STUDIES ON CHRONIC HEPATITIS: I- LIPID PROFILE OF CHRONIC C HEPATITIS AFFECTED PATIENTS WITH SPECIAL REFERENCES TO SERUM TRACE ELEMENTS

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Abstract

This study was conducted on 50 male subjects with an age ranging 31 to 54 years with mean of 43.6 ± 8.1, divided into two groups: group one included 30 male subjects with the diagnosis of chronic hepatitis C, and group two included 20 age matched normal volunteers. Both groups were subjected to clinical examination, liver functions, abdominal sonography, polymerase chain reaction (PCR) for Hepatitis C virus (HCV), determination of serum iron, zinc, copper, and magnesium, lipoprotein profile. In addition patients, group were subjected to liver biopsy and estimation of histology activity index. Results showed no significant difference between patients mean serum iron (129.2 ± 41 ug/ dl) and control (101.45 ± 33.5 ug/dl) "P < 0.269"; between patients mean serum copper (105.4 ± 27.6 ug/dl) and control (104.95 ± 24.29 ug/ dl) " P < 0.359", between patients mean serum zinc level (140.6 ± 12.6 ug/dl) and control (137.63 ± 14.06 ug/dl) " P < 0.347", between patients mean serum magnesium (20.817 ± 2.924 ug/dl) and control (21.66 ± 2.33 ug/dl): P = 0.24". Lipoprotein profile showed no significant difference between serum cholesterol, triglycerides, LDL, HDL in both groups. We found elevated serum iron in 6 patients (20%), elevated serum copper in 5 patients (16.7%) and elevated serum magnesium in two patients (6.7%) in diseased group. Only HDL showed significant positive correlation with histological activity index (P< 0.01). In conclusion, there is no correlation between studied serum trace elements and severity of chronic hepatitis.

Key words: Hepatitis, Nutrition, Lipid profile, and trace elements.

INTRODUCTION

Liver plays a central role in the handling and conversion of many dietary constituents. Liver receives the portal blood directly from the intestine and gets rid of many toxic substances with many water-soluble foodstuffs. Liver plays a major part in the digestion and absorption of most foodstuffs, and fat and this intimate functional relation-

ship between food and the liver has been recognized. The diseases of the liver are often accompanied by dysfunction in anabolism and catabolism of most foodstuffs with great changes in nutritional and biochemical parameters. Chronic hepatitis is one of the major public health problems facing the Egyptian population. Studies in Egypt have demonstrated a strikingly high prevalence of chronic hepatitis among blood donors, patients with chronic liver disease, patients with Schistosomiasis (Arthur *et al.*, 1997), and also patients undergoing haemodialysis (Lopes *et al.*, 1999).

Hepatitis C is slow and silent killer, which is now clearly considered as a cause of excess mortality (Darby *et al.*, 1997). Infections by hepatitis C virus (HCV) are extensive through the world "WHO" estimated in 1997 that about 3 % of the world population has been infected. In Africa and in Egypt prevalence rate is high as 10 % (Hoofnagle and Biscegle, 1997).

Trace metals have an important role in many physiological mechanisms in health and disease. Recent line of evidence had suggested a role for increased iron stores in progression of chronic hepatitis C towards cirrhosis (Piperno *et al.*, 1998). Low serum zinc, elevated serum copper and normal serum calcium, magnesium and phosphorus levels were found in early icteric phase of acute hepatitis B virus infection (Pramoolsinap *et al.*, 1996). Moreover, Ishida *et al.* (1995) reported that heavy metal deposition in the peripheral zones of hepatic lobules may be involved in the progression of viral hepatitis from its acute phase to chronic active hepatitis and finally, to liver cirrhosis. Nagamine *et al.* (1997) reported that serum zinc levels were higher in chronic C hepatitis patients who responded to interferon therapy when compared to those non responded. Lastly, Interferon alpha therapy has been shown to change lipoprotein profile in chronic hepatitis C patients (Fernandez-Miranda *et al.*, 1998).

The aim of this study is to find out the role of some trace elements in the pathogenesis of chronic hepatitis, and their possible correlation with hepatitis activity as assessed by histological activity index, as well as, to investigate the metabolism of lipid and protein (lipoproteins profile changes) in chronic hepatitis, and its relation to hepatitis activity.

MATERIALS AND METHODS

Fifty male subjects were included in this study. Their ages ranged from 31 to 54 years with the mean age of 43.6 ± 8 years. They were classified into two groups: group I included 30 male subjects with the diagnosis of chronic hepatitis C, and group II

included 20 male, age matched, normal volunteers. They were subjected to the following: A) complete history taking and clinical examination with special emphasis on symptoms and signs suggestive of hepatic disorders, dyslipidaemia and nutritional deficiency. B) Patients treated by interferon or receiving drugs that alter lipoprotein profile or hepatic pathology, including alcohol intake, were excluded from the study. C) Liver functions and abdominal sonography according to Schmidt *et al.* (1995). D) HBsAg, HBeAg, HbeAb and HCV antibodies according to Gretch *et al.* (1996). E) PCR for HCV in patients group only according to the method of Haesebe and Sekiya (1994). F) Determination of serum Fe, Zn, Cu and Mg levels according to the method of Sincha and Gabriell (1970). G) Estimation of lipoprotein profile including serum cholesterol, triglycerides, LDL and HDL according to the method of Zollneer and Kirsch (1962) . H) Liver biopsy and estimation of histological activity index (HAI) as described by Desmet *et al.* (1994) in patients group only. I) Results were obtained and computed for student's "t" test and correlation coefficient calculations according to the method of Knap and miller (1992).

RESULTS AND DISCUSSION

In this study, we observed no significant difference between serum iron levels in both groups (Table1), but we observed that in patients group there were 6 patients (20%) who had higher values than normal serum iron level Table 2, In accordance with our results, Adams (1998), reported that increases in serum iron are present in 36% of patients with chronic C hepatitis. On the other hand, Umlauft *et al.* (1998) reported that there was no difference between serum iron in cirrhotic with HCV infection and control. Also, Bonkovsky (1997) reported that most patients with chronic hepatitis have a normal hepatic iron concentration. Beinker *et al.* (1996) did not find any association between histological inflammation and hepatic iron content. We also observed no correlation between histological activity index and serum iron level (Table 3). These conflicting data might be explained by following hypothesis: first, differences of iron intake especially when comparing alcoholics (high iron intake) with non-alcoholics. Also, chronic alcoholics ingestion increase intestinal iron absorption (Adams, 1998). Thus, the presence or absence of chronic alcoholism among patients with chronic hepatitis may explain this conflicting data. Secondly, genetic constitution of patients may alter the iron status. In support of this explanation, Piperno *et al.* (1995) reported that, 45% out of 85 chronic HCV patients had minor or major liver iron loading. Those patients with increased liver iron had a relatively high frequency of HBe-Ag. On the other hand, although, heterozygosity for the haemochromatosis gene was proposed as a cause for

increased iron load in some patients of chronic hepatitis C; emerging studies in explanted livers would not support this hypothesis (Hezode *et al.*, 1998). The third hypothesis is the possibility that HCV infection causes increases in hepatic iron or body iron stores. However, we did not observe correlation between HAI and serum iron, level. Also, Shedlofsky (1998) stated that HCV infection itself probably does not lead to excess body or hepatic iron stores. Although, much remains to be learned, our results and the current data would suggest that the natural history and clinical course of HCV infection in humans is negatively affected by an increased host hepatic iron and there is a lack of consensus about iron effects on histological inflammation and viraemia.

In this study, there was no significant difference between patients group and control group as regarding serum Zinc level (Table 1). Also, zinc levels determined in all patients were within normal range (Table 2), thus, no increased or decreased serum Zn level was observed in any of our patients. Moreover, no significant correlation between serum Zn and HAI was observed in this study Table 3. However, Nagamine *et al.* (1997) observed that basal zinc levels in serum were significantly lower in chronic hepatitis patients than in control. They also reported that serum zinc levels were higher in responders than in non-responders to interferon therapy. Gur *et al.* (1998), reported that as the severity of liver damage increases, the hepatic zinc concentration decreases. However, the possibility of difference severity of hepatitis C infection, being mild to moderate in our group, may explain normal serum zinc observed in our study. The difference of urinary zinc excretion may have a role in explanation of this conflicting results. Patients with liver disease regularly have increased urinary excretion of zinc frequently with the greatest excretion observed in-patients with more severe disease (Khan *et al.*, 1965). Lastly, poor caloric intake due to anorexia is a major mechanism for zinc deficiency (Feinman *et al.*, 1992). Thus, difference of oral caloric intake may explain our finding of normal serum zinc in-patients of chronic hepatitis C.

As regarding copper, we did not find any significant difference in serum copper between both groups (Table 1). However, 5 patients (16.7%) had higher than normal serum copper (Table 2). No correlation between serum copper and HAI as found (Table 3). No available literature reviewed the relation between serum copper and HAI in chronic hepatitis. However, copper deposition was demonstrated in the peripheral zones of hepatic lobules in 53% of chronic hepatitis patients (Ishida *et al.*, 1995). Also, they claimed that cell mediated immune mechanisms causing the disturbance of bile secretion and heavy metals deposition in the peripheral zones of hepatic lobules may be involved in the progression of viral hepatitis. Thus, local hepatic factors rather than serum copper may be involved.

As for magnesium, no difference was found between serum Mg++ levels in both groups but we found that 2 patients (6.7%) had their Mg++ level higher than normal, No correlation was found between serum Mg++ and HAI (Table 3). Mg++ level was found normal in acute hepatitis B (Pramoolsinsap *et al.*, 1996). The elevated serum Mg++ in 6.7% of our patients is possibly related to over use of antiacids. No significant differences between serum triglycerides, cholesterol, LDL, HDL in both groups were found. However, HDL was positively correlated with HAI (Table 1 and Figure 2). Rodreques-Margues *et al.* (1998) reported that ,83.3% of patients with different chronic liver disease showed lipid abnormalities in the form of low cholesterol, HDL, A1, Apo B100 levels, but with normal triglycerides and LDL levels. The reason for the contradiction between our study and their study may be related to several factors: they had a limited number of patients included in their study., heterogeneous etiology of liver disease (alcoholics and non-alcoholics, viral hepatitis) and different degrees of severity ranging from chronic hepatitis to child score B liver cirrhosis. Fabris *et al.* (1997) reported that circulatory cytokines may be correlated to lipid abnormalities observed in chronic hepatitis C. They also reported that interlukin6 correlated positively with triglycerides and negatively with HDL-cholesterol. Interestingly enough, Fernandez-Miranda (1998) reported that , interferon therapy reduced HDL levels in chronic hepatitis C patientes both in responders and non-responders. In our study, HAI, is positively correlated with HDL level, and HDL level changes may reflect abnormal cytokine production, which is related to severity of chronic hepatitis C.

In conclusion, we found no correlation between serum iron, copper, zinc, magnesium and severity of chronic hepatitis C. Moreover, we observed elevated serum iron in 20% of patients, elevated serum copper in 16.7% of patients and elevated magnesium in 6.7% of patients. We observed positive correlation between HDL level and histological activity index in chronic hepatitis C patients.

Table 1. Liver enzymes, lipoproteins profile and some trace elements in serum of patients affected by chronic C hepatitis (means ± S.D., n =30).

Groups Parameters	Affected Group (300)	Normal Group (20)	P value <	Significance
SGPT (U/L)	037.9 ± 12.5	11.05 ± 02.78	0.001	H. S.
SGOT (U/L)	042.4 ± 10.6	12.66 ± 03.04	0.001	H. S.
Alk. Ph. (U/L)	096.2 ± 30.4	59.03 ± 20.26	0.100	N. S.
Cholesterol. (mg/dl)	227.6 ± 25.3	233.0 ± 26.38	0.400	N. S.
Triglycerides. (mg/dl)	136.8 ± 21.9	132.6 ± 20.76	0.460	N. S.
HDL (mg/dl)	040.1 ± 07.1	39.95 ±09.49	0.110	N. S.
LDL (mg/dl)	145.5 ±16.8	150.2 ±16.06	0.473	N. S.
Mg (mg/ L)	20.82 ± 2.924	21.66 ±02.33	0.240	N. S.
Fe (Ug/ dl)	129.2 ± 41.0	101.5 ±33.50	0.269	N. S.
Cu (Ug/ dl)	105.4 ± 27.6	105.0 ±24.30	0.359	N. S.
Zn (Ug/dl)	140.6 ± 12.6	137.6 ±14.10	0.347	N. S.

Table 2. Patients range with number and percentage of patients above and below normal reference range of Zn, Cu, Fe, Mg, HDL, and LDL.

Parameter	Patients range	Number of patients above normal level	Percentage	Number of patients below normal level	Percentage
Zn (Ug/dl)	117 -164	0	00.0	0	00.0
Cu (Ug/dl)	070 -152	5	16.7	0	00.0
Fe (Ug/dl)	060 -200	6	20.0	0	00.0
Mg (mg/L)	016 -020	2	6.70	0	00.0
HDL(mg/dl)	032 -061	1	3.30	4	13.3
LDL(mg/dl)	108 -180	0	00.0	0	00.0

Table 3. Correlation results between Histological activity index and serum liver enzymes, lipid profile and trace elements.

Liver Enzymes			Lipid Profile				Trace Elements			
SGPT	SGOT	Alk. Ph	Choles.	Trigly.	HDL	LDL	Zn	Fe	Mg	Cu
P<0.05	P<0.04	P<0.05	P<0.05	P<0.05	P<0.01	P<0.05	P<0.05	P<0.05	P<0.05	P<0.05
S	N.S.	N.S.	N.S.	N.S.	H.S.	N.S.	N.S.	N.S.	N.S.	N.S.

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دراسات علي مرض الالتهاب الكبدي الوبائي س:١، دراسة صورة دهون الدم وكذلك العناصر النادرة في المرضى المصابين بالالتهاب الكبدي الوبائي س

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تمت الدراسة على عدد ٥٠ من الرجال المصابين بالالتهاب الكبدي الوبائي وأعمارهم تتراوح بين ٣١ – ٥٤ سنة. قسم المرضى إلى مجموعتين: الأولى اشتملت على عدد ٣٠ مصاباً والثانية عدد ٢٠ من المتطوعين الغير مصابين.

بعد الفحص الإكلينيكي تم عمل أشعة فوق صوتية على منطقة البطن مع أخذ عينة من الكبد مع عمل تحليل الـ HCV والـ PCR وكذلك أنزيمات وظائف الكبد المختلفة، تم قياس نسب الحديد والزنك والنحاس والماغنسيوم بالدم مع قياس نسب الدهون المختلفة منخفضة الكثافة منها والعالية.

وقد أوضحت النتائج ارتفاعاً غير معنوي في قيمة الحديد في ٢٠ ٪ من المرضى وكذلك نسبة النحاس ٧. ١٦ ٪ من المرضى وايضاً نسبة الماغسيوم في ٧. ٦ ٪ من المرضى، كما أوضحت النتائج وجود ارتباط إيجابي واضح بين الدهون البروتينية عالية الكثافة ونشاط البيان الهستولوجي لخلايا الكبد.

مما سبق يمكن استنتاج عدم وجود ارتباط واضح بين العناصر الغذائية متمثلة في الحديد والنحاس والزنك والماغنسيوم ومدى شدة الاصابة بمرض الالتهاب الكبدي الوبائي