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Original Research Article

Serum levels of intestinal alkaline phosphatase in type 2 diabetic patients with enteropathy

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ABSTRACT

Background: Type 2 diabetes mellitus patients frequently have various distressing gastrointestinal signs and symptoms and intestinal alkaline phosphatase (IAP) may be linked to it. Even after extensive search, there was dearth of literature related to IAP levels in serum of diabetic enteropathy subjects. So, using a case-control design, levels of IAP in the serum of T2DM subjects were determined.
Methods: Serum IAP was measured by ELISA in 73 type 2 diabetic patients with enteropathy (group 1) and 71 type 2 diabetic patients without enteropathy (group 2). Statistical analysis of the data was performed by using Statistical Package for Social Sciences (SPSS version 16) and inferences were drawn.
Results: Serum IAP was highly significantly reduced in group 1 (3.9 U/L) compared to group 2 (4.2 U/L).
Conclusions: Enteropathy in T2DM may be related to reduction in IAP levels in serum. Estimation of serum IAP may be considered in type 2 diabetic patients with enteropathy, for the elaboration of treatment strategy and monitoring.

Keywords: Diabetes mellitus, Enteropathy, Intestinal alkaline phosphatase

INTRODUCTION

Diabetes mellitus occurs throughout the world, affects all age groups and is a major cause for concern. Diabetes is characterized by hyperglycemia as a result of defects in insulin secretion, insulin resistance, or both. The chronic hyperglycemia of diabetes is associated with long-term damage and dysfunction of several organs.[1] Almost every organ or system in the body is involved in diabetes mellitus. Though diabetes has many complications, patients frequently have various distressing gastrointestinal signs and symptoms, which are an important cause of morbidity.[2] Up to 75% of diabetic patients might have gastrointestinal symptoms, which therefore leads to a notable decline in quality of life and a subsequent increase in health care costs. As the prevalence of diabetes has increased, the gastrointestinal complications also have become increasingly prevalent.[3] Amongst the diabetic complications with the highest symptom burden, yet frequently underrecognized and suboptimally treated, are those associated with alterations in the enteric nervous system, referred to as diabetic enteropathy.[4] In spite of other problems, the major disabling complaints present in patients are intestinal disorders like constipation and diarrhea.[5] Small intestinal and colorectal dysfunctions are common in patients with longstanding diabetes, especially in those with gastroparesis.[6] Diabetic gastroparesis is associated with abnormal motor and sensory functions.[7] Abnormal gastrointestinal motility in diabetes mellitus is incompletely understood and is likely multifactorial. It

results in impaired gastric contractility or abnormal myoelectrical control.[8]

Various studies have been undertaken in order to relate diabetic enteropathy with different parameters; serum levels of intestinal enzymes such as amylase have been evaluated in diabetes to elucidate the pathophysiology of enteric complications.[9] Likewise, the present study tried to link intestinal complications of diabetes to intestinal alkaline phosphatase (IAP), which has been studied rarely, if at all. IAP has significant roles in our gastrointestinal system, for example, it is vital for regulation of lipid absorption, which may be important in diabetic patients.[4,10] But even after extensive search, there was dearth of literature related to IAP levels in serum of diabetic enteropathy subjects. So, using a case-control design we recruited T2DM subjects and determined the levels of IAP in the serum of these participants.

METHODS

This study was a hospital-based, case-control study conducted in the Department of Biochemistry of a tertiary care hospital. The study was approved by the local ethical committee, and all patients and control subjects gave their informed consent to take part in this investigation.

The duration of the present study was 1 year and 3 months and was undertaken from June 2017 to August 2018. The study included 73 T2DM patients (Group 1) attending the outpatient department (OPD) with diabetic enteropathy symptoms. The duration of complaint ranged from 6 years to 14 years. In addition, 71 T2DM subjects (Group 2) who were age and sex-matched with the Group 1 patients served as controls. The controls had attended the OPD with minor unrelated ailments. Complete history and physical examination of all cases and controls were undertaken. Exclusion criteria included subjects who had Crohn's disease, ulcerative colitis, celiac disease, cirrhosis, steatorrhea, chronic renal failure, obesity, etc.

About 5 ml of venous blood sample was collected from each case and control after 12 hours of fasting. All samples were coded and assayed in a blind fashion by an investigator who was unaware of the subjects' clinical status.

Serum IAP levels were assayed using Sandwich ELISA by Human Alkaline Phosphatase, Intestinal ELISA kit, from Bioassay Technology Laboratory, Shanghai.[11,12]

Statistical analysis

Statistical analysis of the data was performed by student's t test; IAP values of the two groups were compared and the results were analyzed using Statistical Package for Social Sciences (SPSS version 16) and inferences were drawn. p values of <0.05 and <0.001were considered to be significant and highly significant respectively.

RESULTS

Total 7 patients out the 80 subjects of group 1 initially included in the study, and 9 subjects out of the initial 80 subjects of group 2, did not complete the study protocol, and as such were excluded from the analysis.

The age of subjects ranged from 46 years to 68 years with a mean age of 59 years. The mean duration of the disease in the patients (including recurrences and remissions) was 8 years. Age and sex distribution of cases and controls are given in Table 1. Serum IAP levels were highly significantly decreased in group 1 subjects with respect to group 2 subjects (Table 2).

Table 1: Age and sex distribution of cases (group 1) and controls (group 2).

Group	46-49 years		50-59 years		60-68 years	
1	M	F	M	F	M	F
	6	8	33	31	34	34
2	M	F	M	F	M	F
	7	6	30	36	34	29

The cases and controls were divided into males (M) and females (F). Then the male and female cases and controls were again subdivided into 3 subgroups, according to age (i.e. 46-49 years, 50-5 years and 60-68 years). The resultant age and sex distribution of the cases and controls are given in the Table.

Table 2: Serum IAP levels (in U/L) of cases (group 1) and controls (group 2).

	Group 1	Group 2
Mean	3.9	4.2
SD	0.4	0.6
SEM	0.047	0.071
N	73	71

Mean values of serum IAP levels (in U/L) in group 1subjects were presented in the table along with N (number of subjects). The Standard deviation (SD) and Standard error of mean (SEM) of serum IAP levels (in U/L) in group 1 subjects were also presented in the table. All the above parameters (Mean values, SD, SEM and N) of group 2 subjects were also presented.

t test results

p value and statistical significance are as follows: The two-tailed p value equals 0.0005. According to conventional criteria, this difference is considered to be statistically highly significant. 95% confidence interval of this difference is from -0.468 to -0.132.

Intermediate values used in calculations are as follows: t value is 3.5393, df equals to 142, standard error of difference is 0.085. There was no significant difference in

serum IAP levels between male and female patients or between different age groups.

DISCUSSION

IAP has important roles in the intestine; for example, intestinal epithelial microvilli-derived vesicles are highly enriched with IAP, which dephosphorylate endotoxin lipopolysaccharides, prevent adhesion of pathogens and commensal bacteria to intestinal epithelial cells, and presence of pathogens stimulate secretion of these vesicles.[13,14] Moreover, IAP maintains normal gut microbial homeostasis.[15] This action of IAP helps our favourable gut bacteria to cooperate with the immune system at the level of our intestinal epithelial cells, to prevent growth and action of pathogenic bacteria. In addition, our normal gut microflora provides us with nutrients essential for our body. Also, IAP regulates bicarbonate secretion and duodenal pH, long chain fatty acid absorption and mitigates intestinal inflammation.[16,17] In short, it is logical to assume that decrease in IAP can cause alteration in intestinal motility leading to diarrhea, constipation, etc.

Malo MS found that compared to healthy nondiabetic controls, T2DM patients had reduced levels of stool IAP levels.[18] Another group of researchers found that mice deficient in IAP had increased intestinal permeability and circulating levels of lipopolysaccharides. The mice also showed features of metabolic syndrome such as increased blood glucose and insulin resistance. When the control group of mice was administered high fat diet and IAP, development of metabolic syndrome was completely prevented; in addition, features of metabolic syndrome were reversed.[19] In another study, antibiotic treatment of mice in early life made them more susceptible to metabolic syndrome in adulthood, but when IAP was administered along with antibiotic treatment, the susceptibility to metabolic syndrome was prevented completely.[20]

In the present study group 1 subjects had highly significantly decreased IAP levels with respect to group 2 subjects (Table 2). Thus, the protective effects of IAP were less in T2DM patients with enteropathy, when compared to T2DM patients without intestinal complications. For example, when IAP is decreased, alteration in intestinal pH may cause impairment of normal digestive process, leading to diarrhea or constipation. In vitro experiments of human enteric glial cells have shown that inflammation induces proinflammatory pathways, which causes changes in functional signalling pathways linked to gastrointestinal motility like mechanical-evoked calcium and purinergic signaling; this provides further evidence of the link between inflammation and gastrointestinal dysfunction, and this is another mechanism for diarrhea or constipation when IAP is reduced.[21] Also, since IAP detoxifies endotoxin lipopolysaccharide leading to local intestinal and systemic anti-inflammatory effects, decrease of IAP enables pathogenic bacteria to attach to intestinal epithelial cells and exert their action via toxins. So, reduction of IAP levels in patients with diabetic enteropathy can lead to decrease in protective effects due to multiple pathways and ultimately cause diarrhea.

Though only further research in this area can corroborate our findings, the present study has limitations that must be considered. IAP was assessed by ELISA. IAP can be estimated by various methods, but the present method was employed as it is a time tested, commonly used, and standard method. Also, the number of patients in the study groups was not large. Thus, care must be taken in extrapolating the present findings to the general population. Further, the patients were taking a number of medications to control enteropathy. However, these treatments are characteristic of patients with diabetic enteropathy and do not affect serum IAP levels. Lastly, we conducted the present study in a tertiary care hospital. However, in our country, most people visit district, sub divisional, and lower tier hospitals for treatment. Hence, results of our study might not reflect the true picture of the population as a whole. Probably, a multicentric study on a larger population would be better in revealing the actual statistics. Despite these limitations, we believe that our study points towards using IAP as an important, promising, potential marker for diabetic enteropathy. As our findings point to a decrease in IAP, the problem of enteropathy in T2DM should also be further investigated, and other markers should be assessed.

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