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Original Article

A clinical study of insulin resistance in patients with chronic pancreatitis

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ABSTRACT

Objective: Insulin resistance (IR) and beta cell dysfunction are the pathophysiological determinants of the diabetes mellitus (DM). We investigated the presence of IR in patients with chronic pancreatitis (CP) and compared the same with the underlying etiology.
Methods: In this cross-sectional, observational study, we included serial patients of CP presented to our hospital. The study population is in different stages of CP and are grouped as alcoholic CP (Group 1; N = 67) and tropical CP (Group 2; N = 35). IR was estimated by the homeostasis model assessment (HOMA) method. The results were analyzed by appropriate statistical methods.
Results: The study participants (85 M and 17F) had a mean age 40.8 ± 12.6 yr, CP duration 3.7 ± 4.7 yr and body mass index (BMI) of 22.5 ± 3.2 kg/m^2. DM was seen in 54 patients with average glycosylated hemoglobin of 7.5 ± 1.6%. A total of 9 patients had HOMA-IR more than 3 suggestive of IR with no significant difference between the two groups. The duration of the DM correlated negatively with glycemic parameters and BMI showed a positive correlation with the fasting insulin and HOMA-IR.
Conclusion: IR was seen in a minority of patients with CP and is not a significant contributor to the pancreatogenic diabetes.

1. Introduction

Pancreatogenic diabetes or type 3c diabetes is a term used to denote diabetes secondary to pancreatic disorders [1]. Chronic pancreatitis (CP) is the commonest cause of pancreatogenic diabetes followed by pancreatic neoplasia. The most common etiologies of the CP include alcohol, gallstone disease and tropical varieties [2]. The natural course of CP is uncertain and the patients may have predominantly either exocrine or endocrine deficiency [3]. Evaluation for hyperglycemia is done in all patients with CP, whereas the converse is not practiced routinely. CP often remains asymptomatic in early stages and is identified during the abdominal imaging for an unrelated reason [4]. CP is characterized by extensive fibrosis, atrophy, collagen deposition and sclerosis of the pancreas resulting in reduced vascularity [5]. This pathology is distinct from the type 1 diabetes, where the inflammation is restricted to islet cells only. Amyloid deposition is a characteristic feature of the type 2 diabetes, which is not commonly observed in pancreatogenic diabetes [6].

Insulin resistance (IR) and beta cell dysfunction are the major contributing factors for the development of diabetes mellitus (DM) [7]. The contributory factors for the diabetes in CP include the amount of beta cell loss, amyloid deposits, atrophy of the pancreas, genetic risk and the advanced age [8]. The literature is conflicting regarding the contribution of the IR in the type 3c DM [9–11]. IR is determined by the homeostasis model assessment (HOMA) method which is shown to correlate with the gold standard method i.e. insulin clamp studies [12]. Few authors have studied the clinical differences of diabetes between the alcoholic CP (ACP) and tropical CP (TCP) [13,14]. Previous reports suggest that DM was observed in 50% and 5% of alcoholic and hereditary CP respectively [13]. Moreover the progression of diabetes is accelerated in patients with ACP, when compared with other types of CP [14]. It is essential to look at the clinical profile of the diabetes based on the underlying cause of CP. Hence, we conducted this study to assess the IR in patients with CP and compare the same based on the underlying etiology of the CP.

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2. Materials and methods

2.1. Study population

We conducted this cross sectional, observational study at a tertiary level referral hospital of the armed forces located in the western part of India. All patients with a known diagnosis of CP (aged 18–60) of any duration under follow up at our hospital were included in the study. We excluded patients with known systemic disorders (chronic liver disease, chronic kidney disease), other types of diabetes (type 1 or latent autoimmune diabetes in adults) and endocrine disorders (Cushing's disease, Acromegaly, Thyroid disorders). The patients were divided into 2 groups based on the underlying etiology for the comparison: Group 1 (ACP) and Group 2 (TCP). The patients with significant exocrine dysfunction were excluded from the study. We also excluded patients who had a diagnosis of DM prior to the detection of the CP. The local ethics committee approved the trial protocol and all patients provided written informed consent.

2.2. Study measures

A detailed history regarding the profile of CP and DM was obtained from all the participants. A general physical examination includes measurement of vital parameters and identification of markers of vitamin deficiency. A fasting venous blood sample after an overnight fast for more than 12 h was collected from each participant at 0800 h. The serum was analyzed for hematological and biochemical parameters including the glycosylated hemoglobin (HbA1c), fasting serum insulin and C-peptide. Fasting plasma glucose (FPG) and lipid panel except low density lipoprotein cholesterol (LDL-C) were analyzed using enzymatic methods with reagents supplied by Roche Diagnostics and Hitachi 911 analyzer. LDL-C was calculated using the Friedewald equation in samples with TG less than 400 mg/dL [15]. HbA1c was analyzed using the high performance liquid chromatography (HPLC) method.

2.3. Study definitions

Diabetes was diagnosed as per the American Diabetes Association (ADA) criteria and also by the self-declaration of the patients [16]. Chronic pancreatitis was diagnosed based on the clinical and imaging criteria [17]. Typically, patients have chronic abdominal pain along with either presence of pancreatic calcification/atrophy on the ultrasound or the presence of ductal changes on the CT or MRI. IR was estimated using the HOMA-IR method with the help of FPG and plasma insulin. HOMA-IR value of more than or equal to 3 was considered as diagnostic of IR [18]. ACP was diagnosed in a patient with alcohol consumption of more than 14 units per week for five years prior to the onset of CP. The normal radiological appearance of gall bladder and normal gamma-glutamyl transpeptidase (GGT) value were essential before the diagnosis of TCP.

2.4. Statistics

Data are presented as mean ± S.D and a comparison between the groups was done using non parametric (Mann-Whitney *U* test) and Fisher's exact tests. Spearman's correlation test was used for correlation between numerical variables and a p value of less than 0.05 was considered significant. The statistical analysis and graph generation was done using the Graph Pad Prism Software, Version 6 (Graph Pad Software, San Deigo, CA, USA).

3. Results

The study participants consist of 85 males and 17 females with a mean age 40.8 ± 12.6 yr, CP duration 3.7 ± 4.7 yr, body weight 63.3 ± 10.8 kg and body mass index (BMI) of 22.5 ± 3.2 kg/m^2. A total of 67 patients had ACP while the remaining 35 had TCP. DM was seen in 54 patients with average glycosylated hemoglobin of 7.5 ± 1.6%. A total of 9 patients had HOMA IR more than 3 suggestive of IR. The differences pertaining to the clinical and biochemical parameters between the two groups are given in Table 1. There was no difference in the IR and the profile of DM between the ACP and TCP. Patients with ACP had a slightly higher glycosylated hemoglobin concentration. We analyzed the data according the status of diabetes and the results are shown in Table 2. Briefly, patients without DM had a higher C-peptide level, but the HOMA IR was similar between the two groups. We did a univariate correlation analysis between certain important clinical and biochemical parameters as shown in Table 3. In brief, the duration of DM correlated negatively with glycemic parameters and BMI showed a positive correlation with the fasting insulin and HOMA-IR as shown in Figs. 1 and 2 respectively. None of the other parameters showed a significant correlation. We didn't perform the multivariate analysis for the small sample size in our study.

Table 1
Comparison of body composition parameters between the two groups of CP.

Feature	Units	Group 1 (Alcoholic CP) n = 67	Group 2 (TCP) n = 35	P value
Demographic parameters				
Age	Years	40.4 (11.8)*	41.4 (14.2)	0.7114
Sex	M:F	67: 0	18: 17	<**0.0001**
Duration of chronic pancreatitis	Years	3.2 (3.2)	4.4 (6.7)	0.2233
Diabetes mellitus	Yes: No	40: 27	14: 21	0.0643
Duration of Diabetes mellitus	Years	1.6 (2.8)	2.1 (5.9)	0.5754
Insulin Resistance (HOMA >3)	Yes: No	5: 61	4: 31	
Weight	Kg	64.6 (10.4)	60.8 (11.1)	0.0927
BMI	Kg/m^2	22.4 (3.2)	22.8 (3.3)	0.4849
Abdominal circumference	Cm	84.4 (8.8)	85.9 (9.1)	0.4431
Biochemical parameters				
Fasting plasma glucose	mg/dL	103.8 (27.8)	98.8 (24.3)	0.3758
Fasting serum insulin	pmol/L	5.6 (5.5)	7.1 (6.7)	0.2739
HOMA-IR	Number	1.5 (1.7)	1.8 (2.2)	0.3996
Fasting C-peptide	ng/mL	1.5 (1.4)	1.6 (1.2)	0.7206
HbA1c	%	6.9 (1.7)	6.3 (1.1)	**0.0497**

* Mean (S.D).

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