

Diabetes Mellitus in Association with Primary Carcinoma of the Pancreas

Robert C. Green, Jr., M.D., Archie H. Baggenstoss, M.D., and Randall G. Sprague, M.D., Rochester, Minnesota

The association of diabetes mellitus and primary carcinoma of the pancreas has been noted for at least a century. Early French clinicians^{1,2} reported several such cases, but there have been relatively few critical comments on the relationship, or lack of relationship, between the two diseases. A further study of the problem was therefore undertaken.

MATERIAL AND METHOD

The study was based on the necropsies in 209 consecutive cases of primary carcinoma of the pancreas at the Mayo Clinic from 1926 to 1952. Information was obtained from the clinical records, gross specimens and histologic sections. The location of the neoplasm was designated as either the head or the body of the organ. The phrase "body of the pancreas" refers in this study to the body or tail of the gland, or both. The neoplasms were classified histologically as either ductal, acinar or indeterminate in origin. The size of the tumor was expressed as the mean of the three greatest dimensions.

The diagnosis of diabetes mellitus was based on one or more fasting venous blood-sugar values of 120 mg. per 100 cc. or more by the Folin-Wu method, with or without glycosuria. Glucose-tolerance tests were not generally employed. It should be noted that in a group of ill patients such tests frequently yield false positive results owing to factors not related to diabetes.

An analysis was made of the relation between the size, cell type and location of the pancreatic tumor, on the one hand, and the presence or absence of diabetes on the other. An effort was made to evaluate the factor of hereditary predisposition to diabetes by study of the family histories.

RESULTS

The frequency of glycosuria and frank diabetes in the 209 cases is shown in table 1. Diabetes was present

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From the Mayo Foundation, Rochester, Minnesota, a part of the Graduate School of the University of Minnesota.

TABLE 1

Primary carcinoma of the pancreas in relation to diabetes: classification of 209 patients

Group	Patients	Per cent
Diabetes present before onset of symptoms of pancreatic carcinoma	9	4.3
Diabetes found after onset of symptoms of pancreatic carcinoma	32	15.3
Diabetes not diagnosed, but glycosuria present	61	29.2
No diabetes or glycosuria	107	51.2
Total	209	100.0

in forty-one cases (19.6 per cent). Of these, diabetes was known to have been present in nine (4.3 per cent) prior to the development of symptoms of carcinoma; in the remaining thirty-two (15.3 per cent), diabetes was discovered after the onset of symptoms referable to the neoplasm. An additional group, sixty-one patients (29.2 per cent), was found to have glycosuria one or more times but a diagnosis of diabetes was not or could not be established. There remained 107 patients (51.2 per cent) in whom no evidence of diabetes or glycosuria was found. In all groups the age and sex distribution, average size of the tumor and distribution of grades of malignancy were similar.

Cases in which diabetes mellitus was known to be present prior to onset of symptoms of pancreatic carcinoma. The average age at which diabetes was discovered in the nine cases in this group was 52.7 years. The average interval between the diagnosis of diabetes and the onset of symptoms of pancreatic carcinoma was 9.7 years (range, 1.5 to 22 years). There was a preponderance of the more severe grades of diabetes in this group, insulin being required in eight of the nine cases. Of eight cases in which information was available, there was a family history of diabetes in four. The neoplasms of the nine patients in this group were located in the head of the pancreas in five and in the body in four. Six of the nine tumors were of the ductal cell type and three were of the acinar type.

Cases in which diabetes mellitus was discovered after onset of symptoms of pancreatic carcinoma. Of the thirty-two patients in this group, only seven had cardinal symptoms of diabetes. Fasting blood-sugar values ranged from 120 to 400 mg. per 100 cc., the average being 182 mg. The diabetes in this group was predominantly mild, insulin being required in only five of the thirty-two cases. Among thirty patients for whom information was available, only four patients had a family history of diabetes. The carcinomas were located in the head of the pancreas in twenty-six cases and in the body in the remaining six. In thirty cases the tumors originated from ductal cells and in two from acinar cells. There was no correlation between size of tumor and severity of diabetes.

An attempt was made in this group to evaluate by simple inspection of microscopic sections the effect of the neoplasm on the remaining uninvolved pancreas, particularly the islet tissue. Extensive fibrosis and some apparent reduction of the amount of islet tissue were found in association with some tumors of either the head or the body of the pancreas but particularly the head. However, extensive fibrosis and reduction of the amount of islet tissue were present in only about a third of the cases of diabetes, while in the remaining two-thirds there was at most only minimal evidence of fibrosis along with an apparently normal number of islets. It appeared doubtful that actual destruction of islet tissue was sufficiently pronounced in most of the thirty-two cases to account for the presence of diabetes.

Cases in which a diagnosis of diabetes was not established. This group totaled 168 cases, including sixty-one* in which glycosuria occurred and 107 in which it did not.

Among 127 cases in the group without diabetes in which information was available, only ten patients had a family history of diabetes. Among the entire group of 168 cases the carcinomas were located in the head of the pancreas in 121 and in the body in forty-seven. There were 141 carcinomas arising from ductal cells and seventeen from acinar cells, while ten were of indeterminate origin. Among the 168 cases in which diabetes was not demonstrated, the fasting blood sugar was de-

termined in thirty-three and was normal in all instances.

Correlations between incidence of diabetes following pancreatic carcinoma, and location and type of tumor and family history of diabetes. The difference in incidence of diabetes in association with tumors of the head (17.7 per cent) and body (11.3 per cent) is not significant, for this difference would occur by chance 28 per cent of the time. Likewise, the difference in incidence of diabetes in association with ductal cell lesions (17.5 per cent) and acinar cell lesions (10.5 per cent) is not statistically significant, for this difference would occur by chance 43 per cent of the time. Even the difference in incidence of diabetes in association with positive (28.6 per cent) and negative (17.0 per cent) family history of diabetes is not significant, for the observed difference here would occur by chance 25 per cent of the time.

Thus, in this series of cases in which diabetes was discovered after the onset of symptoms of primary carcinoma of the pancreas, neither size, cell type, grade of malignancy or location of the tumor nor family history appeared to be a determining factor in the development of diabetes. It is, of course, possible that a larger series of cases might bring out significant differences in the incidence of diabetes in relation to these factors.

COMMENT

Several questions arise from this study. Does the prior presence of diabetes predispose to the development of carcinoma of the pancreas? In this series of 209 cases of primary carcinoma of the pancreas there were nine (4.3 per cent) in which diabetes was present before the onset of symptoms of pancreatic neoplasm. Warren and LeCompte,³ Marble,⁴ and McKittrick and Root⁵ have reported a total of twenty-five similar cases. Neither their data nor ours permit an answer to the question of whether the prior presence of diabetes predisposes to the development of carcinoma of the pancreas.

Does the presence of carcinoma of the pancreas give rise to diabetes in an appreciable number of cases? In this series it appears that coexistence of the two diseases was too frequent to be explained as coincidence, for in 15.3 per cent the presence of diabetes was established after the onset of symptoms of carcinoma of the pancreas. However, as Berkson⁶ has emphasized, the coexistence of two diseases does not necessarily imply a cause-and-effect relationship but may be related to a variety of factors, particularly peculiarities of selection of cases.

What relationship exists between location of tumor and development of diabetes? It has been suggested by Grauer⁷ that tumors in the head of the pancreas are particularly prone to cause diabetes owing to obstruction of

* Among the sixty-one cases in which glycosuria was found one or more times after the onset of symptoms of carcinoma but in which a diagnosis of diabetes mellitus was not established, twenty patients had normal values for fasting blood sugar, while in the remaining forty-one no determinations of blood sugar were recorded. In thirty of the sixty-one cases glycosuria coincided with the parenteral administration of glucose and hence was of doubtful significance.

the pancreatic ducts with subsequent fibrosis and damage to the islet tissue. In a study of the effects of duct ligation in rabbits, cats and dogs, Ssobolew⁸ found that 30 to 120 days after ligation, sclerosis of the islets took place, and glycosuria sometimes occurred. Silver and Lubliner,⁹ in an effort to explain the occurrence of diabetes in association with tumors in the body and tail of the pancreas, suggested that diabetes in such cases may be due to destruction of a portion of the pancreas containing the greatest concentration of islet tissue. However, none of the foregoing observations and speculations seem adequate to explain most of the instances of diabetes in the present study. Tumors in the head of the pancreas did not appear to have a significantly more frequent association with diabetes than did tumors of the body. Furthermore, among the thirty-two patients who were found to have diabetes after the onset of symptoms of carcinoma, extensive pancreatic fibrosis and destruction of islets were present in only about a third. It would thus appear that actual destruction of islet tissue owing to the presence of the neoplasm is not the sole basis for the development of diabetes. The possible presence in some cases of mild unrecognized diabetes prior to the development of carcinoma cannot be ruled out, nor can the factor of hereditary predisposition to diabetes be accurately evaluated solely on the basis of family history. Nevertheless, it would appear that the incidence of diabetes after the onset of symptoms of carcinoma in this study is higher than would be anticipated in the general population of comparable age.

In spite of the fact that only one patient in six in this study was proved to have diabetes following pancreatic carcinoma, it would appear to be good clinical judgment to consider the possibility of such a lesion in any patient with persistent vague abdominal pain and newly discovered diabetes.

SUMMARY

Two hundred and nine cases of primary carcinoma of the pancreas were reviewed after necropsy in an effort to determine the incidence of diabetes and the relationship between diabetes and the pancreatic tumor.

Nine patients (4.3 per cent) had diabetes prior to the onset of symptoms of pancreatic carcinoma. No conclusions could be reached regarding the question of whether the prior presence of diabetes predisposes to the development of carcinoma of the pancreas.

Another thirty-two patients (15.3 per cent) were found to have diabetes after the onset of symptoms of pancreatic carcinoma. The presence of diabetes was not, or could not be, established in 168 (80.4 per cent) of the patients. Among the patients in whom the presence

of diabetes was established after the onset of symptoms of carcinoma of the pancreas, there seemed to be no significant relationship to type, location and size of the neoplasm. In at least two-thirds of the cases in which diabetes appeared after the development of symptoms of neoplasm, there did not appear to be sufficient destruction of islet tissue by fibrosis, tumor invasion or inflammation to account for the presence of diabetes.

It seems probable that the two factors of hereditary predisposition to diabetes and actual destruction of islet tissue owing to the presence of neoplasm, although not shown to be individually significant in the entire series, might in combination account for the observed instances of diabetes. However, other unrecognized factors, including peculiarities of selection of cases in this series, cannot be excluded.

SUMMARIO IN INTERLINGUA

Diabete Mellite In Association Con Primari Carcinoma Del Pancreas

Duo centos e nove casos de primari carcinoma del pancreas esseva studiate al necropsia con le objectivo de determinar le incidentia de diabete e le relation inter diabete e le tumor pancreatic.

Nove patientes (4,3 pro cento) habeva diabete ante le declaration de symptommas de carcinoma pancreatic. Nulle conclusiones esseva derivate con respecto al question de si le presentia anterior de diabete predispone al disveloppamento de carcinoma del pancreas.

Esseva trovate que trenta-duo patientes additional (15,3 pro cento) disveloppava diabete post le declaration del symptommas de carcinoma pancreatic. Le presentia de diabete non esseva establite o non poteva esser establite in 168 del patientes (80,4 pro cento). In le gruppo de patientes in qui le presentia de diabete esseva establite post le declaration del symptommas de carcinoma del pancreas, il non pareva exister ulle correlation significative con le typo, le loco, e le dimension del neoplasma. In al minus duo tertios del casos in que diabete appareva post le disveloppamento de symptommas de neoplasma, le grado de destruction del histos insular per fibrosis e le grado de invasion tumoric o de inflammation non sufficeva pro explicar le presentia de diabete.

Il pare probabile que le duo factores de predisposition hereditari al disveloppamento de diabete e de ver destruction de histos insular in consequentia del presentia de neoplasma (ben que illos non se monstrava individualmente significative in le serie integre) es capace, in combination, a explicar le observate casos de diabete. Tamen, altere, non-recognoscite factores—incluse peculiaritates del selection de casos in le presente serie—non pote esser excludite.

REFERENCES

- ¹ Mirallié, Charles: Cancer primitif du pancréas. *Gazette des hospitaux civils et militaires*. 66:889-98, 1893.
- ² Guillou, François: De la glycosurie dans le cancer primitif du pancréas. Thesis, Paris, 1898, 78 pp.
- ³ Warren, Shields, and LeCompte, P. M.: *The Pathology of Diabetes Mellitus*. Philadelphia, Lea & Febiger, 1952, Ed. 3, p. 271.
- ⁴ Marble, A.: Diabetes and cancer. *New England J. Med.* 211:339-49, Aug. 23, 1934.
- ⁵ McKittrick, L. S., and Root, H. F.: *Diabetic Surgery*. Philadelphia, Lea & Febiger, 1928, pp. 250-51.
- ⁶ Berkson, Joseph: Limitations of the application of fourfold table analysis to hospital data. *Biometrics* 2:47-53, June, 1946.
- ⁷ Grauer, F. W.: Pancreatic carcinoma: Review of 34 autopsies. *Arch. Int. Med.* 63:884-98, May, 1939.
- ⁸ Ssobolew, L. W.: Zur normalen und pathologischen Morphologie der inneren Secretion der Bauchspeicheldrüse. *Arch. path. Anat.* 168:91-128, May, 1902.
- ⁹ Silver, G. B., and Lubliner, R. K.: Carcinoma of pancreas: Clinicopathologic survey. *Surg., Gynec. & Obst.* 86:703-16, June, 1948.

DISCUSSION

PHILIP M. LECOMPTE, M.D., (*Boston*): I should like to ask if the authors used any quantitative methods for determining the amount of beta cell granulation in the pancreas. The reason I ask this is because, in order to determine the actual mass of functioning beta cell tissue in the pancreas, it is necessary to use quantitative methods, such as those of Ogilvie. The reason I bring up this point is that it is conceivable that in some cases the amount of beta cell tissue may be reduced already to a considerable extent, and then the superimposition of a carcinoma might be enough to diminish the mass of beta cells to such a point that diabetes would appear.

ALEXANDER MARBLE, M.D., (*Boston*): Over the years there has been a great deal of discussion as to whether or not cancer is more common among diabetic than nondiabetic individuals. Certain workers have published data which suggest that cancer occurs more commonly in diabetics than in the general population. However, on each occasion that we have analyzed our own data, we have been forced to conclude that there is no conclusive evidence that this is true.

In the study by Dr. Green and his associates, the matter has been approached from the other direction. They have attempted to answer the question whether diabetes is found more commonly among persons with cancer and specifically among those with primary carcinoma of the pancreas. I have no personal data of exactly this type to report but it may be of interest that among our diabetic patients, those with cancer of the pancreas have comprised a significantly higher percentage of the total number of diabetic patients with cancer than is true in the general population. Thus, in our patients, cases of

cancer of the pancreas have formed 8 to 13 per cent of the total of those with cancer whereas in the general population cancer of the pancreas constitutes about 4.5 per cent of all types of malignant disease.

Studies carried out during the past few years at the Memorial Center for Cancer and Allied Diseases in New York City by Glicksman, Myers and Rawson (*Med. Clin. N. Amer.* 40:887, 1956; *Cancer* 9:1,127, 1956) demonstrated abnormal glucose tolerance curves in 36.7 per cent of 628 patients with a tissue diagnosis of cancer as contrasted with only 9.3 per cent positive results in a control group of 322 patients with tumors proved to be benign. Known diabetics were not specifically excluded from the study; they consisted of 4.4 per cent of the control group and 13 per cent of the cancer group. In this study there were only five patients with cancer of the pancreas but four of these showed abnormal glucose tolerance tests.

The relatively high incidence of abnormal glucose tolerance tests among individuals with cancer has been a subject for comment and speculation for many years. In a discussion of the total problem, a distinction should be made between the incidence of abnormal tolerance curves and frank diabetes from a clinical standpoint.

I would like to ask Dr. Green two questions: (1) Have you studied patients with other types of carcinoma as regards possible diabetes in the same manner that you have done with those with carcinoma of the pancreas? If so, what were the results? (2) I believe that you stated that patients were considered to have diabetes if the fasting blood sugar was 120 mg. per 100 cc. or higher, with or without glycosuria. Were there many of the positive cases whose values were borderline with only one or two values of, say, 120 mg. per cent?

DR. GREEN: No quantitative method was used to determine the amount of beta cell granulation in the pancreas of these cases, and no attempt was made to evaluate accurately either the number or the functioning capacity of the islets. Our statement that one third of the diabetic cases had an apparent decrease in the number of islets was only an impression since no special staining technics were used and only routine sections of the pancreas were examined.

In answer to Dr. Marble's first question, I do not believe there have been at the Mayo Clinic any similar studies with other types of malignancy. Certainly, additional studies should be carried out.

In response to Dr. Marble's second question, there were only three patients with borderline blood sugar levels. The remaining cases had a marked elevation of their blood sugar levels.