

Out-hospital Patients with Hyperlipidemia and Hepatitis with Various Backgrounds Improved by Wheat Protein Hydrolysate (Glutamine Peptide) Administration



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ABSTRACT

We encountered an outpatient with steatohepatitis showing an improvement with a wheat protein hydrolysate (glutamine peptide) administration. The improvement in hepatitis and reductions in liver fat accumulation were observed within 1 week. When the administration of wheat protein hydrolysate was discontinued, levels of GOT, GPT and γ -GTP increased, and when administration was resumed, levels of these enzymes decreased. Glutamine peptide was therefore administered to steatohepatic patients with background factors such as hyperlipidemia, diabetes, obesity, hepatitis C, and hepatitis B. Within 4 weeks, improvements in hepatitis and reductions in liver fat accumulation were observed. Improvements in serum lipid levels were also observed in patients with hyperlipidemia. (*Jpn Pharmacol Ther* 2004 ; 32 : 415-20)

KEY WORDS Wheat protein hydrolysate, Glutamine peptide, Hepatitis, Fatty liver, Hyperlipidemia

INTRODUCTION

The spread of workplace and multiphasic health screening as well as recent advances in diagnostic imaging, such as abdominal ultrasonography and CT, has led to increasing numbers of patients being diagnosed as having steatohepatitis (fatty liver). The prognosis for chronic steatohepatitis is generally favorable and patients with this condition usually have few subjective symptoms. Therefore, steatohepatitis is often overlooked. However, several recent reports have found that the risk of primary non-function associated with liver transplantation is greater when a donor has steatohepatitis, and effective treatments for this illness are now actively being sought¹⁾.

Chronic steatohepatitis is considered to be caused by such factors as obesity, diabetes, alcohol or hepatitis²⁾. Fat accumulation in the liver can be caused by increased movement of fatty acids from the periphery to the liver, impaired transportation of fatty acids from the liver to the periphery, elevated fatty acid synthesis in the liver, reduced oxidation of fatty acids in the liver, and increased lipid hyperoxidation.

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The therapy for steatohepatitis is primarily based on the treatment of the underlying disease. When obesity or diabetes is the cause of fatty liver, alimentary or exercise therapy can improve symptoms in about 2 to 3 months. When alcohol is the cause, alimentary or exercise therapy accompanied by reduced alcohol consumption can improve symptoms in about 2 to 3 months. However, because these patients do not exhibit many subjective symptoms, therapy compliance is low in many outpatients, and improvements are often difficult to achieve.

Therefore, to treat steatohepatitis in outpatients of our institution, in addition to recommending a sound diet and exercise program, medications were given to improve the compliance of the therapeutic program. These medications were chosen from the drugs for treating hepatitis such as glycyrrhizin, and polyene phosphatidylcholine, as well as medication to suppress lipid hyperoxidation and subsequent fat accumulation such as vitamin C, vitamin E, glutathione and glutamine, a precursor of glutathione. And also glutamine rich peptide (a wheat protein hydrolysate) was examined.

During the maintenance of a stubborn chronic steatohepatic patient, we experienced a salient improvement with glutamine rich peptide administration. The present report introduces the salient case and ten more cases with the same treatment.

MATERIALS AND METHODS

All subjects were outpatients in whom biochemical analyses and ultrasonography confirmed fat accumulation in the liver. They were informed about the possible risks and discomforts associated with the therapy program and participated with written consent. In compliance with the Declaration of Helsinki the present therapy program was designed with the appropriate ethical considerations and approved by the institution.

The wheat protein hydrolysate used in the present study was glutamine peptide GP-1 (Nisshin Pharma Inc., Japan). This hydrolysate is produced by enzymatic hydrolysis of wheat gluten. It has an average molecular weight of 5,000–10,000 Da (gel filtration) and an approximate glutamine content of 30% (w/w)³⁾.

All biochemical analyses were performed by SRL Inc. (Tokyo, Japan).

RESULTS

The transition of the liver related extravasive enzymes is summarized in the **Table 1**. Although the observation periods differed from 3 weeks to 3 months, the reducing tendency of enzymes was consistent. Comparing the data between before and after the administration by paired *t* test, significant differences were observed in all enzymes : GOT, $p < 0.00005$; GPT, $p < 0.0001$; and γ -GTP, $p < 0.005$.

The details of the cases were as follows.

Cases 1 and 2 : Diabetes and hyperlipidemia

Case 1 was a 58-year-old man with diabetes and hyperlipidemia. He exhibited symptoms of chronic low-grade fever, general malaise, and inappetence. Despite taking an oral antidiabetic (glibenclamide, 2.5 mg/day), glycyrrhizin (150 mg/day), liver hydrolysate (420 mg/day), glutathione (300 mg/day) and L-glutamine (8 g/day), the symptoms had not improved over two years. When 10 g/day of wheat protein hydrolysate was administered to the patient, levels of glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT) and γ -glutamyl transpeptidase (γ -GTP) normalized in 1 to 3 weeks (**Table 1**), and ultrasonography confirmed reduced fat accumulation in the liver. To determine whether these improvements were attributable to the wheat protein

Table 1 Transition of the liver related extravasive enzymes

Patients				Wheat gluten hydrolysate		Enzymes (IU/L)	Treatment					
Case	Age	Sex	Background	(g/day)	(g×times/day)		Before	1 week	3 weeks	4 weeks	2 months	3 months
1	58	M	DM, HL	10	3.3×3	GOT	72	35	16	—	—	20
						GPT	124	85	25	—	—	37
						γ-GTP	70	47	31	—	—	35
2	68	M	DM, HL	4	2×2	GOT	70	—	—	37	—	31
						GPT	124	—	—	67	—	38
						γ-GTP	103	—	—	58	—	49
3	60	M	HL	6	2×3	GOT	56	—	33	—	—	26
						GPT	109	—	56	—	—	34
						γ-GTP	140	—	60	—	—	39
4	50	M	HL	4	2×2	GOT	23	—	—	24	—	20
						GPT	43	—	—	29	—	22
						γ-GTP	61	—	—	27	—	28
5	67	M	DM	6	3×2	GOT	53	—	—	51	—	18
						GPT	52	—	—	52	—	21
						γ-GTP	118	—	—	89	—	83
6	74	F	DM, HL, Obese	6	3×2	GOT	49	—	45	32	—	30
						GPT	63	—	50	39	—	33
						γ-GTP	78	—	58	49	—	42
7	49	M	Hepatitis C	4	2×2	GOT	73	—	47	—	—	—
						GPT	58	—	26	—	—	—
						γ-GTP	68	—	57	—	—	—
8	51	M	Hepatitis C	4	2×2	GOT	81	—	—	39	—	—
						GPT	176	—	—	62	—	—
						γ-GTP	51	—	—	37	—	—
9	60	M	Hepatitis C	6	3×2	GOT	65	—	—	48	—	—
						GPT	129	—	—	92	—	—
						γ-GTP	63	—	—	59	—	—
10	48	M	Hepatitis B	15	5×3	GOT	92	—	—	42	—	—
						GPT	102	—	—	40	—	—
						γ-GTP	129	—	—	49	—	—
11	28	M	—	6	3×2	GOT	50	—	—	30	20	—
						GPT	125	—	—	75	54	—
						γ-GTP	38	—	—	26	12	—

Case 1 has a discontinue and resume test during 4-week and 2 months, details are described in the text.

Abbreviations : M ; male, F ; Female, DM ; Diabetes mellitus, HL ; Hyperlipidemia, — ; not determined.

hydrolysate, the administration was discontinued after 4 weeks. Two weeks following the discontinuation, levels of GOT, GPT and γ-GTP increased to 37, 87 and 50IU/L, respectively. The administration of the wheat protein hydrolysate was subsequently resumed, and within 2 weeks, levels of GOT, GPT and γ-GTP decreased again to 22, 44 and 33IU/L, respectively. These observations suggested that the administration of the wheat protein hydrolysate (glutamine peptide) improves steatohepatitis.

Serum lipid levels also improved by the wheat protein hydrolysate. Prior to the administration, total chole-

terol levels (TChol) and triglyceride levels (TG) were 178 and 218 mg/dL, respectively. However, after two weeks of the administration, the levels decreased to 180 and 159 mg/dL, respectively. Three months into the regimen, TChol and TG levels further improved to 152 and 149 mg/dL, respectively.

Case 2 was also diagnosed as having diabetes and hyperlipidemia, and administration of 8 g/day of glutamine peptide improved both hepatitis (**Table 1**) and fat accumulation in the liver. Prior to the administration, serum levels of TChol, low density lipoprotein cholesterol (LDL-Chol) and TG were 293, 193 and 272 mg/dL, respectively. Three months into the regimen, these levels improved to 211, 134 and 187 mg/dL, respectively.

Cases 3 and 4 : Hyperlipidemia

Cases 3 and 4 were diagnosed as having hyperlipidemia as well as steatohepatitis, and the administration of the glutamine peptide improved both hepatitis (**Table 1**) and fat accumulation in the liver.

Serum lipid levels also improved in both patients. In Case 3, prior to the administration, levels of TChol and LDL-Chol were 256 and 157 mg/dL, respectively, but after 3 months of the administration, these levels improved to 224 and 124 mg/dL, respectively. In Case 4, levels of TChol, LDL-Chol and TG were 215, 105 and 321 mg/dL, before the administration, and improved to 159, 87 and 124 mg/dL, after the 3 months of the regimen.

Cases 5 and 6 : Diabetes

In addition to steatohepatitis Case 5 had diabetes and drank 360 to 540 mL/day of sake (alcohol content : approximately 14% dairy) and Case 6 suffered from diabetes, hyperlipidemia and obesity. In the both patients, the glutamine peptide improved both hepatitis (**Table 1**) and fat accumulation in the liver. Serum lipid levels improved in Case 6 : prior to the administration of glutamine peptide, levels of TChol, LDL-Chol and TG were 226, 128 and 122 mg/dL, respectively, but after 4 weeks these levels improved to 194, 111 and 102 mg/dL. And three months into the regimen, the serum lipid levels further improved to 184, 104 and 83 mg/dL, respectively.

Cases 7, 8 and 9 : Hepatitis C

Cases 7, 8 and 9 were the patients with chronic hepatitis C. In these patients too, the glutamine peptide improved both hepatitis (**Table 1**) and fat accumulation in the liver.

Serum lipid levels remained mostly within the normal range throughout the study period.

Case 10 : Hepatitis B

Case 10 suffered from chronic hepatitis B, and in this patient, the glutamine peptide improved hepatitis (**Table 1**) and fat accumulation in the liver.

The details of this patient will be published elsewhere with several more cases with hepatitis B.

Case 11 : Unknown etiology

Case 11 tested negative for HCV and HBV, and fatty liver was not caused by alcohol, obesity, hyperlipidemia, diabetes, Rye syndrome or a nutritional disorder. The glutamine peptide improved both hepatitis (**Table 1**) and fat accumulation in the liver. Although serum lipid levels remained mostly within the normal range throughout the study period, levels of TG improved from 167 mg/dL prior to the administration to 67 mg/dL at week 4 and 66 mg/dL at 2 months of the regimen.

DISCUSSION

In the steatohepatic patients with hyperlipidemia (cases 1-4, 6 and 11), the improvement in serum lipid levels was observed consistently. Jenkins et al reported that when wheat protein (11% of total caloric intake) was administered to patients with hyperlipidemia, TG, uric acid, creatine, and urea levels, as well as 24-hour urea excretion all improved by 1 month⁴⁾. However, because of the very high dose of 11%, their study cannot be simply compared to ours.

In each of the present patients, wheat protein hydrolysate improved hepatitis. In Cases 1-4, 6 and 11, the hydrolysate could have improved hepatitis by lowering serum lipids, but the mechanism is less clear in those patients who were not hyperlipidemic (Cases 7-10 and 5).

Since lipid hyperoxidation is one of the causes of steatohepatitis, we investigated the effects of free glutamine, a precursor of glutathione, on fatty liver in Cases 1 and 3 (8 and 6 g/day, respectively), but no improvement was observed in either case. And the administration of the glutamine peptide (10 and 6 g/day) decreased the liver related enzymes in the both patients. Because the glutamine content of the wheat protein hydrolysate was about 30%, the amount of glutamine administered was smaller in the wheat protein hydrolysate. Therefore, the improvement dose not seem to be explained as the effect of glutamine.

Recently, Sawaki et al⁵⁾ reported that the administration of the same wheat protein hydrolysate used in our study could improve the plasma glutamine status after prolonged running. Therefore this lysate could be a good glutamine source for oral administration. In the same report they also showed the possibility that the post-exercise increase of extravasative enzymes could be suppressed by the administration. Whether the wheat hydrolysate possibly suppresses the extravasation of tissue enzymes, and if so why and how was an interesting issue.

Motoi reported that wheat protein hydrolysates contain peptides that inhibit the activity of angiotensin-converting enzymes⁶⁾, while Fukudome et al demonstrated that wheat protein hydrolysates contain peptides with opioid-like activities^{7, 8)}. Although there has not been a study about the specific effects of wheat protein hydrolysates on hyperlipidemia or hepatitis, the effect could be explained by some specific peptides. Therefore, further investigation of the action of wheat protein hydrolysates on these conditions is necessary.

Recently, Asami et al⁹⁾ and Asano et al¹⁰⁾ presented that the same glutamine peptide could mitigate the liver cirrhosis induced by chronic injection of carbon tetrachloride in rats. Teran et al hypothesized that glutamine was the conditionally essential amino acid in liver cirrhosis¹¹⁾. This hypothesis is based on the role of glutamine as a precursor of glutathione. As mentioned above, the action of the wheat protein hydrolysates is not solely dependent on glutamine, and we have achieved a fair level of success in administering the present wheat protein hydrolysate to patients with liver cirrhosis (results will be published in another report).

The results of the present study demonstrate that the administration of the wheat protein hydrolysate improves hyperlipidemia and hepatitis. However, due to the small number of patients followed, elucidation of the mechanism of action was not possible.

Future studies will be needed to verify the effectiveness of wheat protein hydrolysate and to elucidate the mechanism of action.

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