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Low Serum Testosterone/Dihydrotestosterone Ratio in Patients with Pancreatic Carcinoma

Guillermo Robles-Diaz, Vicente Diaz-Sanchez, Juan Pablo Mendez, Araceli Altamirano, and Enrique Wolpert

Pancreatic Unit, Departments of Gastroenterology and Reproductive Biology, Instituto Nacional de la Nutrición Salvador Zubiran, México City, México

Summary: Serum testosterone, its metabolite 5α-dihydrotestosterone, and the testosterone/dihydrotestosterone ratio were investigated in 22 male patients with proven pancreatic cancer, and compared with values from male patients with chronic pancreatitis (n = 21) and with nonpancreatic gastrointestinal tumors (n = 19). Testosterone and the testosterone/dihydrotestosterone ratio were significantly lower ($p < 0.001$) in the pancreatic cancer group when they were compared with the other two groups. There was no significant difference in the dihydrotestosterone values between cancer groups. A testosterone/dihydrotestosterone ratio of less than 5 clearly distinguished most of the patients (20/22) with cancer of the pancreas from those with other tumors or chronic pancreatitis. The results suggest an alteration in the serum androgen profile in these patients. Therefore, the testosterone/dihydrotestosterone ratio could be a useful marker in the diagnosis of pancreatic carcinoma in male patients. **Key Words:** Pancreatic carcinoma—Testosterone/dihydrotestosterone ratio in pancreatic carcinoma—Tumor marker.

The frequency of pancreatic cancer has increased in the last few years (1–3). In Mexico, cancer of the pancreas is the fourth most frequent malignant neoplasm of the digestive system (4). Prognosis is very poor once the diagnosis is established, its 2-year survival rate being around 5% (1). Surgical resection of the tumor is the only feasible treatment during the early stages (5,6). Unfortunately, there are no useful diagnostic methods for the early detection of the tumor (7–11). It has been considered that 85% of patients with pancreatic cancer and clinical manifestations from the tumor already have metastases to distant sites at the time of diagnosis (8). The use of tumor markers has gained wide acceptance in the early detection of some types of the cancer. However, tumor markers in pancreatic cancer have been shown to have a very low degree of sensitivity and specificity.

Cancer of the pancreas predominates in males (1–3). Studies in experimental animals have demonstrated a hormonal dependence, as shown by tumor growth stimulation by androgens and tumor growth inhibition by antiandrogens or castration (12–14). Levels of serum testosterone have been found to be consistently low in patients with pancreatic cancer (15–17), whereas sexual steroid metabolism activity in neoplastic tissue has been found to be elevated (18).

The present study was carried out to investigate the serum androgen profile in male patients with proven pancreatic cancer, and to compare it with that obtained from patients with chronic pancreatitis without cancer and with that obtained from

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Address correspondence and reprint requests to Dr. G. Robles Díaz at Calle Vasco de Quiroga 15, Col. Tlalpan, Delg. Tlalpan, 14000 México, D.F.

patients with malignant tumors of the gastrointestinal tract other than the pancreas.

PATIENTS AND METHODS

Data were collected from 62 male patients who were divided into three groups:

Group A: Cancer of the pancreas

Twenty-two patients with a mean age of 59 ± 10.8 (1 SD) years were studied. The tumor was confirmed histologically in 17 subjects, and by surgical exploration and CAT scan in the remaining five patients. Two of the 22 patients had received chemotherapy 1 year before serum samples were obtained. Progression of the disease was the cause for further evaluation and treatment.

Tumor staging (19) was as follows: 4 patients were in stage I, 2 patients in stage II, 3 in stage III, and 13 in stage IV. Ten of the 22 subjects were jaundiced.

Group B: Gastrointestinal cancer other than pancreas

Nineteen patients with a mean age of 59 ± 15.5 (1 SD) years were studied. All subjects had histologically proven malignant tumors (10 gastric cancer, 5 colorectal cancer, 3 carcinoma of the esophagus, and 1 carcinoma of the common bile duct). Four subjects were in stage I, 5 patients in stage II, 4 in stage III, and 6 in stage IV. Two of the 19 patients were jaundiced.

There were no differences between the two groups with cancer in the percentage of ideal body weight calculated, as described by standard references (frame size, height, and age) (20).

Group C: Chronic pancreatitis

Twenty-one patients with a mean age of 55 ± 12.2 (1 SD) years were studied. The diagnosis was established by clinical manifestations of the disease, abnormal exocrine pancreatic function tests, and the presence of pancreatic calculi, abnormal endoscopic retrograde cholangiopancreatography (ERCP), and/or altered biopsy.

Human sera

Serum samples were collected from all patients between 8:00 and 9:00 a.m. after an overnight fast. Each sample was treated by immediate centrifugation at 1,000 *g*, and the serum was stored frozen at −20°C until assayed for testosterone (T) and dihydrotestosterone (DHT).

Radioimmunoassay of T and DHT

Both T and DHT were quantified by radioimmunoassay (RIA) after extraction and separation by celite column chromatography, as described by Abrahams et al. (21). The [1,2,6,7-^{3}H]T (specific activity 94 Ci/mmol) and the [1,2-^{3}H]DHT (specific activity 51.6 Ci/mmol) were obtained from New England Nuclear (Boston, MA, U.S.A.). Testosterone antiserum was kindly provided by the Matched Reagent Programme (WHO, Geneva, Switzerland). The inter- and intra-assay coefficients of variation were 11 and 7.3%, respectively, for T, and 11 and 6.3%, respectively, for DHT.

Statistical analysis

The significance of the differences among groups was investigated using Student's *t* test for unpaired observations.

RESULTS

Results for serum values of T, DHT, and the T/DHT ratio are shown in Table 1.

Significantly low serum levels of T and DHT were found in both groups of patients with cancer. However, T concentration and T/DHT ratio were lower in patients with pancreatic cancer when compared with subjects with other types of gastrointestinal tract tumors or with patients with chronic pancreatitis without neoplasia. Low values of T and the T/DHT ratio were found in most patients with pancreatic cancer, regardless of the clinical stage (Figs. 1 and 2). In fact, the highest value of T and the T/DHT ratio were obtained in a patient in stage IV, and low ratios of T/DHT were observed in all four patients in stage I.

In the pancreatic cancer group, no differences in serum hormone levels were observed between patients with and without jaundice (T/DHT ratio: 2.77 ± 1.87 and 3.16 ± 2.63, respectively).

DISCUSSION

Results obtained in this study demonstrated that a significant alteration in androgen metabolism occurs in male patients with cancer of the pancreas; T serum levels were lower in patients with pancreatic cancer and in subjects with nonpancreatic digestive neoplasm when compared with patients of a similar age with chronic pancreatitis. However, values obtained in the pancreatic cancer group were significantly lower than those found in pa-

TABLE 1. *Results for serum values of testosterone (T), dihydrotestosterone (DHT), and the T/DHT ratio*

	Testosterone (ng/ml)	Dihydrotestosterone (ng/ml)	T:DHT Ratio
Normal values (50–70 years old)	5.73 ± 1.97	0.590 ± 0.220	10.3 ± 2.9
Cancer of the pancreas	1.06 ± 1.22 [a]	0.318 ± 0.201 ns [a]	2.9 ± 2.3 [a]
Other G.I. tumors	2.75 ± 1.22 [a] [a]	0.298 ± 0.123 [a] [b]	9.7 ± 4.1 [a] [a]
Chronic pancreatitis	3.98 ± 1.50 [a]	0.497 ± 0.239 [a]	8.8 ± 2.7 ns [a]

Values are expressed as the mean ± SD.
[a] $p < 0.01$.
[b] $p < 0.05$.
ns, not significant.

tients with gastrointestinal tumors other than pancreas.

Low serum levels of DHT, a reduced metabolite of T, were found to be consistent with the reduced T serum levels found in the malignant tumor groups and significantly different from the chronic pancreatitis subjects. Despite the lower T serum levels found in the pancreatic cancer patients, there were no statistical differences in DHT serum values between both cancer groups, although a striking difference was noticed when comparing the proportion of reduced metabolite derived from testosterone by the T/DHT ratio. In pancreatic cancer patients, this ratio was consistently below 5, whereas for the nonpancreatic tumor patients and the chronic pancreatitis subjects, the T/DHT ratio was over 8, which is considered to be within normal range.

The lower T/DHT ratio and T serum concentration in patients with cancer of the pancreas cannot be attributed to age or nutritional status, since this variable was similar in all three groups. In addition, there were no significant differences in the clinical stage between cancer groups, and values were widely scattered regardless of tumor extension (Figs. 1 and 2). It has been reported that patients

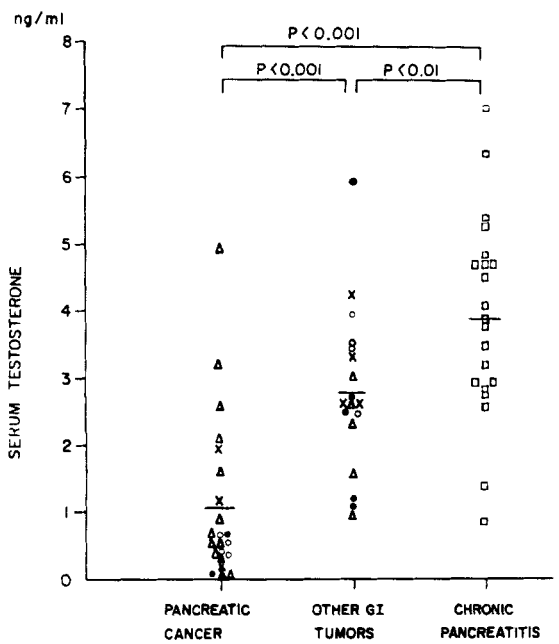

FIG. 1. Serum testosterone concentrations in the three groups of patients studied (tumor staging: ○ Stage I; ● Stage II; × Stage III; △ Stage IV; ▲ Stage IV plus chemotherapy; and □ chronic pancreatitis).

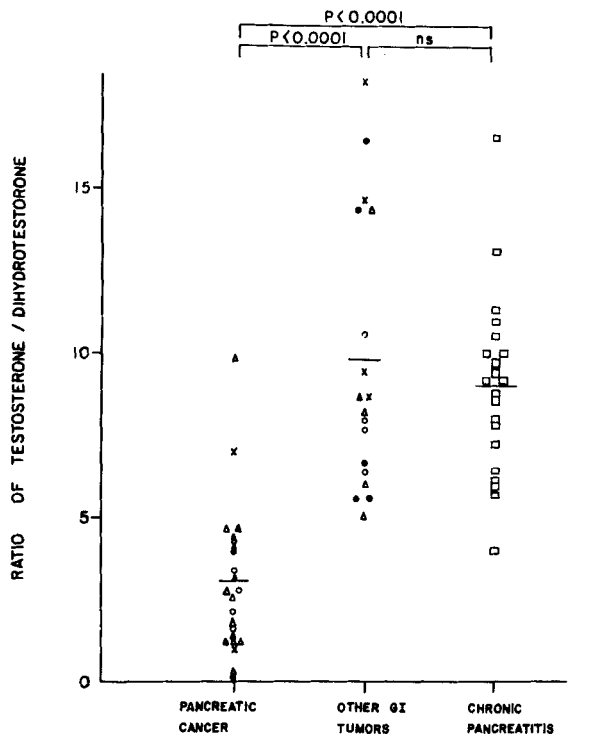

FIG. 2. Ratio of T/DHT (tumor staging: ○ Stage I; ● Stage II; × Stage III; △ Stage IV; ▲ Stage IV plus chemotherapy; and □ chronic pancreatitis).

with chronic hepatic failure have low circulating T levels (22,23). In this study, there was no difference between cases of pancreatic carcinoma with obstructive jaundice and those with normal liver function.

The reduced testosterone serum levels and T/DHT ratio may be explained by two facts: (a) the pancreas has a selective uptake of androgens demonstrated in normal and malignant pancreatic cells (24,25), and (b) there is a high rate of conversion of T to DHT in malignant pancreatic tissue (18).

Hormonal circulating levels reflect the balance among biosynthesis, distribution in tissue and other body fluids, and metabolism. Therefore, if a consistent deviation from the normal pattern is observed in association with a well-defined pathology, the study of the hormonal profile becomes very important to the differential diagnosis, early detection, and surveillance of the population at risk of the disease. In males with cancer of the pancreas, our finding of a low T/DHT ratio (below 5) was a consistent finding that allowed a clear distinction between this pathology and other digestive tract neoplasms, as well as chronic pancreatitis, and it enabled us to recommend this ratio as a sensitive and specific tumor marker of cancer of the pancreas with a cut-off point under 5. More importantly, all patients in early stages showed abnormally low values, which would indicate that this ratio could be used in the detection of pancreatic carcinoma.

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