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EFFECT OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS ON SERUM AMYLASE AND LIPASE IN PATIENTS WITH HYPERTENSION

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ABSTRACT: Introduction: Angiotensin-converting enzyme (ACE) inhibitors are a class of potential drugs used as first-line agents for the treatment of hypertension and heart failure in physiologically young patients despite its side effects. Apart from the other common side effects, they are known to induce bradykinin release which alters vascular permeability leading to pancreatic edema resulting in intrapancreatic entrapment of enzymes, toxins and acute pancreatitis. **Objective:** To determine the effect of long term ACE inhibitors use on serum amylase and lipase levels. **Methods:** A total of 122 patients were divided into two groups as case and control group, were case group the patients using ACE inhibitors for more than 8 months, and control group is the patients who are on other antihypertensive. Pancreatic enzyme levels were measured by ELISA method, and the elevation of pancreatic enzymes was determined in both the group and compared by Unpaired T-test. **Results:** Study showed a significant difference in amylase levels between case and control groups ($P \leq 0.002$) and Lipase level among case and control groups ($P \leq 0.003$). Further, confounding factors were adjusted on ACE inhibitor usage. **Conclusion:** The use of ACE inhibitors showed a significant association with elevated serum amylase and lipase levels in hypertensive patients. Our study suggests the monitoring of serum amylase and lipase levels in patients who are on ACE-inhibitors and its administration must be stopped as soon as an increase of serum amylase and lipase is evident for causing acute pancreatitis.

INTRODUCTION: Angiotensin - converting enzyme (ACE) inhibitors are a class of potential drugs used as first-line agents for the treatment of hypertension and heart failure in physiologically young patients [1]. Despite their profound established role in ensuring adequate control of blood pressure, their use is limited because of associated adverse events.

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ACE inhibitors generally induce bradykinin release and thereby causing a nocturnal dry cough and generalized angioedema that is often manifested in lips, tongue and upper airway [2, 11]. Also, several clinical case studies across the globe have demonstrated a close association between ACE inhibitor use and acute pancreatitis [4, 12].

Numerous etiologic factors can cause acute pancreatitis, among which gallstones and alcohol intake, being the most common. Other factors include hypertriglyceridemia, hyperparathyroidism, toxins, pancreatic structural abnormalities, pancreatic trauma, and infections. Many drugs are also reported to cause acute pancreatitis which includes ACE inhibitors.

It has been postulated that ACE inhibitors elevate bradykinin levels by inhibiting their degradation, this is known to cause vascular permeability, therefore precipitating the risk of angioedema in several blood vessels, lymphatic's and pancreatic duct. Pancreatic edema results in intra-pancreatic entrapment of enzymes, toxins are leading to acute pancreatitis.

However, clinical studies supporting the claim of long term ACE inhibitors use associated with pancreatitis and elevate serum amylase, and lipase is limited. Hence, this study was designed to determine the relationship between long term ACE inhibitors use and elevation of pancreatic enzyme levels.

METHODOLOGY:

Subject Selection: Our study was designed as a prospective cohort for 6 months (December 2017-May 2018). A total number of 122 patients were recruited who signed informed consent, from Employee State Insurance Corporation Multi-specialty Hospital based on the study's inclusion and exclusion criteria, among which 61 patients diagnosed with hypertension and are on ACE inhibitors at least for a period of 8 months were under the case group and patients diagnosed with hypertension and are not on ACE inhibitors were under the control group.

Inclusion Criteria: Patients of both gender within the age of 18-55 years diagnosed with hypertension as per JNC-8 guidelines and are on treatment either with ACE inhibitors monotherapy or regimens containing ACE inhibitors at least for eight months and willing to provide written informed consent during enrolment will be included into the study.

Exclusion Criteria: Patients diagnosed with hypertension and are on treatment with ACE inhibitors for a period of less than eight months and those who have acute or chronic pancreatitis (based on USG-abdomen, baseline serum amylase (>100U/L) and lipase levels (>38U/L)), pancreatic cancer of any origin or pancreatic metastasis, type I diabetes mellitus, renal impairment (GFR not less than 30% from baseline value), or any other pancreatic diseases were excluded from our study. Vulnerable patients and special population were also excluded.

Procedure: Approval of study protocol by the Institutional Ethical Committee (Ref: VISTAS-SPS/IEC/III/2017/02) of VISTAS was obtained before commencement. Blood samples were collected from patients of both the groups by vein puncture method, where the site of injection was cleaned with cotton swab using spirit. Estimation of amylase and lipase in serum matrix was carried out using enzyme-linked immune sorbent assay.

Statistical Analysis: All statistical analysis was carried out using IBM-SPSS 21.0and Graph Prism. Relationship between the long term use of ACE inhibitors and the incidence of pancreatitis was determined using Chi-Square analysis. Effect of confounding variables on ACE inhibitors use causing pancreatitis was determined using Odds ratio. And both the groups on and without ace inhibitors usage were compared using independent t-test analysis.

RESULTS: Out of 122 patients included in the study, 61 patients were cases that are patients diagnosed with hypertension and are on ACE inhibitors at least for 8 months, and 61 patients were controlled that is patients diagnosed with hypertension and are not on ACE inhibitors. In this study, there was a number of male patients compared to female (shown in **Fig. 1**).

Table 1 shows, alcoholics were more, and smokers were less in case group compared to that of the control group. Various comorbid conditions were identified among both the groups as shown in **Table 2**. **Table 3** and **4** show the difference in elevated amylase and lipase level in case and control groups **Fig. 3** and **4**. Various confounding factors were identified in the study that would lead to an elevation in pancreatic enzyme levels in serum other than the use of ACE inhibitors, and their effect was nullified by odds ratio as shown in **Table 7** and **Fig. 8**.

TABLE 1: DISTRIBUTION BASED ON SOCIAL HABITS

Social habits	No. of cases	% of cases	No. of controls	% of controls
Smoker	11	18.03	14	22.95
Alcoholic	11	18.03	6	9.83

TABLE 2: DISTRIBUTION BASED ON COMORBIDITIES

Comorbidity	No. of cases	% of cases	No. of control	% of controls
HTN	61	100	61	100
DM	16	26.22	22	36.06
Liver disease	5	8.19	1	1.63
Dyslipedimia	10	16.39	7	11.475

TABLE 3: OBSERVED PANCREATIC ENZYME LEVELS IN CASE AND CONTROL GROUPS

Parameters	Case group	Control group	P value
amylase	109.2027 ± 12.77	103.79 ± 8.37	.002
lipase	46.32 ± 4.98	40.313 ± 2.71	.003

TABLE 4: ANALYSIS OF ELEVATED PANCREATIC ENZYME LEVELS IN CASE AND CONTROL GROUPS

Pancreatic enzymes	No. of patients in the case group	Incidence in case group	No. of patients in the control group	The incidence in the control group	Relative risk	% of the confidence interval	P value
Amylase	37	60.65%	23	37.70%	1.85	1.273-2.739	0.0016
Lipase	37	60.65%	11	18.03%	2.377	1.672-3.41	<0.0001

*Relative risk 1.000 no risk of the outcome due to exposure, >1.000 increased risk and<1.000 reduced risk.

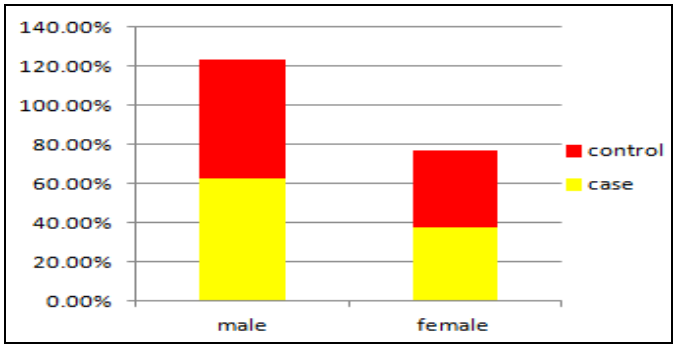

FIG. 1: DISTRIBUTION OF CASE AND CONTROL GROUPS BASED ON GENDER

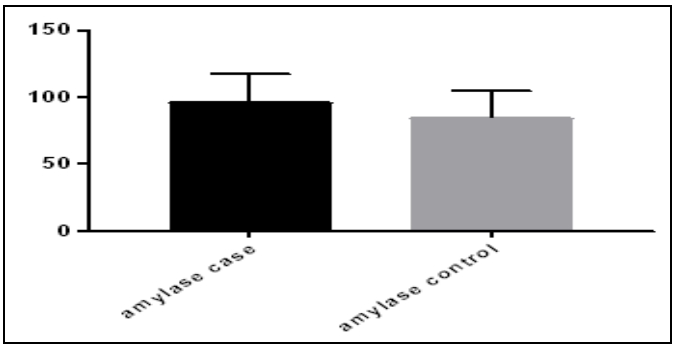

FIG. 2: ELEVATED AMYLASE LEVELS AMONG CASE AND CONTROL GROUPS

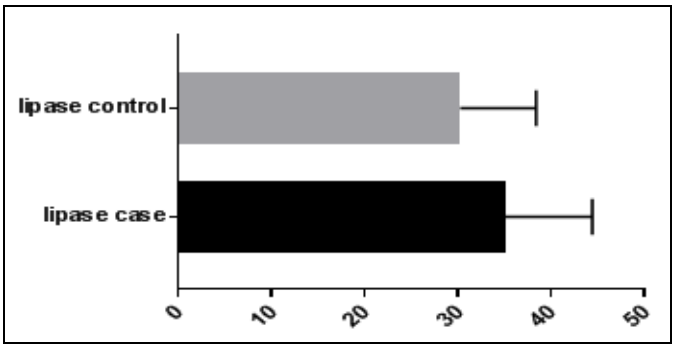

FIG. 3: ELEVATED LIPASE LEVELS AMONG CASE AND CONTROL GROUPS

TABLE 5: ANALYSIS OF FACTORS PREDISPOSING PATIENTS TO ELEVATION OF PANCREATIC ENZYME LEVELS AND CONFOUNDING THEIR EFFECT

Factors	Odds ratio	95% confidence interval	P value
Alcoholic	3.413	1.203-9.728	0.0168
Smoker	1.261	0.5439-2.898	0.6062
DM	0.8649	0.4092-1.852	0.7102
Liver disease	1.308	0.0676-25.17	0.8504
Dyslipidemia	1.103	0.4912 -2.418	0.8445

*Odds Ratio 1.000 no odds of the outcome due to exposure, >1.000 increased risk and<1.000 reduced risk

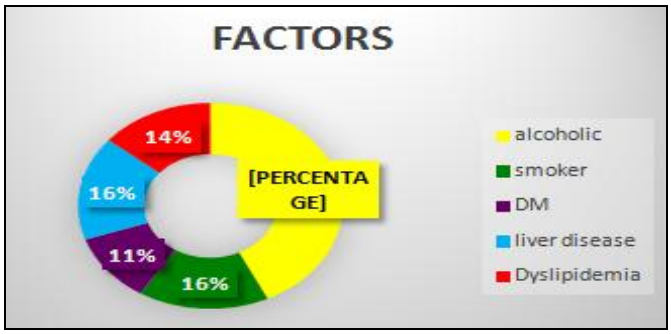

FIG. 4: FACTORS PREDISPOSING PATIENTS TO ELEVATED PANCREATIC ENZYME LEVELS

DISCUSSION: Only a few reports have been published associating pancreatitis with ACE inhibitor therapy. A few cases have been lethal [3]. In many countries, pancreatitis is a labeled adverse effect of ACE inhibitors [2, 3]. However, recent literature on acute pancreatitis does not always recognize ACE inhibitors as potential causative agents. Pancreatitis has been seen about treatment with sulfhydryl ACE inhibitors (captopril) as well as with nonsulfhydryl ACE inhibitors (*e.g.*, lisinopril and enalapril) [11].

The mechanism or mechanisms by which ACE inhibitors may induce pancreatitis are, however, yet unknown. It has been suggested that ACE inhibitors may have a direct toxic effect on the pancreas, or may potentiate the effect of various toxins on the pancreas [10]. A possible mechanism of action for angiotensin-converting enzyme (ACE) inhibitor-induced acute pancreatitis is proposed to follow the mechanism of local angioedema of the pancreatic duct [7]. ACE inhibitors decrease the degradation of bradykinin that is linked to the development of angioedema. Demonstrations show that bradykinins are released during acute pancreatitis, which is in concordance with observed increased vascular permeability in the pancreas during acute pancreatitis.

This release can result in pancreatic edema, causing enzymes and other toxic substances to be trapped within the pancreas and leading to tissue damage in the pancreas and acute pancreatitis [1]. This supports the notion that localized tissue edema may be an important pathogenic factor. With the increasing use of ACE inhibitors, the incidence of rare adverse effects such as potentially lethal pancreatitis is likely to increase. Clinicians should thoroughly review patients, complaints of abdominal pain (and other symptoms associated with acute pancreatitis) and their possible association with ace inhibitor therapy [11].

In this study, we measured serum amylase and lipase levels in both case *i.e.* hypertensive patients on ace inhibitors and controls *i.e.* hypertensive patients those are not on ace inhibitors to identify whether ace inhibitors causes elevation of these pancreatic enzyme levels or not, and it was found that the incidence of pancreatitis was more in case groups than the control group.

A previous study demonstrated that serum amylase and lipase levels are elevated with the use of ace inhibitors. This report is consistent with our finding that use of ace inhibitors causes an elevation in serum amylase and lipase levels [10]. Further, various factors that predispose patients to pancreatitis other than ace inhibitors usage was determined in hypertensive patients of both the groups, And it was found that factors like alcohol consumption, smoking, co-morbidities like Liver disease and dyslipidemia predispose patients to elevation of serum amylase and lipase levels and their effect were confounded over the use of ace inhibitors.

The mechanisms of these factors causing pancreatitis are still unknown, but various common theories have been proposed. A few laboratory studies show the mechanism by which smoking contributes to pancreatic injury or by which smoking accelerates the pancreatic inflammatory process and have found that activation of multiple signal transduction pathways due to nicotine exposure results in high levels of intracellular calcium release and may be responsible for cell cytotoxicity and cell injury in pancreas [9].

According to the most common theory, the excess of triglycerides is hydrolyzed by pancreatic lipase, and free fatty acids (FFAs) are formed in high concentrations. This FFAs overwhelm the binding capacity of albumin and self-aggregate to micellar structures with detergent properties. Thus, acinar cell and pancreatic capillary injury are promoted. The resultant ischemia creates an acidic environment, which further enhances FFA toxicity [6, 7, 10]. A further underlying pathophysiological principle may be hyperviscosity due to elevated levels of chylomicrons. Hyperviscosity due to hyperchylomicronemia supposedly leads to ischemia and acidosis in pancreatic capillaries.

Additionally, there is evidence that FFAs damage the endothelium and, thus, acute pancreatitis may be associated with (micro-) thrombosis and further ischemia [8]. Endoplasmic reticulum stress has also been implicated in hyperglycemia [4]. Other studies showed the effects of alcohol on the pancreas are most likely due to direct toxic effects of its metabolites (such as acetaldehyde and fatty acid ethyl esters), and the by-products of ethanol metabolism such as reactive oxygen species.

Recent experimental evidence indicates that endotoxinemia (known to occur in alcoholics secondary to an alcohol-induced increase in gut mucosal permeability), may be an important cofactor in alcohol-related pancreatic injury. The three major cell types in the pancreas affected by alcohol exposure include acinar cells, ductal cells, and stellate cells; damage to these cells drives the acinar cell death, calcification and fibrosis of alcoholic pancreatitis [2].

CONCLUSION: In our study, the use of ACE inhibitors showed significant association with elevated serum amylase and lipase levels in hypertensive patients. The incidence of elevated serum amylase and lipase levels on ace inhibitor usage was confounded from various risk factors like alcoholism, smoking, dyslipidemia and liver disease that may predispose patients to pancreatitis. Our study suggests the monitoring of serum amylase and lipase levels in patients who are given ACE-inhibitors even with or without clinical evidence of abdominal pain to prevent the incidence of acute pancreatitis. We support the theory that ACE-inhibitor administration must be stopped as soon as an increase of serum amylase and lipase is evident without waiting for clinical or instrumental evidence of acute pancreatitis and substituted with some other safe drug.

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