Nutrition in cryptogenic cirrhosis and chronic aggressive hepatitis

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SUMMARY The nutritional status of 80 patients with non-alcoholic chronic liver disease was assessed by determination of various nutritional parameters in body fluids. With the exception of vitamin C there was a higher incidence (40%) of fat soluble vitamin deficiency (vitamins A, E, and carotene) than of the water soluble vitamins. Less than 10% of patients showed evidence of vitamin B₁₂, nicotinic acid, thiamin, or riboflavin deficiency, and 17% had evidence of folic acid deficiency. The presence of deficiency was not related to age of the patient or fat absorption, and an inadequate dietary intake was not a major cause of deficiency. The incidence of nutritional deficiency is less frequent in non-alcoholic as compared with alcoholic liver disease.

Malnutrition in chronic liver disease may have many causes including diminished food intake (Leevy *et al.*, 1965; Leevy *et al.*, 1970a, b; Linscheer, 1970) impaired intestinal absorption (Losowsky and Walker, 1969), and abnormal metabolism (Leevy *et al.*, 1970a) and storage (Baker *et al.*, 1964). While this is well documented in the American literature, it refers mainly to alcoholic liver disease which, in contrast with the British Isles (Stone *et al.*, 1968), accounts for almost all the chronic liver disease seen in the United States of America (Powell and Klat-skin, 1968).

In alcoholic liver disease, there are the additional factors of gastritis and anorexia produced by excess alcohol, diminished vitamin and protein intake due to social factors, maldigestion due to alcohol-induced pancreatic disease (van Goidsenhoven *et al.*, 1963; Sun *et al.*, 1967; Marin *et al.*, 1969), and mal-absorption due to alcohol (Halsted *et al.*, 1973). Thus, it cannot be assumed that the nutritional status of patients with liver disease in this country is similar to that of the United States of America.

We know of no detailed nutritional information for chronic liver disease of the non-alcoholic variety and therefore we have carried out a broadly-based nutritional survey in patients with non-alcoholic cirrhosis and chronic aggressive hepatitis.

Methods

SUBJECTS

A total of 80 patients with non-alcoholic liver disease

were studied. Sixty had cryptogenic cirrhosis (26 men and 34 women). Patients below the age of 40 years were screened for Wilson's disease, and all patients had a liver biopsy which was stained for iron to exclude haemochromatosis. Tests for Australia antigen were negative in all. Twenty patients had liver biopsy findings of chronic aggressive hepatitis (three men and 17 women). The ages and relevant liver function tests for these patients are shown in Table 1.

The extent of alcohol ingestion was obtained from the history, discussion with members of the family, and medical observation. The patients who were included fell within the definitions of mild or moderate drinkers as used by Soterakis *et al.* (1973). No patient was included who either ingested alcohol daily or suffered from acute alcoholic intoxication. No patient showed liver biopsy features of alcoholic liver disease.

The nutritional parameters in the patients with liver disease were compared with those in 50 normal volunteer control subjects. These were fit, asymptomatic, friends or colleagues, with no past history of liver disease. Clinical examination was not performed but routine liver function tests were all within normal limits.

PROCEDURES

Plasma vitamin A was measured spectrofluorimetrically (Kahan, 1966), plasma carotene spectrophotometrically at 520 m μ on a petroleum ether extract (Varley, 1962), and plasma vitamin E spectrofluorimetrically (Hanson and Warwick, 1966). Faecal fat

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Age		Bilirubin		ALAT		Albumin	
No.	Years	No.	$\mu\text{M/l}$	No.	IU/l	No.	g/l
7	Under 30	30	0 - 17.0	34	0- 50	4	10-20
13	30-44	24	17.1- 34.2	10	51-100	16	21-30
29	45-59	15	34.3- 68.4	10	101-200	40	31-40
30	60-74	6	68.5-102.6	1	201-500	20	41-50
1	75+	6	102.7-171.0	2	500+		

Table 1 Distribution of age, bilirubin, ALAT (alanine amino-transferase, EC 2 6 1 2) and albumin in 80 patients with chronic non-alcoholic liver disease

was measured on two to seven day inpatient faecal collections on a constant fat diet, by the method of van de Kamer *et al.* (1949), using polyethylene glycol as a continuous marker after at least a five day equilibration period. Leucocyte vitamin C was measured by the method of Denson and Bowers (1961), whole blood riboflavin as described by Burch *et al.* (1948), urinary N-methyl nicotinamide by the method of Pelletier and Campbell (1962), on two successive 24 hour urine collections, transketolase (and thiamine pyrophosphate stimulation TPP) by the method of Schouten *et al.* (1964). Serum folate (Waters and Mollin, 1961), red cell folate (Hoffbrand *et al.*, 1966), and serum vitamin B₁₂ (Anderson, 1964), concentration were measured by microbiological assay, using *Lactobacillus casei* (Hoffbrand *et al.*, 1966) and *Euglena gracilis* (Anderson, 1964) respectively. Serum iron and total iron binding capacity (TIBC) were determined on an auto-analyser by a modification of the method of Giovanniello *et al.* (1968). All samples for vitamin assays were collected after an overnight fast; heparin was used as an anticoagulant for determinations on plasma. All samples were stored frozen unless assayed on the same day of collection.

Results

The following levels were calculated as nutritionally abnormal (more than two standard deviations from control mean) for the various nutritional parameters. Vitamin A less than 1.53 $\mu\text{M/l}$, carotene less than 0.85 $\mu\text{M/l}$, vitamin E less than 145 $\mu\text{M/l}$, vitamin C less than 0.83 fM/WBC, riboflavin less than 170 $\mu\text{M/l}$, N-methyl-nicotinamide less than 146 $\mu\text{M/24h}$, transketolase less than 29 IU/l, TPP stimulation greater than 56%, serum folic acid less than 2.2 $\mu\text{g/l}$, red blood cell folate less than 110 $\mu\text{g/l}$, vitamin B₁₂ less than 118 ng/l, iron less than 10 $\mu\text{M/l}$, and total iron binding capacity 50.6-80 $\mu\text{M/l}$.

The measurements were grouped as fat soluble vitamins (E, A, and carotene), water soluble vitamins (vitamin C, riboflavin, nicotinic acid, and thiamin) and haematinics (folic acid, vitamin B₁₂, iron, and iron binding capacity). There was no signi-

ficant difference for any measurements between those with chronic aggressive hepatitis and cirrhosis, and thus they have been combined.

DIETARY INTAKE

In 39 patients a detailed dietary history for the week before admission to hospital, was taken by a dietitian (Fig. 1).

Fig. 1 Calorie intake, protein intake, the percentage calories from fat and faecal fat in patients with chronic liver disease. The dotted line represents the lower limit of normal for fat absorption.

Seventeen patients had a calorie intake more than 10% below that recommended by the Department of Health and Social Security (1969) (*Recommended Intakes of Nutrients for the United Kingdom*). Of these, 11 had calorie intakes more than 20%; five more than 30%; and one more than 40% below the recommended values. These recommended values assume average weight, but seven of the patients were very much underweight (average 13 kg, range 9-25 kg below ideal weight).

The protein intake in four out of the 15 men, and six out of the 24 women was slightly below the recommended intake, but all were well above the minimum of 0.85 g protein/kg body weight recommended by Davidson and Passmore (1966).

In 14 out of the 39 patients, fat accounted for less than the desirable minimum of 35% of the total calorie intake.

FAECAL FAT

Faecal fat was measured in 43 patients. Steatorrhoea (absorption less than 93% dietary intake) was found in 19; eight absorbed between 80-90%, and a further six patients absorbed less than 80% (Fig. 1).

FAT SOLUBLE VITAMINS (Fig. 2)

Plasma vitamin E levels were estimated in 60 patients and subnormal levels were demonstrated in 23 (38%).

Plasma vitamin A levels were low in 42% of patients tested (19 out of 45) and plasma carotene levels were low in nine out of 34 patients (26%). In the 34 patients for whom both carotene and vitamin A levels were available, there was no correlation between these two parameters.

WATER SOLUBLE VITAMINS (Fig. 2)

Leucocyte vitamin C levels were low in 35% of the patients tested (18 out of 52). Leucocyte vitamin C levels were subnormal in 25% of the patients with steatorrhoea, compared with 19% in those with normal faecal fats.

Whole blood riboflavin levels were estimated in 25 patients and was abnormal in one only.

Transketolase and TPP effect was measured in 31 patients. The transketolase was low in one patient only and the TPP effect was abnormally high in this patient. In two further patients, the TPP effect was abnormally high but the transketolase levels were within normal limits.

Twenty-four hour urinary N-methyl nicotinamide levels were estimated in 30 patients and were abnormal in four (13%), and in four patients very high levels were found (above 560 μ M/24 h).

HAEMATINICS (Fig. 3)

Serum folate was subnormal in 17% of the patients (13 out of 75), red cell folate in 24% (nine out of 38), but these did not always occur in the same patient. Serum vitamin B₁₂ was below 110 ng/l in three patients and above 1000 ng/l in six patients.

Serum iron was estimated in 73 patients and 17 had subnormal values, three were below 3.6 μ M/l. The percentage of saturation of transferrin was plotted against serum iron, and a close correlation was shown ($r = 0.93$, $p < 0.001$). If we accept as abnormal only those patients with low values for both parameters (less than 10 μ M/l and less than 16% saturation) evidence of iron deficiency was found in 14 out of 64 patients studied.

Fig. 2 Plasma levels of vitamins E, A, carotene and vitamin C, whole blood levels of riboflavin, and transketolase activity and urinary N-methyl nicotinamide excretion in patients with chronic liver disease. The dotted lines represent the lower limit of normal.

Fig. 3 Serum levels of folate, vitamin B₁₂ and iron, and red blood cell folate levels in patients with chronic liver disease. The dotted lines represent the lower limit of normal.

Frequency of abnormal tests

In Table 2 the results for the 58 patients who had five or more nutritional parameters measured, are summarized. The abnormal results are expressed as a percentage of the total tests performed on each patient. Sixteen per cent of these patients had no abnormal tests; 54% had between 10% and 30% abnormal.

Including results for all 80 patients, there was a higher incidence (37%) of abnormal values for fat soluble vitamins than for water soluble vitamins (17%) or haematinics (17%).

The effect of age and steatorrhoea on both the fat and water soluble vitamins was determined and no significant correlation could be found.

Discussion

Single parameters of nutrition have been widely studied in patients with alcohol-induced liver disease and there is one broadly based nutritional survey (Leevy *et al.*, 1965). In such patients, nutritional intake is frequently inadequate and unbalanced (Leevy *et al.*, 1965; 1970b; Linscheer 1970; Leevy *et al.* 1970 a). Furthermore, alcohol, especially if combined with folate deficiency interferes with small bowel absorption (Halsted *et al.*, 1973), may result in chronic pancreatitis (Sun *et al.*, 1967), and can alter both vitamin storage and metabolism by its direct hepatotoxic effect (Leevy *et al.*, 1965).

These factors are not applicable to most of the chronic liver disease seen in Great Britain.

Steatorrhoea is well documented in acute and chronic liver disease, whatever the aetiology (Sun *et al.*, 1967; Marin *et al.*, 1969; Losowsky and Walker, 1969; Williams and Sidorov, 1971), and even if anicteric (Summerskill and Moertel, 1962). Steatorrhoea, present in 44% of the 43 patients we studied, was never severe and seems unlikely to have been a major factor in the causation of nutritional deficiencies which were not infrequent in its absence.

Plasma levels of fat soluble vitamins were low in over a third of subjects. These subnormal levels were not related to age, or steatorrhoea. Subnormal plasma vitamin A levels are common in all liver disease (White *et al.*, 1950; Ditlefsen and Støa, 1954) due to a defect in synthesis of the specific transport protein (Smith and Goodman, 1971). These low levels may nevertheless imply a defect in delivery of vitamin A to the tissues.

Blood thiamin levels, as measured by Leevy *et al.* (1965) provide an index of tissue thiamin stores, while the normal level for blood transketolase activity, present in almost all our patients, reflects both availability of thiamin and the ability of the liver to convert thiamin into its metabolically active form (Fennelly *et al.*, 1967). In the one patient with a low transketolase activity, the addition *in vitro* of thiamine pyrophosphate produced an abnormally large effect, indicating either pre-existing thiamin deficiency, or a failure of its phosphorylation, a defect sometimes seen in alcoholic cirrhosis (Konttinen *et al.*, 1970). The absence of evidence of thiamin deficiency in our patients contrasts strikingly with the data of Leevy *et al.* (1965) in patients with alcoholic liver disease and with the data of Konttinen *et al.* (1970) in chronic alcoholic subjects. The latter authors found low blood transketolase activities, and, in those patients with marked evidence of liver disease, this was not corrected by thiamine pyrophosphate, suggesting apoenzyme deficiency.

In man, nicotinic acid is mainly excreted as N-methylnicotinamide (NMN) or the 6 pyridine derivative. A small proportion of our patients had very high urinary NMN levels, as reported in alcoholic cirrhosis by Gabuzda and Davidson (1962); the explanation for this is unknown. Leevy *et al.* (1965) found low blood nicotinic acid levels in almost a quarter of patients with alcoholic cirrhosis, while only 13% of our patients had low urinary NMN levels.

	<i>% of abnormal tests per patient</i>						
	<i>0</i>	<i>0-9</i>	<i>10-19</i>	<i>20-29</i>	<i>30-39</i>	<i>40-49</i>	<i>50-59</i>
% of patients	16	5	25	29	14	3	5

Table 2 Incidence of abnormal nutritional parameters in 58 patients who had more than five tests performed

Leucocyte ascorbic acid estimations gave low results in 35% of our patients. This was not age related, although vitamin C levels fall with age in normal subjects (Brook and Grimshaw, 1968). A higher proportion of our patients had evidence of ascorbic deficiency than those of Leevy *et al.* (1965) probably reflecting greater sensitivity of leucocyte ascorbic acid than serum levels as a test of deficiency. Iron deficiency may mask ascorbic acid deficiency (Jacobs *et al.*, 1971) and leucocyte vitamin C was subnormal in 40% of our patients (16 out of 40) with a normal serum iron, but only in 10% (one out of 10) in those with low serum iron.

Low red cell folate occurred in 24% and low serum folate in 17% of our patients but not always together (Williams and Girdwood, 1970) and in none was there megaloblastic change or anaemia. Severe folic acid deficiency with associated megaloblastic change is common in alcoholic liver disease (Herbert *et al.*, 1963; Klipstein and Lindenbaum, 1965; Leevy *et al.*, 1965; Eichner and Hillman 1971); dietary deficiency appears to be the major cause (Klipstein and Lindenbaum, 1965; Eichner and Hillman, 1971) but contributory factors may be impaired absorption (Halsted *et al.*, 1971), increased requirements due to gastrointestinal bleeding, hypersplenism, or haemolysis (Klipstein and Lindenbaum, 1965), and decreased hepatic storage (Cherrick *et al.*, 1965).

Serum B₁₂ was low in three patients only and these three had a megaloblastic marrow. In six patients the B₁₂ level was above 1000 ng/l, perhaps mirroring the presence of hepatocellular damage and subsequent B₁₂ release (Joske, 1963). Five of these six patients were jaundiced and three out of four had a raised serum ALAT.

It appears that serum iron and percentage saturation of transferrin can be used to indicate iron status in patients with liver disease, since we found they were closely correlated despite the complicating factors of increased circulating ferritin (Lipschitz *et al.*, 1974) and changes in transferrin concentration consequent upon the liver disease. Evidence of iron deficiency was found in almost a quarter of the patients. Iron stores of alcohol abusers and patients with cirrhosis are usually diminished or normal (Kimber *et al.*, 1964; Lundvall *et al.*, 1969) but a small proportion of patients with cirrhosis have increased iron stores (Kimber *et al.*, 1964).

Fat soluble vitamin deficiency was commoner than deficiency of water soluble vitamins. This may reflect malabsorption of fat soluble vitamins due to bile salt deficiency in liver disease. Leevy *et al.* (1965) found that all of his patients with alcoholic cirrhosis had low circulating levels of at least two vitamins, while abnormalities in our patients were much less common probably because our patients reflect the

nutritional effects of the liver disease without the added effects of alcoholism and its dietary and metabolic concomitants.

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