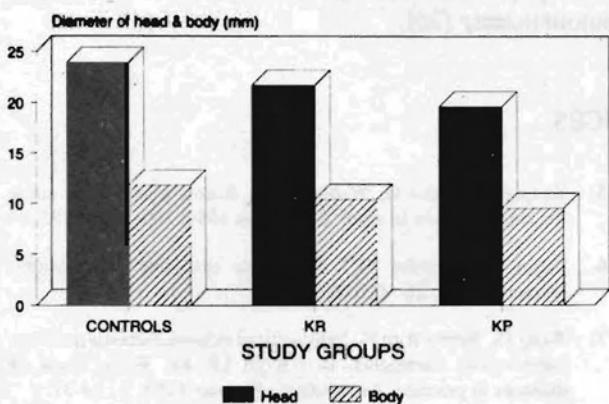


Fig. 2 : Pancreatic size in insulin requiring young diabetics : ketosis resistant (KR) and ketosis prone (KP).

Islet B cell dysfunctions : KR patients had higher basal and stimulated C-peptide levels than those of KP subjects ($P < 0.05$) (Table II). The C-peptide levels of

both KR and KP patients are less than those of controls (basal : $P < 0.01$ and $P < 0.001$, stimulated : $P < 0.05$ and $P < 0.001$).

TABLE II : Endogenous insulin reserve of insulin requiring young diabetics : Ketosis resistant (KR) and Ketosis prone (KP).

	Basal c-peptide (pmol/ml)	Stimulated c-peptide (pmol/ml)
KR (n=34)	0.12 (0.13)**	0.17 (0.17)*
KP (n=24)	0.06 (0.08)***	0.07 (0.08)***
Controls (CO)	0.38 (0.25)	0.44 (0.31)

** $P < 0.01$ KR vs CO.
 *** $P < 0.001$ KP vs CO.
 * $P < 0.05$ KR vs KP.
 † $P < 0.05$ KR vs CO.
 ‡ $P < 0.001$ KP vs CO.

Exocrine-Endocrine correlation : There is a direct positive correlation between FCT levels and basal C-peptide levels in KR patients ($r_s = 0.70$, $P < 0.05$).

DISCUSSION

A combined investigation on both exocrine and endocrine pancreatic reserves in KR young diabetics is conceptually stimulating because it can shed light on their pathophysiology and pathogenesis.

In contrast to the KP-classical IDDM patients, our KR subjects suffered from diabetes at a slightly later age. They demonstrated relatively higher endogenous insulin reserves, thus suggesting that the KR subset is a milder form of disease as compared to the KP subset of young diabetics.

Resistance to ketosis is clearly documented in our KR subjects. This is attributable to better insulin reserves in them. These conclusions are in accord with the results of other workers (2, 7). Other factors such as lower levels of nonesterified fatty acid (NEFA) and of acetone in KR patients (8, 9) along with a postprandial glucagon suppressibility in KR are contributory to their resistance to ketosis (10).

In the present study, it was noted that the FCT levels of KR and KP patients were significantly lower

than that of controls. The mean FCT levels of both subgroups of IRDY were grossly similar. This is a clear evidence of subclinical exocrine dysfunction, in both subgroups of IRDY. A recent study has demonstrated the presence of steatorrhoea in KR patients and its partial recovery following a period of nutritional rehabilitation (2). In contrast, Samal surprisingly found no evidence of exocrine insufficiency on performing a secretin-pancreozymin test in these patients (11). Bajaj et al (7) have theorised that chronic malnutrition causes an isolated B cell dysfunction in PDDM, similar to Kwashiorkor in children and induced PCM in rhesus monkeys. But the disorganisation of acinar cells and loss of zymogen granules have been clearly recorded in Kwashiorkor (13) and in experimentally induced protein deprivation in animals (14). Concordantly, a significant depression of pancreatic enzyme secretion has also been reported in both Kwashiorkor (15) and animal studies (16). Finally these malnutrition induced structural and functional changes in the pancreas are reversible following restitution of a high protein diet (17).

On sonography the pancreatic size was smaller in both subsets of young diabetics as compared to controls. This is in accord with a previous autopsy study (18) and a recent study from our centre using CT and US (19). There is thus structural as well as

functional evidence for a generalised pancreatopathy in IRDY. A good correlation between endocrine and exocrine pancreatic dysfunction previously documented in classical IDDM patients was also present in the KR patients is the present study.

The reduced trophic effect of insulin on acinar cells and the associated malnutrition possibly contribute to the exocrine pancreatic dysfunction in KR patients. However, the role of malnutrition *per se* in the pathogenesis of diabetes is unclear ("cause versus consequence"). Two hypotheses are being proposed for the pathogenesis of the atypical KR subset of young diabetics referred to as PDDM by WHO (1) :

- (1) Natural selection/survival advantage (during periods of socioeconomically driven insulin abstinence) conferred by slightly better preserved residual islet B cell function and
- (2) Malnutrition related (subtle) immunodeficiency resulting in subtotal autoimmune B cell destruction.

In support we have data from experimental animal models of IDDM suggesting that complex dietary proteins can act as triggers of islet cells autoimmunity (20).

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