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Pancreatic cancer and glucose metabolism

Pankreas kanseri ve glukoz metabolizması

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Background/aims: *The mechanism of impaired glucose metabolism that develops in most patients with pancreatic cancer is obscure. The association between pancreatic cancer and diabetes is controversial. Impaired glucose tolerance or diabetes mellitus may develop as a clinical manifestation of pancreatic cancer; however, diabetes may be a predisposing risk factor for pancreatic cancer. We aimed to investigate the relationship between diabetes and pancreatic cancer, and also the impact of tumor removal on glucose metabolism.* ***Methods:*** *Eighteen pancreatic cancer patients with resectable tumors and without previous diabetes history were enrolled. All patients underwent oral glucose tolerance test and measurement of insulin levels before and after Whipple procedure.* ***Results:*** *Eight of 18 (44.4%) patients were diabetic before surgery whereas 4 (22.2%) had impaired glucose tolerance. Only 6 (33.3%) patients had normal glucose metabolism at the first clinical admission. After pancreatectomy, only 4 (22.2%) patients were diabetic and 1 (5%) had impaired glucose tolerance. Thirteen patients (72%) had normal glucose metabolism after tumor removal. In 8 patients, impaired glucose metabolism improved after surgery. Only 1 patient out of 6 (16%) with normal glucose metabolism initially developed impaired glucose tolerance after surgery. All patients with diabetes and impaired glucose tolerance had hyperinsulinemia before and after surgery. Insulin levels were lower after surgery than before surgery, and glucose metabolism was improved postoperatively.* ***Conclusions:*** *Our results showed that tumor removal in pancreatic cancer patients improved glucose metabolism. This occurred despite a postoperative reduction in endocrine pancreas mass, which may suggest the presence of insulin resistance and diabetogenic effect of pancreatic cancer. The elucidation of the mechanism is of immense importance for providing an early tumor marker and preventative and therapeutic modalities.*

Key words: Pancreatic cancer, diabetes, glucose metabolism, islet cells

Amaç: *Pankreas kanserli bir çok hastada ortaya çıkan glukoz metabolizma bozukluğunun nedeni tam olarak açıklığa kavuşmamıştır. Pankreas kanseri ile diabet arasındaki ilişki karmaşıktır. Bozulmuş glukoz toleransı veya diabetus mellitus pankreas kanseri'nin klinik bir belirtisi olarak ortaya çıkabileceği gibi, diabette pankreas kanseri gelişimi için bir risk faktörü olarak kabul edilebilir. Bu çalışmada pankreas kanseri ile diabet arasındaki ilişki irdelenmiş, tümörün uzaklaştırılmasının glukoz metabolizması üzerine etkisinin değerlendirilmesi amaçlanmıştır.* ***Yöntem:*** *Onsekiz rezektabıl tümörlü ve daha önce diabet öyküsü bulunmayan pankreas kanseri hastası çalışmaya alındı. Whipple operasyonu öncesi ve sonrası, tüm hastalarda oral glukoz tolerans testi yapıldı ve serum insülin düzeyi belirlendi.* ***Bulgular:*** *Operasyon öncesi 8 hastada bulunan bozulmuş glukoz toleransı ameliyat sonrası düzeldi. Operasyon öncesi normal glukoz metabolizması bulunan altı hastadan sadece 1 hastada operasyon sonrası bozulmuş glukoz toleransı gelişti. Cerrahi öncesi onsekiz hastanın 8'i (%44.4) diabetik, 4'ü ise (%22.2) bozulmuş glukoz toleransı idi. İlk başvuruda sadece 6 (%33.3) hasta normal glukoz metabolizmasına sahipti. Pankreatektomi sonrası sadece 4 (%22.2) hasta diabetik ve 1 (%5) hastada ise bozulmuş glukoz toleransı olduğu bulundu. Onüç hasta (%72) tümörün çıkartılması sonrası normal glukoz metabolizmasına sahipti. Cerrahi öncesi veya sonrası diabet veya bozulmuş glukoz toleransı bulunan tüm hastalarda hiperinsülinemi saptandı. Cerrahi sonrası insülin seviyesi düşen hastalarda bile glukoz metabolizmasında düzelme izlendi.* ***Sonuç:*** *Çalışmanın sonuçları pankreas kanseri'de tümörün rezeksiyonunun glukoz metabolizmasında iyileşmeye neden olduğunu göstermektedir. Bu iyileşme, ameliyat sonrası azalmış endokrin pankreas kitlesine rağmen ortaya çıkmaktadır. Tümörün uzaklaştırılması, pankreas kanseri'nin insülin direnci yapıcı, diabtojenik etkilerinin de yok edilmesini sağlamaktadır. Bu mekanizmanın tam olarak aydınlatılması pankreas kanseri'de erken tümör markerlarının geliştirilmesi, koruyucu ve iyileştirici tedavilerin yaşama geçirilmesinde önemli ipuçları sağlayacaktır.*

Anahtar kelimeler: Pankreas kanseri, diabet, glukoz metabolizması, islet hücre

INTRODUCTION

Pancreatic cancer (PC) is still the fifth leading cause of cancer death in both men and women (1). In spite of significant diagnostic tools, there is no possibility for early detection, nor are there any ef-

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ficient therapeutic modalities. The only effective therapy, surgery, is still limited to about 25% of the patients and, even in these patients, cancer recurrence has remained unavoidable (2). These problems are based on our inability to understand the natural course and biology of the disease.

The mechanism of impaired glucose metabolism that develops in most patients with PC is obscure (3). The association between PC and diabetes is controversial. Some authors suggest that impaired glucose tolerance (IGT) or diabetes mellitus develops shortly before the clinical manifestation of PC, or it is diagnosed at the first clinical admission (3-6). There are, however, others who believe that diabetes is a predisposing risk factor for PC, especially in cases where the diabetes existed for more than five years before the cancer diagnosis (7, 8).

The early symptoms of PC, such as abdominal pain, weight loss, fatigue, jaundice, and nausea, are nonspecific and occur late in the course of the disease (6). If the association between PC and glucose metabolism is understood, then it may be easier to clarify the main cell producing cancer, the risk factors and natural course, and achieve an earlier diagnosis and more satisfactory therapies in this disease. Toward this aim, we investigated the relationship between diabetes and PC, and also the impact of tumor removal on glucose metabolism.

MATERIALS AND METHODS

Eighteen PC patients with resectable tumors and without previous diabetes history were enrolled. Inclusion criteria were resectable PC shown by imaging modalities such as computerized tomography, magnetic resonance or endosonography, which was proven by histopathology after surgery. Patients with previously known diabetes mellitus, nonresectable tumors, insulin resistance, metabolic syndrome, or coexistence of other malignancies were excluded. We also excluded the patients who did not survive at least two months after surgery.

Oral Glucose Tolerance Test: All patients including those with frank diabetes underwent oral glucose tolerance test and measurement of insulin levels before and six weeks after Whipple procedure. The patients were instructed not to restrict carbohydrate intake in the days or weeks before the test. The test was done during an illness other than PC, as results might not reflect the patient's glucose metabolism when healthy. A full adult dose should not be given to a person weighing less than 43 kg (94 lb), or exaggerated glucose may produce a false-positive result. No patient weighed less than 43 kg in our study group. The patients were fasted for the previous 8-14 hours.

Oral glucose tolerance test was scheduled to begin in the morning (0700-0800), as glucose tolerance exhibits a diurnal rhythm with a significant decrease in the afternoon. A zero time (baseline) blood sample was drawn. It was a fasting blood or fasting midstream.

The patients were then given a glucose solution to drink. The standard dose since the late 1970s has been 1.75 g of glucose per kilogram of body weight, to a maximum dose of 75 g. It was consumed within 5 minutes.

Blood was drawn at intervals for measurement of glucose, insulin and C-peptide levels. Blood samples were taken at 0 and 2 hours.

Interpretation of oral glucose tolerance test

Fasting plasma glucose should be below 110

Table 1. Preoperative and postoperative glucose metabolism in the patients with pancreatic cancer

	Preoperative		Postoperative	
	n	(%)	n	(%)
Patients with normal glucose metabolism	6	(33.3)	13	(72.2)
Patients with impaired glucose tolerance	4	(22.2)	1	(5.5)
Patients with diabetes mellitus	8	(44.4)	4	(22.2)

Table 2. Comparison of patients' preoperative and postoperative glucose metabolism status

		POSTOPERATIVE			
		Normal glucose metabolism	Impaired glucose metabolism	Diabetes mellitus	Total
PREOPERATIVE	**Normal glucose metabolism**	5	1	-	6
	Impaired glucose metabolism	4	-	-	4
	Diabetes mellitus	4	-	4	8
	Total	13	1	4	18

mg/dl. Fasting levels between 110 and 126 mg/dl are considered borderline ("impaired fasting glucose"), and fasting levels repeatedly at or above 126 mg/dl are diagnostic of diabetes.

The 2-hour glucose level should be below 140 mg/dl. Levels between this and 200 mg/dl indicate IGT. Glucose levels above 200 mg/dl at 2 hours confirm a diagnosis of diabetes (1999 World Health Organization [WHO] diabetes criteria).

Histology

Tumor tissues derived from surgical materials were embedded in paraffin and cut into 4 µm serial sections. Sections were stained with hematoxylin and eosin for the determination of morphological type, invasion and extent of necrosis. Two experienced pathologists blinded to the glucose metabolism of patients evaluated the samples.

Statistics

Data associated with glucose metabolism were compared in the same patients before and after surgery and the relation of these metabolic findings with histopathological features of the surgical specimens was investigated. The analyses were carried out using the Statistical Package for the Social Sciences® computer program with analysis of variance (ANOVA) with the Bonferroni post test for multiple comparisons. The data are presented as means ± SE. A p value of <0.05 was considered significant.

RESULTS

The average age in our study group was 68.3±9.7 years, and 10 of them were male. Eight of 18 (44.4%) patients were diabetic before surgery whereas 4 (22.2%) had IGT. Only 6 (33.3%) patients had normal glucose metabolism at the first clinical admission. Six weeks after pancreatectomy, only 4 (22.2%) patients were diabetic and 1 (5%) patient had IGT. Thirteen patients (72%) had normal glucose metabolism after tumor removal. In 8 patients, impaired glucose metabolism improved after surgery. Only 1 patient out of the 6 (16%) with normal glucose metabolism initially developed IGT after surgery. Table 1, Table 2, and Figure 1 show the numbers and percentages of the patients before and after surgery according to their glucose metabolism. All patients with diabetes and IGT had hyperinsulinemia and elevated C-peptide levels before and after surgery. Despite lower insulin levels after surgery, glucose metabolism was improved. The patients with improvement in glucose metabolism survived longer than those without improvement ($p<0.05$).

DISCUSSION

In our study, approximately 66% of PC patients without previous diabetes history had IGT or frank diabetes at the time of their PC diagnosis. Insulin and C-peptide levels were at high levels in the serum, indicating existence of the insulin resistance as a cause of impaired glucose metabolism in the patients with PC. After pancreatectomy, glucose metabolism improved in most of the patients. This occurred despite a postoperative reduction in insulin secretion and can be explained by the observed augmentation of whole-body insulin sensitivity after tumor removal.

It is presently unclear why most PC patients develop IGT or frank diabetes and the minority do not (4, 9-13). Although IGT improves after surgery in many patients (11,14,15), in some it either does not improve (12,14-16) or worsens (14). There are conflicting reports on the incidence of peripheral insulin resistance, IGT, and diabetes before and after surgery. According to previous studies, it can be assumed that 10-40% of PC patients either do not show any improvement of the abnormality after surgery or glucose metabolism worsens (3, 14). The percentage of worsening metabolism could be even higher if one considers that the postoperative improvement in IGT and diabetes could be due to the postoperative physical condition and dietary regimens of the patients rather than the consequence of the tumor removal.

Why is the association between PC and glucose metabolism so important? It has been proposed that amylin, a peptide with a molecular weight of 2030, or other yet unknown substances released from cancer cells are responsible for the development of impaired glucose metabolism (11, 12, 15, 17, 18). Nearly 30 years ago, one of the authors of

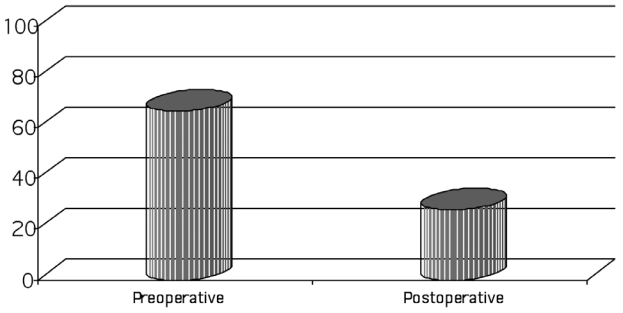

Figure 1. Percentage of the patients with impaired glucose metabolism before and after surgery.

this paper, Pour, conceived of and has continued to support the theory that the pancreatic ductal adenocancers arise from altered islet cells (3, 19-21). The production of these substances from cancer cells is self-explanatory. Cancer cells are known to inherit some of the biologic properties of the cells from which they are derived. Several studies have shown the expression of neuroendocrine markers in PC cells (22-24). From the pathophysiological point of view, the production of diabetogenic material from islet cells appears more plausible, as it is well known that islet cells have the potential to produce many different pancreatic and extra-pancreatic peptides simultaneously (3).

Although there could be many reasons explaining the lack of postoperative improvement in glucose metabolism in a subset of patients, it is highly possible that either the altered islet cells producing the diabetogenic substance exist in the tele-tumoral area not removed by surgery or some hidden (metastatic) tumors are left behind (3,25). In a follow-up study, the glucose homeostasis increasingly worsened in patients who did not have curative surgery (14). Our results revealed that the patients with improvement in glucose metabolism after surgery survived longer than those without improvement.

In conclusion, our results showed that tumor removal in PC patients improved glucose metabolism. This occurred despite a postoperative reduction in endocrine pancreas reserve, which may suggest the presence of insulin resistance and diabetogenic effect of PC. The elucidation of the mechanism is of immense importance for providing an early tumor and prognostic marker and preventative and therapeutic modalities.

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