ORIGINAL ARTICLE

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Total Cholesterol Level for Assessing Pancreatic Insufficiency Due to Chronic Pancreatitis

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Background/Aims: To determine the nutritional markers important for assessing the degree of pancreatic insufficiency due to chronic pancreatitis in routine clinical practice. **Methods:** A total of 137 patients with chronic pancreatitis were followed up for more than 1 year. They were divided into two groups: a pancreatic diabetes mellitus (DM) group, consisting of 47 patients undergoing medical treatment for DM of pancreatic origin, and a nonpancreatic DM group, consisting of 90 other patients (including 86 patients without DM). Serum albumin, prealbumin, total cholesterol, cholinesterase, magnesium, and hemoglobin were compared between the two groups. **Results:** The total cholesterol was significantly lower in the pancreatic than the nonpancreatic DM group (164 mg/dL vs 183 mg/dL, respectively; p=0.0028). Cholinesterase was significantly lower in the former group (263 U/L vs 291 U/L, respectively; p=0.016). Among the 37 patients with nonalcoholic pancreatitis, there was no difference in the cholinesterase levels between the pancreatic and nonpancreatic (296 U/L vs 304 U/L, respectively; p=0.752) DM groups, although cholesterol levels remained lower in the former (165 mg/dL vs 187 mg/dL, respectively; p=0.052). **Conclusions:** Cholinesterase levels are possibly affected by concomitant alcoholic liver injury. The total cholesterol level should be considered when assessing pancreatic insufficiency due to chronic pancreatitis. **(Gut Liver 2014;8:563-568)**

Key Words: Chronic pancreatitis; Pancreatic exocrine insufficiency; Diabetes mellitus; Cholesterol; Cholinesterase

INTRODUCTION

Pancreatic exocrine insufficiency (PEI) leading to maldigestion, steatorrhea, and malnutrition is an important complication of chronic pancreatitis (CP). Early detection of PEI is clinically crucial, because PEI can be treated with oral administration of pancreatic enzyme drug. Although the evaluation of pancreatic exocrine function is difficult, it is essential for PEI diagnosis.

PEI can be determined by several tests. Fecal fat quantification performed over a period of three days, with calculation of the coefficient of fat absorption is considered as the gold standard,[1] but this is limited to specialized centers because it is both cumbersome and unpleasant for patients and laboratory personnel. Another useful method is the secretin test, but this is also time consuming, invasive, and very expensive.[2] The ^{13}C breath tests appear to be ideal tools in terms of noninvasiveness and accuracy, but they are also limited to specific institutions.[3] Fecal elastase test is often used because it is easy to perform, but it is insensitive and is rarely properly tested against the coefficient of fat absorption in patients with CP.[4] In Japan, the primary test used is the BT-PABA (Bz-Tyr-Ala and the N-benzoyl-L-tyrosyl-p-aminobenzoic acid) test, which is covered by Japanese medical insurance. It is invasive, but it has poor accuracy.[5] In addition, BT-PABA test is not suitable for use in outpatient departments, because it requires urine to be stored for 6 hours. Thus, with these available tests, it is difficult to evaluate pancreatic exocrine function in routine clinical practice in Japan.

Clinically apparent steatorrhea tends to less frequently occur in Japanese patients than in Western patients with CP, because daily fat intake is lower in the Japanese diet, which makes PEI diagnosis more difficult.[6] In practice, clinicians therefore depend on nutritional markers to indicate the presence of PEI in patients without the symptoms, such as diarrhea and steatorrhea. However, it is not easy to diagnose PEI based on nutritional markers alone. These markers are affected not only by pancreatic exo-

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crine function but also by age, food intake, other concomitant diseases, and so forth. A potentially easy and useful method when suspecting PEI may be to focus on comorbid pancreatic diabetes mellitus (DM). Pancreatic endocrine and exocrine functions tend to correlate,[7] enabling identification of potential PEI patients even though this may be also insufficient. It is known that various nutritional markers are aggravated in CP, but it is unknown which is more important or whether all markers are equally important. Due to the nature of steatorrhea, cholesterol and fat-soluble vitamins appear to be important. Certainly, there is a previous report that serum cholesterol level is an important marker indicating nutritional status in CP.[8] On the other hand, another report emphasizes albumin levels.[9] A recent study revealed that magnesium levels were useful for detecting PEI.[10] However, this situation remains unresolved. In the present study, we aimed to determine the nutritional markers most closely associated with pancreatic dysfunction. We focused on nutritional markers that are easily measured even in nonspecialist hospitals.

MATERIALS AND METHODS

Patients with CP attending the outpatient department at our institute from July 2012 to January 2013 were enrolled. CP was diagnosed on the basis of the revised Japanese clinical diagnostic criteria for CP.[11] That is to say, in 108 patients (73%), the diagnosis of CP was made mainly due to pancreatic calcification. In 29 patients (27%) without pancreatic calcification, the diagnosis was made due to irregular dilatation of main pancreatic duct. The following were excluded from the study: patients with early-stage CP which is diagnosed mainly based on endoscopic ultrasound findings;[11] patients with less than 1-year follow-up; patients who experienced acute aggravation within 6 months; patients with autoimmune pancreatitis; and patients with concomitant malignancy. This ensured that patients were stable, that their food intake remained consistent throughout the study period, and that concurrent medications did not interfere with the results, e.g., steroid treatment in autoimmune pancreatitis may affect diabetes and the values of several nutritional markers.[12] As a result, the final study population included 137 patients.

As representative nutritional markers, albumin, prealbumin, total cholesterol, cholinesterase, and hemoglobin were measured. In addition, the following were recorded: hemoglobin A1c (HbA1c) levels; magnesium levels; body mass index (BMI); the underlying cause of CP (alcoholic or nonalcoholic); whether pancreatic calcification was present; and medication (e.g., pancreatic enzyme drug, antihyperlipidemic agents, magnesium oxide, etc.). The presence or absence of DM and the type was obtained by reviewing medical records. Based on fasting blood glucose, immunoreactive insulin, C-peptide immunoreactivity and so on, DM was classified according to the assessment described by DM specialists into three types: purely pancreatic, nonpancreatic (mainly type 2 DM), and mixed (pancreatic and type 2 DM). In general, DM of patients with insufficiency of insulin secretion (e.g., homeostasis model assessment β [HOMA-β] <40%) and normal insulin resistance (e.g., HOMA-R <1.6) was classified into purely pancreatic DM. DM of patients without insufficiency of insulin secretion and with abnormal insulin resistance was classified into type 2 DM. In other cases, they were classified into mixed type DM. In this study, we considered "purely pancreatic" and "mixed" types and combined them into "pancreatic DM." In order to select patients with higher possibilities of PEI, we divided the 137 patients into two groups: the "pancreatic DM group" consisting of 47 patients with pancreatic DM (23 pure pancreatic and 24 mixed type DM) requiring medical therapy (oral hypoglycemic agent or insulin) and the "other" group consisting of 90 patients who did not meet these criteria. A patient with pancreatic DM may not always suffer from severe PEI; however, pancreatic exocrine function can be expected to be worse in this group.[7] Thus, we assumed that comparing these two groups would enable us to determine which nutritional marker is most closely associated with PEI. Subgroup analyses based on the drugs administered and the cause of CP (alcoholic or nonalcoholic) were performed. The review board of our institute approved this retrospective study.

RESULTS

A total of 137 patients (112 men and 25 women) were enrolled, with an average age of 62.4 years (range, 33 to 87 years) and a mean BMI of 21.3 kg/m^2 (range, 12.6 to 28.8 kg/m^2). The mean follow-up period was 72 months (range, 13 to 213 months). Alcohol consumption was the cause of CP in 100 patients (73%). Pancreatic calcification was observed in 122 patients (89%), and none had obstructive jaundice due to biliary stricture. Clinical steatorrhea was observed in only four patients (2.9%).

There were 51 patients (37%) with DM requiring medical therapy: 23 had pancreatic DM, 24 had mixed DM, and four had nonpancreatic DM (three with type 2 DM and one with steroid-induced DM). Thus, 47 patients with pancreatic and mixed type DM receiving medical treatment were selected and referred to as the "pancreatic DM group."

Comparison between the pancreatic DM (n=47) and the other (nonpancreatic DM, n=90) groups, is shown in Table 1. There were no significant differences in age, sex, follow-up period, cause of CP, or pancreatic calcification. Concerning nutritional markers, both total cholesterol and cholinesterase levels were significantly lower in the pancreatic DM group, while no differences were observed in other markers.

We performed several subgroup analyses for further clarification. First, subgroup analysis based on pancreatic enzyme drug use was performed (Table 2A and B). Significant differences in

Table 1. Comparison between Pancreatic and Nonpancreatic Diabetes Mellitus Groups

	Pancreatic DM (n=47)	Nonpancreatic DM (n=90)*	p-value
Backgrounds			
Age, yr	63.6±9.37	61.7±12.6	0.297
Sex, male/female	41/6	71/19	0.333
Follow-up period, mo	77±42	69±42	0.339
Cause of CP, alcoholic/nonalcoholic	37/10	63/27	0.275
Pancreatic calcification	44/3	78/12	0.262
Hemoglobin A1c, % (normal range, 4.6–6.2)	6.9±0.90	5.9±0.47	<0.001
Administered drug			
Pancreatic enzyme drug, +/-	12/35	26/64	0.677
Camostat mesilate, +/-	14/33	28/62	0.873
Antihyperlipidemic agents, +/-	12/35	15/75	0.216
Neutritional marker			
BMI, kg/m^2	21.7±2.72	21.2±2.93	0.341
Albumin, g/dL (range, 3.9–4.9)	4.06±0.284	4.14±0.331	0.166
Prealbumin, mg/dL (range, 19–24)	26.1±6.70	26.5±6.12	0.705
Total cholesterol, mg/dL (range, 129–232)	164±30.0	183±36.6	0.003
Cholinesterase, U/L (range, 203–460)	263±68.9	291±60.0	0.016
Magnesium, mg/dL (range, 1.6–2.4)	2.01±0.213 (n=43)	2.05±0.198 (n=77)	0.381
Hemoglobin, g/dL (range, 13.8–16.6)	13.5±1.58	13.5±1.57	0.940

Data are presented as mean±SD or number.
DM, diabetes mellitus; CP, chronic pancreatitis; BMI, body mass index.
*86 patients without DM+3 patients with type 2 DM+1 patient with steroid-induced DM.

Table 2A. Comparison of Patients Treated with a Pancreatic Enzyme Drug between the Pancreatic and Nonpancreatic Diabetes Mellitus Groups

	Pancreatic DM (n=12)	Nonpancreatic DM (n=26)	p-value
BMI, kg/m^2	21.0±2.70	20.0±2.92	0.320
Albumin, g/dL	4.08±0.241	4.07±0.378	0.932
Prealbumin, mg/dL	25.2±6.97	25.1±6.24	0.965
Total cholesterol, mg/dL	161±39.9	173±39.0	0.419
Cholinesterase, U/L	269±59.6	272±50.0	0.872
Magnesium, mg/dL	2.02±0.185	2.05±0.197	0.610
Hemoglobin, g/dL	13.4±1.31	13.0±1.29	0.419

Data are presented as mean±SD.
DM, diabetes mellitus; BMI, body mass index.

Table 2B. Comparison of Patients Not Treated with a Pancreatic Enzyme Drug between the Pancreatic and Nonpancreatic Diabetes Mellitus Groups

	Pancreatic DM (n=35)	Nonpancreatic DM (n=64)	p-value
BMI, kg/m^2	21.9±2.74	21.6±2.82	0.679
Albumin, g/dL	4.05±0.30	4.17±0.31	0.080
Prealbumin, mg/dL	26.4±6.68	27.1±6.03	0.594
Total cholesterol, mg/dL	165±26.5	187±35.1	0.002
Cholinesterase, U/L	261±72.5	299±62.2	0.008
Magnesium, mg/dL	2.01±0.226 (n=31)	2.05±0.200 (n=53)	0.425
Hemoglobin, g/dL	13.5±1.68	13.7±1.64	0.590

Data are presented as mean±SD.
DM, diabetes mellitus; BMI, body mass index.

total cholesterol and cholinesterase levels were observed only in those patients not treated with pancreatic enzyme drug.

The second subgroup analysis was based on the cause of CP. The pancreatic DM group was expected to exhibit a poorer liver function in the presence of alcoholic when compared with nonalcoholic CP. Because serum cholinesterase levels reflect liver synthetic function and therefore liver damage more sensitively than other markers such as albumin and prothrombin activity,[13] its levels are probably affected more by liver than by pancreatic function. Thus, we expected this analysis to clarify whether the decrease in cholinesterase levels resulted from PEI or liver dysfunction. Table 3A and B summarize the results. In the patients with alcoholic CP, significant differences existed in both total cholesterol and cholinesterase levels. In the patients with non-

Table 3A. Comparison between the Pancreatic and Nonpancreatic Diabetes Mellitus Groups with Alcoholic Chronic Pancreatitis

	Pancreatic DM (n=37)	Nonpancreatic DM (n=63)	p-value
Daily alcohol consumption, g/day (≥80/<80)	23/14	32/31	0.270
Total cholesterol, mg/dL	164±31.0	181±39.0	0.0241
Cholinesterase, U/L	255±67.9	285±54.6	0.0143

Data are presented as mean±SD or number.
DM, diabetes mellitus.

Table 3B. Comparison between the Pancreatic and Nonpancreatic Diabetes Mellitus Groups with Nonalcoholic Chronic Pancreatitis

	Pancreatic DM (n=10)	Nonpancreatic DM (n=27)	p-value
Total cholesterol, mg/dL	165±27.6	187±30.4	0.0520
Cholinesterase, U/L	296±65.3	304±70.3	0.752

Data are presented as mean±SD.
DM, diabetes mellitus.

alcoholic CP, the tendency of lower cholesterol levels remained in the pancreatic DM group (p=0.0520), but the difference in cholinesterase levels disappeared. Thus, the differences in cholinesterase levels shown in Table 1 appear to mainly result from concomitant alcoholic liver injury, rather than PEI.

A further subgroup analysis, based on the administration of antihyperlipidemic agents, was performed to improve the evaluation of the difference in total cholesterol. Limited to the patients receiving no antihyperlipidemic agents, total cholesterol levels in pancreatic DM group were still lower than that of nonpancreatic DM group (Table 4A and B).

Magnesium levels were analyzed in patients not consuming magnesium oxide (39 in pancreatic DM group and 72 in nonpancreatic DM group). Comparison between these groups revealed that there was no significant difference in magnesium levels (2.00±0.211 mg/dL vs 2.04±0.196 mg/dL, respectively; p=0.306).

DISCUSSION

Albumin levels are frequently used as the most representative and important nutritional marker for many clinicians. In the well-known Glasgow Prognostic Score used in cancer patients, for example, C-reactive protein and albumin level are essential component.[14-16] Albumin levels were periodically measured in 80 of 82 patients (98%) with pancreatic cancer receiving chemotherapy at our institute in 2010 and 2011. However, total cholesterol was measured in only 10 of 82 patients (13%). This study implies the importance of total cholesterol levels as a nutritional marker for pancreatic disease. As our series included few patients with severe steatorrhea, the differences that exist in pancreatic exocrine function between the pancreatic and nonpancreatic DM groups are probably small. Considering that total cholesterol levels could reflect the mild or moderate difference, which albumin levels could not, the former may be more sensitive than the latter as a nutritional marker of pancreatic disease.

Table 4A. Comparison of Patients Treated with Antihyperlipidemic Agents between the Pancreatic and Nonpancreatic Diabetes Mellitus Groups

	Pancreatic DM (n=12)	Nonpancreatic DM (n=15)	p-value
Total cholesterol, mg/dL	171±23.0	186±34.8	0.228

Data are presented as mean±SD.
DM, diabetes mellitus.

Table 4B. Comparison of Patients Not Receiving Antihyperlipidemic Agents between the Pancreatic and Nonpancreatic Diabetes Mellitus Groups

	Pancreatic DM (n=35)	Nonpancreatic DM (n=75)	p-value
Total cholesterol, mg/dL	162±32.0	182±37.1	0.0054

Data are presented as mean±SD.
DM, diabetes mellitus.

Pancreatic enzyme drugs affect nutritional markers, as supported by the marked difference in nutritional marker levels in patients not treated with pancreatic enzyme drugs. It was difficult to evaluate the drug effect in detail for several reasons. These included a lack of standardized indications for use, variation in both the type and dose of drug administered, and the small number of patients studied.

When alcoholic liver cirrhosis and chronic pancreatitis coexist, the severities of the two conditions are often unequal,[17] when one is clinically severe, the other is often mild. However, despite these differences in severity in patients with increased alcoholic consumption, the two frequently coexist,[18] making it necessary to consider whether CP is alcoholic or nonalcoholic in origin. Previous reports have failed to consider concomitant alcoholic liver dysfunction when evaluating nutritional markers in patients with CP. Thus, we performed a subgroup analysis based on the cause of CP. Further, we examined cholinesterase levels, which are generally exacerbated in malnutrition, but is affected by the liver function in particular. As shown in Table 3A and B, the decreased cholinesterase levels appeared to be affected by liver function, which may suggest that total cholesterol level is more important as a nutritional marker of pancreatic exocrine function.

Despite the lower average total cholesterol levels, antihyperlipidemic agents were more frequently administered in the pancreatic DM than in the nonpancreatic DM group (26% vs 17%, respectively; p=0.216). While aggravation of pancreatic function

is very mild, total cholesterol levels may not be influenced so much. In addition, perhaps because hyperlipidemia represents a stronger risk factor for cerebrovascular disease when associated with DM,[19] patients in the pancreatic DM group were probably treated more aggressively by DM specialists (Table 4A). We therefore conclude that it is unlikely that the increased use of antihyperlipidemic agents in the pancreatic DM group resulted in the differences in total cholesterol levels between the two groups.

A previous report by Lindkvist *et al*.[10] proposed that serum magnesium was useful for discriminating patients with and without PEI. However, the proposed cutoff value of 2.05 mg/dL, which was the median of the normal range for magnesium, made it unrealistic to depend on magnesium alone. They recommend using magnesium levels in combination with other nutritional markers. This may also be true for cholesterol, considering that total cholesterol levels are unaffected by pancreatic exocrine function alone. The difference in total cholesterol levels between pancreatic and nonpancreatic DM groups was certainly significant but was not particularly large (19 mg/dL) (Table 1). It would be prudent to consider the absolute total cholesterol level, in combination with its transition, other nutritional markers, and clinical symptoms when diagnosing PEI. In addition, it should be considered that obstructive jaundice due to biliary stricture raises total cholesterol levels and that measuring them will be sometimes meaningless in such circumstances.

The major limitation of this study is that, by design, pancreatic exocrine function was not directly assessed. However, tests that directly assess function, such as the secretin test, the ^{13}C breath test, and the fecal elastase test, are presently unavailable in almost all Japanese institutions. This presents many doctors with significant difficulties in diagnosing mild or moderate PEI. We aimed to propose a method to overcome this impasse. Although imperfect, we believe it will have benefits in grasping a general trend. We do not intend to allege that low cholesterol is equal to PEI, but noticing cholesterol level might contribute to suspecting PEI. If a similar study to the present one is performed in future, more accurate assessment of insulin secretion ability, such as glucagon tolerance test, may be desirable because picking up pancreatic DM adequately is essential in the present method.[20] In addition, increasing the number of patients with nonalcoholic CP may contribute to the credibility of the study because excessive alcohol intake affect the function of other organs, which makes the nutritional assessment complicated. If there are researchers who try to confirm our results with a conventional method using the coefficient of fat absorption or ^{13}C breath tests, it will be our great pleasure.

In conclusion, total serum cholesterol may more accurately reflect PEI than other nutritional markers such as albumin. We believe that more weight should be given to it when assessing the presence or degree of PEI in CP. It is likely that many clinicians fail to administer pancreatic enzyme drugs due to normal serum albumin levels, indicating that the patient's nutritional status seems good. As it is certain that cholesterol levels are affected by various factors besides PEI, its level cannot be a decisive factor for diagnosing PEI only by itself. In order to make a more comprehensive assessment of nutritional status, however, it is still important that cholesterol is not ignored.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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