Should pancreas imaging be recommended in patients over 50 years when diabetes is discovered because of acute symptoms?

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Summary

The relationship between diabetes mellitus and cancer of the pancreas is complex and incompletely understood. Nevertheless, it is generally agreed that new-onset diabetes in a patient over 50 years old is a classical indication of pancreatic cancer. But there is no official directive in France that a scan should routinely be performed in such cases. We have studied 115 patients aged over 50 who were hospitalized for new-onset diabetes (fewer than 30 days) whose instability required insulin treatment. Routine imaging revealed abdominal disorders in 14 patients, 6 (5.2%) of whom were suffering from pancreatic adenocarcinomas. No clinical indication or laboratory test, apart from an unusually severe anorexia, suggested the discovered disorders. We therefore routinely carry out a pancreas scan, preferably by MRI, on all patients over 50 years old presenting with new-onset diabetes, even if there are not clinical or laboratory indications of cancer. This is the only way in which small pancreatic cancers can be detected, thus providing the best hopes for successful treatment. Unfortunately, too often, this approach also detects only tumors that are already well developed. However, nowadays, it is not conceivable for a clinical team to discharge a patient from hospital with such a serious disease undiagnosed.

Key-words: Diabetes mellitus - Pancreatic cancer - Pancreas - Risk factors - Medical imaging.

RésuMÉ

Une imagerie pancréatique est-elle recommandée chez les patients de plus de 50 ans dont le diabète est découvert sur des symptômes aigus ?

Les relations qui unissent le diabète sucré et le cancer du pancréas sont complexes et incomplètement élucidées. Cependant, il est admis que la survenue, après 50 ans, d’un diabète aigu est un mode classique de révélation d’un cancer du pancréas. Pourtant, aucune recommandation officielle ne préconise de réaliser de façon systématique une imagerie pancréatique dans ce cas de figure. Notre étude portait sur 115 malades, âgés de plus de 50 ans, hospitalisés pour un diabète aigu (moins de 30 jours) dont le déséquilibre nécessitait une insulinothérapie. L’imagerie systématique a permis de mettre en évidence une pathologie abdominale chez 14 malades dont 6 adénocarcinomes du pancréas (5,2 %). Aucun critère clinique, hormis une perte de poids plus importante, ni aucun critère biologique simple ne permettait de soupçonner les pathologies retrouvées. Ainsi nous préconisons, quel que soit le contexte de survenue, c’est à dire même sans facteur de risque associé, ni signe clinique ou biologique évocateur, de réaliser une imagerie pancréatique systématique, si possible par scanner, chez tout patient de plus de 50 ans présentant un diabète aigu. C’est le seul moyen de pouvoir découvrir des cancers pancréatiques de petite taille avec alors un meilleur espoir thérapeutique. Malheureusement, cette démarche risque de ne permettre, le plus souvent, que de découvrir des tumeurs déjà évoluées. Cependant, il n’est pas concevable aujourd’hui, ni pour le malade, ni pour l’équipe soignante, de pouvoir quitter un service hospitalier avec une pathologie d’une telle gravité dont le diagnostic n’aurait pas été fait.

Mots-clés : Diabète sucré - Cancer du pancréas - Pancrées - Facteurs de risque - Imagerie médicale.
A bout 3,000 new cases of Pancreatic Cancer (PC), the most common of which are adenocarcinomas, are discovered each year in France. They account for one-sixth of the Gastro Intestinal (GI) tract cancers and are the fifth most common cause of death from cancer in the western world. Their incidence increased between 1950 and 1970, but now seems to be stable. These cancers are very rare in people under 50, and twice as common in men as in women. Although our knowledge of the epidemiology and treatment of pancreatic cancer has improved, prognosis remains very negative, with an overall survival rate of 3% at 5 years [1]. The main problem associated with PC is the rarity of early diagnosis, when the cancer is still treatable. Thus the only treatment presently available is excision.

Most cases of PC are seen by endocrinologists, because of the diabetes involved, particularly the possibility that new-onset diabetes indicates PC. Nevertheless, there is presently no official recommendation that a pancreas scan should be performed on patients over 50 presenting with new-onset diabetes.

We have therefore evaluated the advantage of routine pancreatic scans for these cases. Our findings shed new light on the complex relationship between diabetes and PC.

**Patients and methods**

This prospective study was carried out on men and women patients aged over 50 seen in our department between 1992 and 2002. None had a history of diabetes and they were all hospitalized in emergency following the recent (fewer than 30 days) discovery of diabetes. The diabetes was so unstable that subcutaneous or intravenous insulin, delivered by an insulin pump, was required.

All clinical features were noted. The laboratory tests included measurements of erythrocyte sedimentation rate, and the activities of transaminase, alkaline phosphatase and gamma glutamyl transferase. All the patients also underwent a pancreas scan, which was by sonography, CT scan, or magnetic resonance imaging (MRI), depending on the equipment available. A CT scan or MRI was carried out in those cases for which echograph was unclear.

The main objective of this study was to evaluate the effectiveness of routine imaging in terms of the number of cases of pancreatic disorders, particularly PC, discovered. We have also looked for clinical and laboratory indications that might indicate pancreatic disease.

**Results**

The pancreatic imaging of our 115 patients revealed 14 cases (12.2%) suffering from severe abdominal disorders. These included 6 cases of adenocarcinoma (5.2% of patients) one patient with a benign pancreatic tumor, one duodenal cancer that had spread to the pancreas, a tumor of the neuroendocrine pancreas, one bile duct cancer, one non-Hodgkin’s lymphoma with pancreas involvement, plus 2 cases of ovarian cancer and one case of renal cancer.

There was no clinical feature that distinguished these patients from the other 101 whose pancreatic imaging was normal. The two groups were of the same age (66.5 ± 12 and 65.7 ± 10 years, NS), with no particular symptoms, except for a more severe loss of weight (6.9 ± 5.8 kg) in the tumor-bearers than in the others (3.8 ± 4.5 kg; p < 0.05). They also did not differ in their laboratory parameters-indicators of inflammation, cholestasis and cytolyis.

The cancers found in 5 cases were large and caudally located. Only one patient had a small tumor. The most common initial imaging method was sonography, with second images by CT scan or MRI in 65% of cases because the pancreas image was not clear enough.

**Discussion**

There are three aspects to the relationship between diabetes and PC.

**PC revealed by new-onset diabetes**

It is difficult to assess how frequently glucose metabolism is abnormal in cases of PC; it varies between 20 and 80% of cases [4]. This is because the various published studies have focused on both carbohydrate intolerance and diabetes, with no single set of diagnostic criteria. Both the occurrence of new-onset diabetes and the instability of an existing diabetes indicate a PC. This is not a new idea. Bright [2] reported in 1833 the case of a patient who presented with symptoms of diabetes mellitus who subsequently lost a great deal of weight and died of PC 6 months later. This relationship was subsequently confirmed with numerous reports of patients with unstable new-onset diabetes but no ketoacid imbalance who were found to have PC at the same time or soon afterwards [3]. Rosa [4] pointed this out in 1989 in his report of a man aged 51 who was found to have a PC just six months after the appearance of diabetes requiring insulin treatment. He thus predicted that a PC should be suspected in cases where there is massive anorexia once the diabetes has been stabilized or when there are GI symptoms such as abdominal pain or diarrhoea.

Our results clearly show that there is no practical clinical or laboratory criterion that can eliminate the possibility of a PC. Patients suffering from PC are, on average, more anorexic than those with no PC, but this is a poor criterion for use with individuals. The initial anorexia of some of our patients who were subsequently shown to have PC was no more severe than that of patients with no cancer. There are neither gastrointestinal nor laboratory indicators that point to a PC. Thus, cases of PC will not be discovered unless they are routinely scanned because nothing points to a suspected PC.
Cancer of the pancreas can lead to diabetes in two ways. It can cause a lack of insulin as a result of invasion by the tumor and its secretion of a factor causing resistance to insulin. As in autoimmune diabetes, the signs of insulin lack appear only when 90% of the islets have been destroyed, and this occurs only when the tumor is extensive. This clinical latency is mainly associated with large tumors in the caudal region as they are only discovered after the onset of diabetes. Nevertheless it is possible that upstream pancreatitis could also be a factor in this type of new-onset onset diabetes.

Insulin resistance seems to be a definitive factor that is more important that the site or size of the tumor in the onset of diabetes during pancreatic cancer. This is the only valid explanation when the tumor that is discovered is small. The insulin resistance is caused by a hormonal factor produced the beta cells of the islets of Langerhans. Islet amyloid peptide (IAAP), or amylin makes cells less sensitive to insulin in vivo and prevents glycogen synthesis in vitro. Its circulating concentration is elevated in cases of cancer with diabetes [5]. However, the plasmatic IAAP concentration is not elevated in cases of PC in which there is no diabetes or in other types of cancer [6]. Sensitivity to insulin and glucose tolerance can be improved by subtotal pancreatectomy to remove the tumor. A soluble factor produced by the cancer cells selectively stimulates the secretion of amylin by the islet cells, and this accounts for the elevated secretion of amylin in cases of PC. But an elevated plasma IAAP is not sufficiently specific for it to be used as an indication of PC.

Diabetes favors the development of a PC

The discovery of a small pancreatic tumor brings to light the complex relationship between PC and diabetes. It is difficult to rule out the prior existence of diabetes unless blood level glucose is measured. But is the PC itself responsible for the diabetes under these circumstances, or is the undetected diabetes a factor favoring the development of PC?

A multicenter study of 720 patients with PC and 720 controls by Gullo did not reveal any evidence that PC favoured the onset of diabetes [7]. Similarly, La Vecchia [8] found that the relative risk of PC diminished as the time the patient had suffered from diabetes increased.

However, several epidemiological studies have indicated that the risk of PC is greater in patients who are already diabetic. Cuzik and Babiker [9] reported that 13% of 216 patients presenting with PC were diabetic, as against 2% of the 279 controls. The risk of these patients who had been diabetic for at least one year developing a PC was 4.1 times greater than for the controls. A number of published studies indicate that PC is more common in diabetics, but it is often difficult to determine a direct causal link between the two because of the problem of determining the exact duration of diabetes in retrospective studies. Nevertheless, prospective studies have shown that there is enough elapsed time to show that the pancreatic tumor was the consequence of diabetes. Thus Hiatt [10] found that patients who had been diabetic for at least 5 years before the cancer was detected ran a 4.5-fold greater risk of developing a PC. In the same way, the epidemiological study of Ekoe [11] on 179 patients with PC showed that 16% of them were diabetic, while only 6% of the 239 controls were. Thus the risk was 2.2-fold greater. Most, 9 out of 10 cases were not insulin dependent; 89% had suffered from diabetes for at least 2 years and 50% had been diabetic for 10 years. Diabetes was the third most important risk factor in this study, after smoking and a high-fat diet. Balkau [12] analysed 312 diabetic subjects taken from a cohort of 6888 middle aged men who had been followed for 17 years. He found that the relative risk of dying from PC was 4.9 fold greater than for subjects with normal glycaemia. Once again, diabetes appeared to be a real risk factor for PC. Silvermann [13] also found that diabetics were at greater risk of developing PC, and the risk increased with the time they were diabetic. This risk was confirmed even after adjusting for the potentially confounding variables such as smoking and alcohol consumption, the BMI and food intake. The meta-analysis of 20 studies carried out by Everhart and Wright [14] indicated that the relative risk of patients who had been diabetic for at least 5 years developing PC was 2-fold greater than in controls.

The reasons why diabetes favours the development of PC are well known. Type 2 diabetes, whose onset is always difficult to determine because of its insidious nature, acts via hyperinsulinemia and the cross-activation of insulin-like growth factor I (IGF-1) receptors [15]. The anabolic signals of insulin or IGF-1 can favour tumor development by inhibiting apoptosis and stimulate cell proliferation. This system could thus increase the frequency of other types of cancer in diabetics. This is even more disturbing as 3 non-pancreatic cancers were found in our patients. It is now believed that certain cancers can be favoured in diabetics. These include cancers of the colon, breast, endometrium and liver. However, it seems that other predisposing factors like hepatitis B or C virus or alcohol-based cirrhosis, are also important in liver cancer.

In contrast, extra-pancreatic cancers may be involved in the development of new-onset diabetes. There are no published reports of this, but the secretion of cytokines by cancer cells could increase resistance to insulin or reduce insulin production.

Once we have examined the complex relationship, which is still not completely understood, between diabetes and PC, we must look at the indications of PC in diabetics and the methods used to detect it.

Detection of pancreatic cancer

Imaging should be able to provide both a positive diagnosis of a pancreatic tumor and show just how extensive it is, so as to differentiate between patients who might benefit from resection and those requiring palliative treatment. This re-
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It is extremely sensitive (better than 90%) for assessing the extent of metastases in the liver and suitable for assessing the extent of metastases in the liver and secondary bile ducts if the lesion is of the head of the pancreas, and atrophic pancreatic parenchyma upstream of the obstacle. Ultrasound is extremely sensitive for detecting the first two indications.

— Computerized densitometry (CT scan), particularly helical CT, is a powerful method of detecting tumors and clearly shows the extent of a tumor. Diagnosis of a PC by CT is based on detecting direct and indirect signs, as with ultrasound. The direct sign of an adenocarcinoma is a mass, generally hypodense, after injection of contrast agent [17]. The indirect signs, which are frequently the only ones present, are a deformed pancreas outline and loss of the normal lobulation, dilated bile ducts within and outside the liver and dilatation of the main pancreatic duct. Hypertrophy of the pancreatic parenchyma is cause by obstruction of the pancreatic duct and is generally found together with a dilated pancreatic duct. The detection of two signs, the classical two-duct dilatation, is a strong indication of a cancer, even if they occur alone. The combination of these direct and indirect signs ensures detection of over 90% of adenocarcinomas by helical CT [18].

— The main advantage of magnetic resonance imaging (MRI) is that it provides images of the pancreas parenchyma, specific images of the bile and pancreatic ducts and images of the vascular system using angiographic sequences. These images are almost as good as those obtained by conventional angiography [19]. MRI is more sensitive than CT for detecting direct signs of PC, particularly for small tumors that do not deform the outline of the pancreas, as these tumors are hypointense compared to the normal pancreas. But the use of MRI is limited, in practice, by the restricted availability of scanners, despite the fact that it is an excellent method for exploring the pancreas.

— Endoscopic ultrasound is a powerful tool for diagnosing PC [20], but is a second-string tool because it is an invasive method and requires a general anesthetic. It also is not suitable for assessing the extent of metastases in the liver and peritoneum. It is extremely sensitive (better than 90%) for diagnosing adenocarcinomas and is also good at detecting small tumors measuring less than 2 cm diameter. The main advantage of this method is that a needle biopsy can be taken of the mass visualized and subjected to cytological and histological examination. Histological confirmation of a cancer is indispensable for chemotherapy or radiotherapy.

**Conclusion: the indications for using pancreatic imaging in diabetics**

The increasing frequency of pancreatic cancer in type 2 diabetics, whose numbers are increasing strongly, promises to become a problem. But it is not possible to perform pancreatic imaging on all diabetics after they have been diabetic for some, as yet undetermined, period. Similarly routine testing for a non-pancreatic cancer that diabetes may encourage cannot be recommended. However, the clinician must be aware of the increased risk of cancer in these situations and must actively look for the slightest clinical or laboratory indication.

More particularly, there is now enough evidence that the development of new-onset diabetes in subjects over the age of 50 is a means of detecting pancreatic cancer. It is thus reasonable to routinely include a helical CT abdominal scan for these individuals, as this method is both available and reliable. We include this approach whatever the context, even with no associated risk factors or suspicious clinical or laboratory indications. This is the only method of detecting small cancers of the pancreas, which are more likely to be treatable. Unfortunately, a scan is often not be permitted until the tumor has grown too large. However, neither patients nor clinicians should be unaware, in this day and age, of such a powerful diagnostic tool.

However, in this work, no pancreatic cancer has been tracted sufficiently precocious manner to allow a curative surgical treatment. In the absence of others well-led prospective studies, this strategy cannot be formally recommended today.

**References**

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