Original article

HbA1c, a gold standard parameter, is really a gold standard in chronic alcoholic liver disease?

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Abstract

Introduction: Liver is the important organ to regulate glucose level in the body and uncontrolled glucose level in chronic liver disease will have poor prognosis. One of the major cause of chronic liver disease is alcohol ingestion. So,the study was undertaken to see the markers of chronic glucose control i.e. serum fructosamine and HbA1c along with the known markers of liver disease like SGOT to see the severity of the disease and serum total protein to see the synthetic capacity of liver.

Method:30 cases of chronic alcoholic liver disease patients with 30 age and sex matched healthy controls were taken.

Result: The mean concentration of serum total protein and HbA1c were decreased in cases. The mean concentrations of SGOT and serum fructosamine were increased in cases. SGOT was considered for correlation, it was found out that it had significant negative correlation with serum total protein, significant positive correlation with serum fructosamine and no correlation with HbA1c. Significant negative correlation was found between serum total protein and serum fructosamine.

Conclusion: This study shows that serum fructosamine is a better marker to monitor chronic glucose control in chronic alcoholic liver disease compared to HbA1c.

Key Words: Chronic alcoholic liver disease, HbA1c, serum fructosamine

Introduction:

Chronic liver disease in the clinical context is a disease of the liver that involves a process of progressive destruction and regeneration of the liver parenchyma leading to fibrosis and cirrhosis where clinical or biochemical features of liver disease persists for more than six months. Chronic alcoholic liver disease is a part of chronic liver disease.[1, 2]Alcoholic liver disease represents a spectrum of clinical illness and morphological changes that range from fatty liver to hepatic inflammation and necrosis to progressive fibrosis. Fatty liver is present in >90% of binge and chronic drinkers, which is a reversible condition, resolving with abstinence. Still the prognosis of severe alcoholic liver disease is dismal and the mortality of patients with alcoholic hepatitis concurrent with cirrhosis is nearly 60% at 4 years. [3, 4, 5]

Liver is a pivotal organ regulating plasma glucose level and liver plays a major role in regulating glucose metabolism, glucose metabolic abnormalities occur frequently in patients with chronic liver disease. It is also a major source of endogenous glucose and major site involved in insulin metabolism. It is important to maintain a good glycemic control status because it has been revealed that patients with chronic liver disease whose plasma glucose level is inadequately controlled often have poor prognosis and can develop complications related

to high or low blood glucose level. So it is necessary to monitor and maintain adequate glucose level.[6, 7]

Concentration of HbA1c provides a means of assessing long term glycemic status and correlate well with development of complications. The impairment of liver function has influence on result of HbA1c determination.[6]There will be increased activity of SGOT in alcoholics in comparison to healthy controls as well as in heavy drinkers in comparison to moderate drinkers which is dependent on hepatocyte damage.[8]Serum fructosamine (glycated protein) is used to document glycemic status over a period of 2-4 weeks. Fructosamine is a glycated protein, so fructosamine result depends on glycation of serum protein. The result might be altered by reduced hepatic protein synthesis due to impairment of liver function.[6]So the study is undertaken to see the levels of HbA1c and serum fructosamine in chronic alcoholic liver disease patients and in healthy controls and also to see relation between SGOT with HbA1c and serum fructosamine and serum total protein with serum fructosamine and SGOT.

Materials and Methods

A case-control study of glycated haemoglobin (HbA1c), SGOT, serum Total protein and serum fructosamine in chronic alcoholic liver disease subjects was carried out from May 2012 to April 2013. The study was carried out in chronic alcoholic liver disease and healthy controls selected from Bapuji Hospital and Chigateri General Hospital, Davangere (both these hospitals are attached to teaching institute, JJM Medical College, Davangere) and from general populations. Each subjects gave informed consent.

Subjects:

Based on inclusion and exclusion criteria a total number of 60 subjects were selected for the present study. Of the 60 subjects, 30 were chronic alcoholic liver disease cases and 30 were healthy controls.

Inclusion criteria:

Cases: 30cases of chronic alcoholic liver disease patients who were diagnosed with clinical history, liver function test and/or ultrasonography of the age group 20–70 years of both sexes.

30 cases were further divided into two groups.

Controls: 30 age and sex matched healthy controls.

Exclusion criteria:

Patient with the any other liver diseases except chronic alcoholic liver disease,Diabetes Mellitus, Renal Disease,History of blood loss, History of blood transfusion, Anaemia, Reticulocytosis, Erythropoietin treatment, Myocardial infarction, IHD, Hypertension were excluded from the study.

Based on the inclusion and exclusion criteria, age matched cases and controls were included in the study after obtaining informed consent.

Collection of blood sample:

About 5 ml of blood was drawn under all aseptic precautions from a large peripheral vein by using a sterile disposable syringe and collected in a sterile plain bulb and sterile EDTA bulb. The blood in the plain bulb was allowed to clot for about 30 minutes and then the serum was separated by centrifugation at 5000 rpm and kept at 4^0C until analysis was carried out. EDTA blood was kept at 4°c until analysis was carried out, which was used to prepare hemolysate for HbA1c.

Statistical analysis:

Statistical analysis was done by using SPSS software, version 17.0. Descriptive data were presented as mean ± SD and range values. Student't' test was used for comparing the means of two groups. Relationship between two parameters was assessed by Pearson's correlation coefficient.

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For all the tests, the probability value (p value) of less than 0.05 was considered statistically significant.

Result

The mean age of cases group was 45.3 ± 10.0 years with the range of 30 to 70 years. The mean age of control group was 45.1 ± 13.2 years with the range of 26 to 65 years. There was no significant difference among cases and control group for the age (p value > 0.96).

Table no. 1. Comparisons of serum total protein, SGOT, serum fructosamine and HbA1c among cases and controls.

Groups		S. Total protein (gm/dl)	SGOT (U/L)	S.Fructosamine (µmol/l)	HbA1c (%)
Cases	Mean ± SD	6.31 ± 0.73	58.30 ± 34.65	325.6 ± 51.5	4.38 ± 1.07
	Range	4.87 – 7.68	14.14 - 131.6	224.9 – 489.7	3.1 – 6.5
Controls	Mean ± SD	7.19 ± 0.85	18.86 ± 8.1	253.5 ± 43.1	6.35 ± 0.93
	Range	5.61 – 8.88	6.72 – 35.36	168 – 372.1	4.3 – 7.7
Cases and controls	Mean difference	0.88	39.44	72.1	1.97
	t value*	4.32	6.07	5.88	7.64
	p value	< 0.001	< 0.001	< 0.001	< 0.001

* Unpaired student‘t’ test

p value: > 0.05 - not significant, < 0.05 – significant, < 0.001- highly significant.

The statistical analysis done by unpaired student ‘t’ test showed that there was highly significant decrease in the serum total protein and HbA1c levels in cases with compare to controls (p value < 0.001). It also showed that there was highly significant increase in SGOT and fructosaminelevels in cases with compare to controls (p value < 0.001).

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Table no 2. Correlation of SGOT with serum fructosamine and HbA1c, serum total protein with serum fructosamine, SGOT with serum total protein.

Relation between	r – value	Significance (p value)
SGOT and HbA1c	- 0.08*	0.66
SGOT and serum fructosamine	+ 0.85**	< 0.001
SGOT and serum total protein	- 0.92**	< 0.001
Serum Total protein and serum fructosamine	- 0.86**	< 0.001

* Not significant, ** highly significant

+ sign: positive correlation; - sign: negative (inverse) correlation

r: Pearson's correlation coefficient.

As shown in table no. 2 there was negative correlation between SGOT and HbA1c (r value - 0.08), but it was not significant (p value 0.66). There was positive correlation between SGOT and serum fructosamine levels (r value + 0.85) which was statistically significant (p value < 0.001). There was negative correlation between SGOT and serum total protein (r value - 0.92), which was statistically significant (p value < 0.001). There was negative correlation between serum total protein and serum fructosamine (r value – 0.86), which was statistically significant (p value < 0.001).

Discussion

Liver is a pivotal organ in our body which plays a central role in the maintenance of metabolic homeostasis.In chronic liver disease there will be a process of progressive destruction and regeneration of the liver parenchyma leading to fibrosis and cirrhosis which is irreversible process and most of the deaths from alcoholic liver disease are attributable to complication of cirrhosis.[1, 9, 10]

In chronic alcoholic liver disease, glucose metabolic abnormalities occur frequently. It has been revealed that patients with chronic liver disease whose glucose level is inadequately controlled often have poor prognosis.[6, 7]In our study we found out that there significant decrease in the serum total protein level which is accordance with the studies done by Iliana Bouneva et al.[10], Kevin Walsh et al.[9] and D.M. Vasudevan et al.[11] Decrease in the hepatic synthetic function in the chronic alcoholic liver disease is quoted as the main reason of decrease in the serum total protein levels.

There is also significant increase in the SGOT levels in our study which supported by the studies done by H. Nyblom et al.[12], D.M. Vasudevan et al.[11] and Darius Sorbi et al.[13] The reason of increase in SGOT levels in chronic alcoholic liver disease is its presence in high concentration in hepatocytes. This enzyme leak into the circulation when hepatocytes or their cell membranes are damaged.[11] Negative correlation between serum total protein and SGOT suggests that as the SGOT values

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were increasing there is decrease in the serum total protein values. The SGOT value shows the hepatocytic function, as the values of SGOT values increases the hepatocytic damage increases. Serum total protein value shows the hepatocytic synthetic function. As the serum total protein values are decreasing, liver synthetic function is decreasing. This correlation is showing that as the hepatocytic damage is increasing, there is decrease in the hepatic synthetic function.

The serum fructosamine level was significantly increase in the case which is in accordance with the studies done by Theresa Lahousen et al.[6], Trenti T et al.[14] and Waad-Allah S Mula-Abed et al.[15] The reason behind the increase in the serum fructosamine levels was due to its dependence on the glycation of proteins and its half-life. The low levels of serum total proteins concentration diminishes its catabolism leading to an increase in its half-life and so to a greater degree of glycation on molar basis.[59]. The negative correlation between serum fructosamine and serum total protein is also due to increase in the half-life of the serum total protein.

The positive correlation between serum fructosamine and SGOT suggests that as the hepatocytic damage increases the serum fructosamine level also increases.In our study we also found out that the HbA1c level was significantly decreased in cases which is supported by the studies done by Theresa Lahousen et al.[6], Nomura Y et al.[16] and Trenti T et al.[14] The reasons behind the decrease in the HbA1c levels were either due to impairment of liver function which lead to glucose imbalance or due to disturbed erythropoiesis and decreased red cell survival.[6]There is negative correlation between HbA1c and SGOT but not significant which suggests that as hepatocytic damage increases, HbA1c will not be decreased accordingly. HbA1c, a gold standard marker to see the glycemic control over period of 3-4 months,HbA1c levels are dependent on the glucose concentration and life span of the RBCs mainly.This shows that decrease in the RBCs life span is the causative factor for the decrease in the HbA1c concentration. HbA1c can't be used as the glycemic control marker in the chronic alcoholic liver disease.

Conclusion

HbA1c, a gold standard marker to see the glycemic control over period of 3-4 months, is decreased in cases compared to controls in the present study. HbA1c levels are dependent on the glucose concentration and life span of the RBCs mainly. In the present study as the level of SGOT increases, which shows hepatic function that maintains glucose concentration, there is no decrease in the HbA1c levels.HbA1c can't be used as the glycemic control marker in the chronic alcoholic liver disease.This study shows that serum fructosamine is a better marker to check the long term glucose control compared to gold standard long term glucose control marker HbA1c.

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