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Research Article

THE IMPACT OF HEAVY ALCOHOL CONSUMPTION AND CIGARETTE SMOKING ON LIVER FUNCTION – A CLINICAL SURVEY

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ABSTRACT

Objective: In the present study, attempts are made to evaluate the impact of alcohol consumption and cigarette smoking on the normal functioning of liver. Low and high alcoholic smokers and non smokers were compared with normal healthy persons.

Methods: Hematological, Biochemical and enzymatic parameters were analyzed using standard procedures.

Results: The levels of polymorphic cells, lymphocytes, hemoglobin, red blood cells, packed cell volume, platelet count were decreased in alcoholic smokers when compared to normal where as Eosinophils and Mean corpuscular volume were increased. The levels of urea, creatinine, uric acid and total bilirubin and globulin were increased in the alcoholic smokers where as total protein and albumin levels were decreased. There was an increase in the levels of total cholesterol, low density lipoprotein, very low density lipoprotein, triglycerides and decrease in high density lipoprotein levels of alcoholic smokers. Elevated levels of liver marker enzymes such as Aspartate transaminase, Alanine transaminase, Alkaline phosphatase and gamma glutamyl transferase further support the hepatic damage caused by alcoholism together with smoking.

Conclusion: The results of the present study clearly demonstrate the deranged functioning of the liver cells due to heavy alcohol consumption along with smoking.

Keywords: Alcoholism, Alcoholic liver disease, Cigarette smoking, Cigarette smoke induced liver disease, Gamma glutamyl transferase.

INTRODUCTION

Alcohol consumption is well entrenched in the social fabric of many adult populations, virtually constituting a behavioural norm. It is legal, readily available and cheap. Sustained excessive alcohol consumption is a brain-centred addictive behavioural disorder that crosses all boundaries of gender, race, age, economic strata and in many patients, might lead to alcoholic liver disease (ALD)[1,2,3]. Heavy drinking significantly increases morbidity and mortality from infectious diseases [4] and the risk of cardiovascular, brain, pancreatic, renal, cerebral and oncological diseases.

Alcoholic liver disease represents a spectrum of clinical illness and morphological changes that range from fatty liver to hepatic inflammation and necrosis (alcoholic hepatitis) to progressive fibrosis. Furthermore, sustained excessive alcohol intake favours the progression of other liver diseases, such as virus-related chronic hepatitis, also increasing the risk of hepatocellular carcinoma [5,6,7].The mechanisms of alcohol hepatotoxicity are complex and multifactorial. It is likely that several primary and secondary factors interact to initiate and perpetuate alcoholic liver injury. Primary factors certainly include genetic background and its complex interrelationship with direct ethanol hepatotoxicity and alcohol-induced metabolic and immunological changes. Secondary factors, such as nutritional and hepatotoxic co-morbid conditions, can critically contribute to the development of liver disease [8, 9].

Extensive research supports the popular observation that "smokers drink and drinkers smoke". Moreover, the heaviest alcohol consumers are also the heaviest consumers of tobacco. Concurrent use of these drugs poses a significant public health threat. Adolescents who begin smoking are 3 times more likely to begin using alcohol [10] and smokers are 10 times more likely to develop alcoholism than are nonsmokers [11]. Smoking and excessive alcohol consumption is risk factors for cardiovascular, liver, lung diseases and for some forms of cancer.

Hence in the present study, attempts are made to carry out a clinical survey of 50 male persons from the villages in and around Pattukkottai, Tamil nadu, to evaluate the impact of heavy alcohol consumption and cigarette smoking on the normal functioning of liver.

MATERIALS AND METHODS

Study Protocol

A total of 50 male persons residing in the villages around Pattukkottai, Tamilnadu were selected for the present study. They were all age matched and had same socio-economic status. Patients suffering from disease of any origin other than alcohol intake and cigarette smoking were excluded from the study. The selected persons were subjected to detailed clinical examination and laboratory investigations.

Study Design

The selected persons were divided in to 5 groups (n=10).

Group 1: The persons in this group are normal and healthy persons.

Group 2: The persons of this group are low alcoholic (weekly twice) non smokers

Group 3: The persons of group 3 are low alcoholic smokers.

Group 4: This group includes the persons with a history of high alcohol intake (daily) without smoking.

Group 5: The persons of this group are high alcoholic smokers.

Demographic Profile

The persons for the present study are with in the age group of 35 – 45 years. The height, weight and body mass index of the selected persons are measured according to the standard procedures.

Biochemical Profile

Hematological, Biochemical and Enzymatic parameters are analyzed using standard procedures.

Statistical analysis

The data of the present investigation are expressed as mean ± standard error (n=10).

RESULTS AND DISCUSSION

Alcoholism is a major public health problem worldwide. Chronic alcohol consumption produces many harmful effects to the vital internal organs. Liver is an important organ which is considered as

central metabolic machinery. Chronic alcoholism affects the normal functioning of the liver to a great extent. Severity of liver damage is often correlated with the amount of alcohol consumption. Alcoholic liver disease has a known etiology but a complex and incompletely known pathogenesis. It is an extremely common disease with significant morbidity and mortality. In addition to the cumulative amount of alcohol intake and alcohol consumption patterns, factors such as gender and ethnicity, genetic background, nutritional factors, energy metabolism abnormalities, oxidative stress, immunological mechanisms and co-morbid conditions like cigarette smoking play a key role in the genesis and progression of alcoholic liver injury. Understanding the pathogenesis and risk factors of alcoholic liver disease should provide insight into the development of therapeutic strategies. Hence in the present study attempts are made to evaluate the impact of alcoholism and cigarette smoking on liver function.

In the present study, low alcoholic smokers and non smokers, high alcoholic smokers and non smokers were compared with a group of normal healthy persons. Their mean age, height, weight and body mass index (BMI) were determined (Table 1).

Table 1: Demographic profile of Normal healthy persons, Low alcoholic non smokers and smokers, High alcoholic non smokers and smokers

Parameters	Group I	Group II	Group III	Group IV	Group V
Age (yrs)	38.37 ± 1.14	39.86 ± 1.84	41.02 ± 1.41	42.75 ± 1.78	44.53 ± 1.54
Height (cm)	162.4 ± 60.45	162.68 ± 0.82	162.72 ± 0.39	162.81 ± 0.88	162.68 ± 0.65
Weight (kg)	64.8 ± 0.34	64.2 ± 0.31	64.1 ± 0.44	61.56 ± 0.56	58.25 ± 0.54
BMI (kg/m^2)	24.24 ± 0.85	24.18 ± 0.15	24.11 ± 0.11	23.15 ± 0.20	23.05 ± 0.14

High alcoholic smokers had significantly low body weight and low BMI compared to other groups. It was observed that alcoholics, as compared with social drinkers showed a lower body weight due essentially to fat mass reduction[12]. The same may be true for the present study also. A fall in body weight was the best clinical indicator of apparently continuing alcohol abuse [13]. Reduced adipose tissue is one cause of lower body weights in such patients. Loss of adipose tissue in chronic alcoholics who continue to drink and smoke is probably due to simultaneous inadequate nutritional intake. As ethanol can supply >50% of the dietary energy in alcoholics and chemicals of smoke produce an aversive feeling, body composition alterations may easily occur.

Alcohol has a variety of pathologic effects on hematopoiesis. It directly damages erythroid precursors, thereby contributing to macrocytosis and the anemic state of chronic alcoholics. Ethanol induces sideroblastic anemia, perhaps by direct interference with heme synthesis. Further, chronic ingestion of alcohol can lead to various types of hemolytic anemia caused by alterations in the erythrocyte membrane lipids that occur in association with alcoholic liver disease[14]. In the present study, the percentage of hemoglobin and total number of Red Blood Cells were found to be significantly decreased, whereas mean corpuscular volume (MCV) significantly increased in alcoholic liver disease with heavy alcohol intake and smoking in comparison to normal persons (Table 2). Significant difference in these values is also noted between non smokers and smokers. Because the red blood cell survive for 120 days after it has been released into the circulation, an mean corpuscular volume result may remain elevated for up to 3 months after a person has stopped drinking. But increase in mean corpuscular volume has been reported in other conditions such as thyroid disease, folate deficiency, recent blood loss and a number of hematological conditions, and liver disease from other causes[15]. Thus it cannot be taken as a sole parameter for alcoholic liver disease. However, no significant variation in either of the groups tested was observed in case of polymorphonuclear cells, lymphocytes. Eosinophil count is significantly increased in high alcoholic smokers, which might have been due to the smoke induced allergic reaction. Packed cell volume and platelet count were decreased in all the groups when compared with normal healthy persons.

Table 2: Haematological profile of Normal healthy persons, Low alcoholic non smokers and smokers, High alcoholic non smokers and smokers

Parameters	Group I	Group II	Group III	Group IV	Group V
Polymorphs (%)	60.4 ± 0.56	59.18 ± 0.41	58.7 ± 0.38	57.76 ± 0.72	57.68 ± 0.74
Lymphocytes (%)	36.8 ± 0.64	36.4 ± 0.46	35.4 ± 0.68	34.8 ± 0.54	34.2 ± 0.91
Eosinophils (%)	2.8 ± 0.24	3.2 ± 0.22	3.5 ± 0.26	3.6 ± 0.19	3.8 ± 0.25
Hemoglobin (g/dL)	14.8 ± 0.11	14.75 ± 0.12	14.23 ± 0.15	12.86 ± 0.26	11.01 ± 0.15
Red Blood Cell Count (millions/cu.mm)	5.1 ± 0.30	5.0 ± 0.15	4.9 ± 0.17	4.8 ± 0.94	4.7 ± 0.75
Packed cell volume (%)	46.6 ± 0.56	42.6 ± 1.51	42.2 ± 0.52	41.5 ± 0.25	41.3 ± 0.69
Mean Corpuscular Volume	85.36 ± 0.70	90.2 ± 0.86	91.6 ± 0.92	94.4 ± 0.65	101 ± 0.6
Platelet count (lakhs/cu.mm)	3.26 ± 0.10	3.32 ± 0.17	3.3 ± 0.78	3.4 ± 0.14	2.9 ± 0.01

Patients with various forms of liver disorders showed hyperbilirubinemia. In the present study, there is an increase in total bilirubin level of serum of moderate and heavy alcoholic non smokers and smokers (Table 3) respectively. It was also found that serum bilirubin level was elevated in nonalcoholic liver disease[16].Further it was observed that the maximum patients were showing either elevated mono conjugated or albumin-bound bilirubin in serum. Uptake and excretory functions of liver is constrained depending upon the increment of bilirubin level of serum.

Even though the urea level was found to be within normal range in all the tested groups, there was an elevation in the urea level from healthy persons to heavy alcoholic smokers. Significant increase in uric acid level was observed in alcoholic liver disease groups with respect to other two groups, and high alcohol intake group showed significantly higher uric acid value when compared with moderate alcohol intake group (Table 3). Therefore, the bilirubin level in association with urea, creatinine, and uric acid may be used as markers for the diagnosis of alcohol and smoke induced liver damage. Creatinine level was also gradually increased in all the groups compared with normal persons suggesting the alcohol and smoke induced renal damage.

Though only heavy alcoholic group showed significant increase in globulin level in comparison to other groups, the albumin level was found to be significantly decreased in all the tested groups when compared with normal group. Hypoalbuminemia was observed in all the tested groups. Like the albumin values, same pattern of alterations

was observed in albumin: globulin ratios (Table 4). Common features of chronic alcoholic liver disease are progressive hypoalbuminemia [17]. Acute exposure to alcohol depressed albumin. The decrease in serum albumin level is attributed to nutritional status of the subjects [18]. On the other hand, the albumin is a potential subject of formation of adduct by acetaldehyde, an alcohol metabolite. This albumin or other protein adducts can stimulate the formation of immunoglobulins, thus causing a rise in serum globulin level[19]. In the present study significant decrease in total protein was observed in all the tested groups when compared with normal healthy group, and heavy drinkers were found significantly low value compared to any other groups.

Table 3: Levels of Urea, Creatinine, Uric acid and Total bilirubin in Normal healthy persons, Low alcoholic non smokers and smokers, High alcoholic non smokers and smokers.

Parameters	Group I	Group II	Group III	Group IV	Group V
Urea (mg/dL)	26.6 ± 0.51	25.2 ± 1.75	22.1 ± 0.85	20.02 ± 1.75	21.6 ± 1.65
Creatinine (mg/dL)	0.92 ± 0.02	1.02 ± 0.03	1.10 ±0.01	0.86 ± 0.04	0.82 ±0.05
Uric acid (mg/dL)	4.12 ± 0.29	4.46 ± 0.24	4.43 ± 0.18	5.36 ±0.25	5.43 ± 0.19
Total bilirubin (g/dL)	0.62 ± 0.23	0.68 ± 0.05	0.7 ± 0.08	2.08 ± 0.15	2.19 ± 0.81

Table 4: Levels of Total Protein, Albumin, Globulin and A/G Ratio in Normal healthy persons, Low alcoholic non smokers and smokers, High alcoholic non smokers and smokers.

Parameters	Group I	Group II	Group III	Group IV	Group V
Total protein (gm/dL)	7.64 ± 0.19	7.04 ± 0.08	7.76 ± 0.11	6.7 ± 0.12	6.68 ± 0.11
Albumin (gm/dL)	4.52 ± 0.16	4.28 ± 0.04	4.40 ± 0.07	4.62 ± 0.10	4.34 ± 0.06
Globulin (gm/dL)	3.06 ± 0.55	3.28 ± 0.33	3.08 ± 0.07	3.18 ±0.34	3.16 ± 0.15
A/G Ratio (gm/d)	1.44 ± 0.28	1.50 ± 0.11	1.42 ± 0.14	1.42 ± 0.14	1.42 ±0.16

Smoking is a significant risk factor for Ischemic heart disease. There are several studies showing association between cigarette smoking and altered serum lipid and lipoprotein concentrations. These alterations, which are associated with smoking, are higher serum levels of Total Cholesterol, Triglycerides, Very Low Density Lipoprotein-Cholesterol, Low Density Lipoprotein-Cholesterol and lower serum levels of High Density Lipoprotein-Cholesterol and Apo protein. Many of these variables have been associated with an increased risk of Ischemic heart disease[20] (Table 5). Several studies have reported that serum High Density Lipoprotein-Cholesterol level is found to be lower in smokers than in non-smokers [21,22, 23].

Table 5: Lipid profile of Normal healthy persons, Low alcoholic non smokers and smokers, High alcoholic non smokers and smokers.

Parameters	Group I	Group II	Group III	Group IV	Group V
HDL Cholesterol (gm/dL)	53.8 ± 1.62	48.4 ± 0.86	42.2 ±0.50	38.5 ± 0.96	38.9 ± 0.98
LDL Cholesterol (gm/dL)	116.6 ± 4.44	117.4 ± 3.55	118.4 ± 2.24	129.6 ± 2.78	129.9 ± 2.98
VLDL Cholesterol (gm/dL)	27.2 ± 3.47	28.8 ± 0.19	29.6 ± 0.90	35.4 ± 0.85	37.8 ± 0.78
Triglycerides (mg/dL)	136.8 ± 2.22	140.8 ± 2.80	142.8 ± 2.84	154.2 ± 3.58	155.8 ± 3.79
LDL/HDL Ratio	3.08 ± 0.17	3.10 ± 0.18	3.62 ± 0.13	4.12 ±0.20	4.16 ± 0.26

Significant increase in alkaline phosphatase, gamma glutamyltransferase, aspartate aminotransferase and alanine aminotransferase activities were observed in alcoholics in comparison to healthy controls as well as in heavy drinkers in comparison to moderate drinkers (Table 6). Alanine amino transferase (ALT) and aspartate amino transferase (AST) are present in high concentration in hepatocytes. These enzymes leak into the circulation when hepatocytes or their cell membranes are damaged. Although these aminotransferases are sensitive indicators of liver cell damage, neither alone is an ideal marker. In the non-alcoholic liver disease, the activities of Asparatate aminotransferase, and Alanine aminotransferase were increased significantly in comparison to normal healthy individuals. Significant increase in activities of these enzymes were also observed in the moderate and heavy alcohol intake groups in comparison to normal healthy individuals; Serum aminotransferase concentrations are moderately raised in chronic and milder cases of acute viral or drug-induced hepatitis, autoimmune hepatitis, and alcoholic liver disease . Slightly raised serum aminotransferase levels characterize cirrhosis, non-alcoholic steato hepatitis, cholestatic liver disease, fatty liver, and hepatic neoplasms.

Deficiency of pyridoxal-5'-phosphate, a necessary coenzyme for both aminotransferases, is common in alcoholic liver disease. This deficiency decreases hepatic Alanine aminotransferase to a greater extent than Asparatate aminotransferase, with corresponding changes in serum concentration. Hence, the AST/ALT ratio is a good marker of Alcoholic Liver Disease.

In the present study, the serum ALP level was significantly higher in all the groups and heavy groups of alcoholics in comparison to healthy volunteers. This study shows that chronic intake of ethanol increases serum activities of enzymes originating from liver plasma membranes but has different effects on the enzyme activity in liver plasma membranes itself, suggesting that the alcohol mediated increase of serum activities of various enzymes originating from liver plasma membranes might be due to different mechanisms. Monitoring alkaline phosphatase level is also helpful in identifying the cause and severity of liver damage.

In case of γGT, all the groups showed significantly higher activities than the normal healthy volunteers (Table 6). γ-glutamyltransferase (γGT) is a biliary canalicular enzyme, which is induced by alcohol, and serum levels also rise in response to acute hepatocellular damage. γGT characterizes chronic, long-term misuse of alcohol. Even significant difference was also observed between the moderate and heavy alcoholics. Experimental evidence present that the determination of γGT activity in serum is useful in the assessment of alcohol-induced liver disease. However, there was no significant correlation between the severity of liver damage and the extent of γGT increase at the beginning and at the end of the follow-up period[24]. With several studies, serum γGT is the most sensitive, moderate specificity, most widely employed marker of alcohol consumption. Recently it has been suggested that subjects with very high γGT seem to demonstrate a more intense vulnerability to alcohol, a characteristic that appears to be stable over time[25]. Thus in the present study, moderately high level of γGT in moderate

group of alcoholics and very high levels of γGT in heavy group of alcoholics indicating that these patients are consuming high amount of alcohol and they are really at the risk or suffering from liver disorders.

Table 6: Serum Enzyme markers of Normal healthy persons, Low alcoholic non smokers and smokers, High alcoholic non smokers and smokers

Parameters	Group I	Group II	Group III	Group IV	Group V
Asparatate transaminase (IU/L)	20.8 ± 0.25	45.6 ± 0.35	47.8 ± 0.84	132.4 ± 11.74	134.7 ± 12.53
Alanine transaminase (IU/L)	19.8 ± 0.98	37.1 ± 0.76	38.4 ±0.15	90.6 ± 8.56	91.7 ± 8.88
Alkaline phosphatase (IU/L)	208 ± 3.30	289 ±11.29	296 ± 12.19	340 ± 29.27	348 ± 28.26
Gamma glutamate transferase (IU/L)	19.6 ± 1.42	54.4 ± 3.46	56.7 ± 3.65	232 ± 29.22	254 ± 29.78

The findings of the present study clearly demonstrates the impact of alcoholism and smoking on the liver function. Heavy alcoholism alone is a major factor to cause liver disease but when it is associated with the co-morbid conditions like cigarette smoking, smoke induced generation of free radicals aggravates the condition to the greatest extent, and results in mortality. Hence Government should take the necessary initiatives to ban such harmful practices in order to develop a healthier and prosperous society.

REFERENCES

1. Lelbach, W.K. Cirrhosis in the alcoholic and its relation to the volume of alcohol abuse. Ann N Y Acad. Sci.1975, 252: 85–105.
2. Becker, U., Deis, A., Sorensen, T.I. Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. Hepatology. 1996,23: 1025–1029.
3. Tome, S. and Lucey, M. R.Review article: current management of alcoholic liver disease. Aliment Pharmacol Ther . 2004, 19: 707–714.
4. Cook, R. T. Alcohol abuse, alcoholism, and damage to the immune system – a review. Alcohol Clin Exp Res.1998, 22: 1927–1942.
5. Bellentani, S., Saccoccio, G., Costa G.. Drinking habits as cofactors of risk for alcohol induced liver damage. The Dionysos Study Group. Gut.,1997, 41: 845–850.
6. Safdar, K. and Schiff, E.R. Alcohol and hepatitis C. Semin Liver Dis., 2004,24: 305–315.
7. Mandayam, S., Jamal, M.M. and Morgan, T.R. Epidemiology of alcoholic liver disease. Semin Liver Dis.,2004, 24: 217–232.
8. Neuberger, J., Schulz, K.H., Day, C. Transplantation for alcoholic liver disease. J Hepatol.,2002, 36: 130–137.
9. Arteel, G., Marsano, L, Mendez, C., Bentley, F., McClain, C.J. Advances in alcoholic liver disease. Best Pract. Res. ClinGastroenterol., 2003,17: 625–647.
10. Hughes, J.R. Clinical implications of the association between smoking and alcoholism. Alcohol and Tobacco: From Basic Science to Clinical Practice. 1995,171-185.
11. Hurt, R.D., Eberman, K.M. and Croghan, I.T. Nicotine dependence treatment during inpatient treatment for other addictions: A prospective intervention trial. Alcohol Clin Exp Res.,1994, 18:867-872.
12. Addolorato, G., Capristo, E., Greco, A,V., Stefanini, G.F. and Gasbarrini G. Influence of chronic alcohol abuse on body weight and energy metabolism: Is excess ethanol consumption a risk factor for obesity or malnutrition. J Intern Med,1998, 244(5): 387- 395.
13. World MJ, Ryle PR, Jones D, Shaw GK, Thomson AD .Differential effect of chronic alcohol intake and poor nutrition on body weight and fat stores. Alcohol Alcohol,1984, 19(4): 281-290.
14. Nordmann, R. and Rouach, H. Alcohol and free radicals: from basic research to clinical prospects. Gastroenterol Hepatol,1996, 32(3): 128-133.
15. Whitfield, J,B., Hensley, W,J., Bryden, D. and Gallagher, H. Some laboratory correlates of drinking habits. Annals Clin Biochem,1978, 15: 297-303
16. Ahlgren, A., Hedenborg, G., Norman, A. and Wisen, O. Serum bilirubin subfractions in patients with alcohol abuse during detoxication. Scand J Clin Lab Invest,1988, 48(4): 319-26.
17. Annoni, G., Arosio, B., Santambrogio, D., Gagliano, N. and Zern, M.A. Albumin and procollagen type I gene regulation in alcohol and viral-induced human liver disease. Boll Ist Sieroter Milan,1991, 70(1- 2): 391-397.
18. Oratz, M., Rothschild, M.A and Schreiber, S.S. Alcohol, amino acids, and albumin synthesis. II. Alcohol inhibition of albumin synthesis reversed by arginine and spermine. Gastroenterology,1976, 71(1), 123-127.
19. Waern, A.U. and Hellsing, K. Indices of alcohol intake. Comparison between serum concentrations of alkaline phosphatase and gamma glutamyltransferase in middle-aged men. Ups J Med Sci.,1980, 85(2), 159-163..
20. Craig, W.Y., Palomaki, G.E and Haddow, J.E. Cigarette smoking and serum lipid and lipoprotein concentrations : an analysis of published data. Br Med J.,1989,98 : 784-788.
21. Criqui, M.H., Wallace, R.B., Heiss, G., Mishkel, M., Schnfeld, G., Jones, G.T.L. Cigarette smoking and plasma high-density lipoprotein cholesterol.The Lipid Research Clinics Program PrevalenceStudy1980, Circulation 62 (4) : 70-76.
22. Ito, T., Nishiwaki, M., Ishikawa, T. and Nakamura, H. CETP and LCAT activities are unrelated to smoking and moderate alcohol consumption in healthy normo lipidemic men. Jpn Circ J.,1995, 59 (8) : 541-546.
23. Siekmeier, R., Marz, W., Kronenberger, H., Seiffert, U.B and Groβ, W. Effects of cigarette smoking on plasma lipids, apolipoproteins and lipoprotein (a) in healthy subjects. Clin Chem.,1994, 40 (7) : 1350- 1351.
24. Krastev Z, Mateva L, Danev S, Nikolov R Clinical meaning of GGT activity in follow-up of patients with alcohol-related liver injury and cholestasis. Ital J Gastroenterol,1992, 24(4), 185-187.
25. Daeppen JB, Schoenfeld-Smith K, Smith TL, Schuckit MA. Characteristics of alcohol dependent subjects with very elevated levels of Gamma-Glutamyltransferase (GGT). J Stud Alcohol,1999, 60(5), 589-594.