Elevated Serum CA19-9 Levels in Poorly Controlled Diabetic Patients

Naoto Nakamura*, Osamu Aoji*, Toshikazu Yoshikawa, Kazuki Mori, Shizuo Kajiyama, Yoshihiro Kitagawa, Takahiro Kanatsuna and Motoharu Kondo

Serum CA19-9 levels were measured in 60 diabetic patients and 40 healthy volunteers. Serum CA19-9 concentration was correlated with hemoglobin A1 (HbA1) (r=0.4368 P<0.005) and fasting plasma glucose levels (r=0.3410 P<0.01). None of the 40 healthy subjects showed elevated CA19-9 concentrations over 37 units/ml as the upper normal value. The percentage of positive serum CA19-9 levels in poorly controlled patients (fasting plasma glucose > 200 mg/dl or HbA1>13%) and moderately to well controlled patients was 50% and 10%, respectively. No correlation was found between the level of CA19-9 and those total cholesterol, and triglycerides, or the duration of diabetes. In patients who had diabetic retinopathy or persistent proteinuria, the CA19-9 concentration was significantly elevated when compared with those without these complications. It has been shown that patients with adenocarcinoma of the gastrointestinal tract have high plasma CA19-9 levels and those who have benign disease have normal CA19-9 levels. Even though diabetes mellitus is not a malignant disease, serum CA19-9 levels were increased in diabetic patients. These results indicate that HbA1 and fasting plasma glucose should be examined in patients with high CA19-9 levels.

Key Words: CA19-9, Diabetes, HbA1, Fasting plasma glucose

CA19-9, a colorectal carcinoma antigen, was detected by hybridoma antibody in 1979 by Koprowski[1]. This monoclonal antibody was produced by hybridomas derived from the fusion of mouse myeloma cells with mice splenocytes immunized with human colorectal carcinoma cells (SW 1116). It was reported that this antibody reacts with a carbohydrate antigenic determinant (CA19-9) found at low concentrations in sera from healthy individuals but frequently increased in sera from patients with gastrointestinal adenocarcinoma, especially those of the pancreas[2,3]. This study investigated CA19-9 levels in diabetic patients.

MATERIALS AND METHODS

Sixty diabetic patients (18 males and 42 females, mean age of 61.2 ± 11.7 yr, range 33–83 yr) and 40 healthy volunteers (20 males and 20 females, mean age of 60.3 ± 9.6 yr, range 36–60 yr) were studied. Coexisting malignant neoplasia in the digestive system was excluded by computed tomography of the abdomen, an upper gastrointestinal series, ultrasonic tomography of the abdomen and a barium enema in those patients who had complaints, symptoms, abnormal physical findings or abnormal laboratory data other than those attributed to diabetes.

In patients with high serum CA19-9 levels, all of these examinations were performed to exclude gastrointestinal malignant disease. All pa-
Patients showed normal serum BUN and creatinine levels. Measurement of plasma glucose, hemoglobin A1 (HbA1), total cholesterol, triglycerides, urinary protein and fundoscopic examination were carried out in all patients. Patients with high fasting plasma glucose levels (>200 mg/dl) or HbA1 levels (>13%) were defined as poorly controlled diabetics.

Fasting blood samples were collected, centrifuged immediately and stored at -20°C. Within 5 days all samples were analyzed. CA19-9 was assayed with a "forward sandwich" radioimmunometric assay using CA19-9™ RIA kits (CENTOCOR, Malvern, PA, USA). Quantities of CA19-9 were expressed in units of CA19-9 per milliliter determined from a standard curve. Assay standards were prepared from partially purified antigen preparations that had been isolated from supernates of a cultured human colorectal adenocarcinoma derived cell line (SW 1116). Levels of CA19-9 greater than 37 units/ml were considered to be positive.

Plasma glucose, HbA1, total cholesterol and triglycerides were measured by the following standard methods: glucose oxidase method using Beckman's glucose analyzer, liquid chromatography, enzymatic cholesterol assay and Kreutz's enzymatic method.

Data are reported as mean ± standard deviation. Student’s t-test was used for statistical analysis.

RESULTS

For diabetic patients, mean serum levels of CA19-9, fasting plasma glucose, HbA1, total cholesterol and triglycerides were 21.9 ± 22.3 U/ml, 151.2 ± 39.0 mg/dl, 10.9 ± 2.0%, 221.6 ± 40.2 mg/dl and 122.1 ± 75.4 mg/dl, respectively. Eleven patients had diabetic retinopathy, 11 persistent proteinuria, and 5 had both. In all of the diabetic patients, serum CA19-9 concentration was correlated with HbA1 (r=0.4368, P<0.005, Fig. 1) and fasting plasma glucose (r=0.3410, P<0.01, Fig. 2). No correlation was found between CA19-9 and total cholesterol, triglycerides or the duration of diabetes. Serum concentrations of CA19-9 were significantly elevated in poorly controlled patients (32.8 ± 25.8 U/ml, P<0.005, n=14) compared with those of fairly or well controlled patients (16.5 ± 13.1 U/ml, n=46).

Using 37 units/ml as the reference value, none of the 40 healthy subjects showed elevated CA19-9 concentrations. However, the percentage of patients with positive serum CA19-9 in poorly controlled patients and fairly or well controlled patients were 50% and 10%, respectively. Serum concentrations of CA19-9 were significantly elevated in the patients who had diabetic retinopathy (44.7 ± 34.9 U/ml, P<0.005, n=11) or persistent proteinuria (39.8 ± 36.8 U/ml, P<0.005, n=11) compared with those without diabetic retinopathy (16.9 ± 14.7 U/ml, n=49) or without persistent proteinuria (17.4 ± 15.3 U/ml, n=49).

Positive serum CA19-9 levels were observed in 10 of the 60 patients, while those patients with diabetic retinopathy or persistent proteinuria were positive in 5 of 11 cases. In patients with diabetic retinopathy
retinopathy or persistent proteinuria, HbA1 and fasting plasma glucose levels were elevated when compared with patients without either of these disorders.

**DISCUSSION**

We had reported that CA19-9 provides excellent sensitivity for adenocarcinoma of the pancreas, while only a small number of the patients with benign disease and none of the healthy subjects showed elevated CA19-9 concentrations over 37 units/ml as the upper normal value.

In this study, we found elevated serum concentrations of CA19-9 in poorly controlled diabetic patients, and a correlation between CA19-9 and HbA1 or fasting plasma glucose. High serum CA19-9 levels were also found in patients with diabetic retinopathy or persistent proteinuria. Additionally, in these patients, HbA1 and fasting plasma glucose levels were elevated. Therefore, the elevation of CA19-9 may be associated with poor control of diabetes.

There are some reports that patients who have gastrointestinal adenocarcinoma, especially pancreatic cancer, show high plasma CA19-9 levels and those who have benign disease show normal CA19-9 levels. Serum concentrations of carcinoembryonic antigen, which is an oncogenic antigen, was also reported to be increased in diabetic patients, and correlated with fasting plasma glucose levels. The reason why carcinoembryonic antigen appeared elevated in poorly controlled diabetic patients is still unknown.

In our investigation, serum CA19-9 levels were also elevated in poorly controlled diabetic patients, which leads to speculation that hyperglycemia plays a role in the elevation of these two tumor markers.

Consequently, evaluating the serum level of CA19-9 in diabetic patients, HbA1 and fasting plasma glucose levels should be performed.

**REFERENCES**


