New-onset type 2 diabetes mellitus – a high-risk group suitable for the screening of pancreatic cancer?

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Background: Type 2 diabetes mellitus is widely considered to be associated with pancreatic cancer.

Objective: To determine the incidence of pancreatic cancer in new-onset type 2 diabetic patients by measuring the serum level of CA 19-9 and performing abdominal ultrasonography (US).

Patients and Methods: Consecutive type 2 diabetic patients in whom diabetes was diagnosed within 36 months were included in this prospective study. Serum CA 19-9 measurement and US were performed in all patients. If any of two was positive, abdominal computer tomography (CT) was carried out. Endoscopic ultrasound-guided fine needle aspiration or direct surgical referral was performed on patients with CT-identified lesions.

Results: A total of 115 patients were enrolled. CA 19-9 was elevated in 10 patients but pancreatic cancer diagnosed in neither of them. Pancreatic cancer was revealed by morphological means in three patients without elevated CA 19-9 level. The sensitivity, specificity, positive-, negative predictive values and validity were 0%, 90.4%, 0%, 97.9% and 87.9% for CA 19-9, 66.7%, 100%, 100%, 99% and 99% for US, respectively. The value of the Standardized Incidence Ratio for pancreatic cancer in new-onset type-2 diabetic patients was 198.6 (95% CI=6.25-46.9).

Conclusions: The prevalence of pancreatic cancer in patients with new-onset type-2 diabetes is significantly higher than that in the general population and screening is beneficial for detecting PaC in this patient population. CA 19-9 and US is not reliable screening modality for pancreatic cancer screening in this population.

Study Highlights: diabetes mellitus; pancreatic cancer; screening; Ca 19-9; abdominal ultrasonography; Standardized Incidence Ratio

INTRODUCTION

The reported annual incidence of pancreatic cancer (PaC) lies in the range 1-10 cases/100.000 persons worldwide (1), and is 5.4 cases/100.000 persons in Hungary (2). Although the disease accounts for only 3% of all cancer cases (3), it has a very high mortality rate: it is the fourth and the fifth leading cause of cancer-related death in the USA (4) and in Europe (5), respectively. Surgery is the only possibility as curative treatment, but unfortunately only 15% of the patients are eligible for curative resection at the time of the diagnosis because of the presence of metastases and locoregional infiltration (6). An efficient screening programme for the early diagnosis of PaC in the asymptomatic stage is needed to improve the prognosis. Population-wide screening is not feasible and not cost-effective, because the lifetime prevalence of PaC is only 1.39% (7). It is recommended that subjects at high risk of PaC should be screened.

The prevalence of type 2 diabetes mellitus (T2DM) in PaC patients has been reported to be 40%, and 50% of T2DM patients with PaC have T2DM with a duration of 2 years or less (8). Patients with short-term T2DM (< 4 years) have more than 1.5-fold risk of displaying PaC as compared with patients who have DM with a duration of ≥5 years (9). Pannala et al. reported that patients diagnosed with T2DM have an 8-fold higher risk of PaC developing within 2-3 years after the diagnosis of T2DM relative to the general population (10). The fasting blood glucose level is known to be elevated in 85% of PaC cases (11), which suggests that new-onset T2DM is a paraneoplastic sign of PaC, caused by the malignancy itself. Individuals with new-onset T2DM might serve as an appropriate group to be screened for PaC.

Attention has turned to tumourmarkers as possible screening modalities, because they are cheap, easy to perform and widely available. The carbohydrate antigen 19-9 (CA 19-9) is the most reliable tumourmarker for PaC. CA 19-9 is a tumour-associated, but not tumour-specific epitope of sialyated Lewis A blood group antigen (12), which occurs in the epithelium of the salivary glands and in the ductal cells of the biliary tracts and is secreted by the exocrine pancreas too (13). The sensitivity of this marker for PaC is 70-90%, the specificity is 90%, the positive predictive value is 69% and the negative predictive value is 90% (14-19). However, even a test with a sensitivity and a specificity of 95% would yield numerous false-positive findings besides each true-positive result and it is therefore recommended to combine CA 19-9 measurement with an imaging tool for more efficient screening (20).

Imaging modalities are the gold standard for the diagnosis of PaC. A weekness of these examinations is that they are not able to detect PaC measuring < 1cm, when the tumour is frequently resectable. The most effective imaging techniques for the detection of PaC are multidetector computer tomography (CT) and endoscopic ultrasonography (EUS) (21). The sensitivity of transabdominal ultrasonography (US) in the diagnosis of PaC is only 50-70% (22). However, US is easy to use, widely available, non-invasive and relatively inexpensive, making it an ideal screening modality.

We set out to determine the incidence of PaC prospectively in new-onset T2DM patients by measuring the serum level of CA 19-9 and performing US.

PATIENTS AND METHODS

Patients

Between March 2012 and October 2014, 115 consecutive patients with new-onset T2DM were enrolled by diabetologists of our clinic into this prospective study. The diagnosis of T2DM was made in accordance with the criteria of the American Diabetes Association (ADA) (23). New-onset DM is defined as DM diagnosed first within the last 36 months before the time of enrolment (11). Cases with T1DM and any kind of symptoms indicative of pancreatic disease were excluded. The duration of follow-up was 36 months from the first visit. All patients provided their written informed consent to participation. The study protocol was in full accordance with the most recent revisions of the Helsinki Declaration and was approved by the ethics committee at the University of Szeged (approval No. 97/2012).

Methods

The serum CA 19-9 level was measured and transabdominal US was performed at the first visit. In accordance with local laboratory standards, the cut-off serum CA 19-9 level was 27 U/mL. If the transabdominal US indicated any abnormality (with either a normal or an elevated CA 19-9 level), abdominal CT was performed. EUS, EUS-guided fine-needle aspiration (EUS-FNA) and surgical referral were carried out if the CT revealed a pancreatic lesion.

In the event of an elevated serum CA 19-9 level without any US abnormality, abdominal CT was performed. When the CT did not show any lesion the serum CA 19-9 level was repeated

in 3 months' time. When the CA 19-9 level was normal and the US was negative, the CA 19-9 level was measured 6-monthly and US was performed yearly (Figure 1).

Potential risk factors for PaC, i.e. an age > 65 years) (24), hereditary syndromes predisposing to PaC and any first-degree relatives with PaC besides DM, were documented at the first visit and were each scored with one point. The body mass index (BMI; abnormally high if ≥ 25 kg/m^2) (25) and the smoking status were also registered.

Person-time incidence rate has been calculated, because we compared two populations where exposures are changing within subjects over time (26).

To assess the eligibility of the patients with new-onset T2DM as a risk group for PaC, the standardized incidence ratio (SIR) was calculated with the person time incidence based on our study and the age-adjusted incidence of PaC in Hungary (9.3 cases/100.000 persons) (1). The SIR is used to determine whether the occurrence of cancer in a comparatively small, specific group is higher or lower than that in the normal population (27). A SIR of 1 indicates that the number of cancer cases observed in the population evaluated is equal to the number of cancer cases expected in the general population. An SIR> 1 indicates that more cancer cases occurred than expected. (28)

To examine the efficacy of CA 19-9 and US as potential diagnostic tools for PaC, the sensitivity, specificity and positive and negative predictive values were calculated.

RESULTS

A total of 115 patients with new-onset T2DM were enrolled into the study (49 male, 66 female, mean age: 58±11 y, range: 32 - 85 y). 7 patients were subsequently excluded for various reasons: 1 man had T1DM, 1 woman had polycystic ovarium syndrome and 5 patients later declined to participate. The average time between the diagnosis of T2DM and inclusion in the study was 3.5±4.4 months (range 0-20 months).

Three patients (2.78%) each had one first-degree relative with PaC. Of them, one patient had PaC. Sixty-nine (64%) of the participants scored 1 point, 38 (35%) scored 2 points and 1 patient (1%) scored 3 points on our risk-estimating system (Table 1). Patients had no specific symptoms suspicious for PaC.

The serum CA 19-9 level was elevated in 10 patients (9%) (52.613±23.13 U/mL), but none of them exhibited morphological abnormalities on either US or CT.

The imaging examinations revealed a mass in the pancreas in 3 patients (2.78%) without an elevated serum CA 19-9 level. The mean age of the patients with PaC was 70±7 years and their average BMI was 30.1±5.1 kg/m^2 vs. 58±11 years and 30.5±4.6 kg/m^2, respectively in the patients with T2DM only. The time between CA 19-9 test/US examination and CT examinations was 1±1.7 months. These 3 cases are discussed below.

Case 1

A 67-year-old non-smoking woman was diagnosed with T2DM 8 months before the first study visit. She had a positive history for various tumours (kidney, parotid and thyroid gland) and had a first-degree relative with PaC. Her BMI was 25.4 kg/m^2. She scored 3 points (new-onset DM, age, positive familiy history for PaC) on our risk-estimating system. The CA 19-9 level was normal. US demonstrated a 30 mm hypoechogenic solid lesion, which was confirmed by CT. EUS-FNA revealed pancreatic ductal adenocarcinoma. The patient was inoperable due to the presence of multiple metastases in the right lung. Chemotherapy induced regression and the patient was still alive at the writing of the manuscript (Figure 2).

Case 2

A 65-year-old man was diagnosed with T2DM 3 months before inclusion. His BMI was 29.4 kg/m^2. He has not smoked for 7 years. The patient scored 2 points (new-onset DM, age) on our risk-estimating system.

The CA 19-9 level was initially 24.55 U/mL. The US findings were incomplete because the body and tail of the pancreas were not visible. 3 months after the US CT examination revealed an inhomogeneous hypodense mass with calcification in the tail, about 80 mm in size, and the peripancreatic area was moderately infiltrated. Laparotomy was performed, but the tumour was inoperable because of advanced local invasion. The histological examination indicated ductal adenocarcinoma. At the 6-month control, CA 19-9 level was 25.90 U/mL. Chemotherapy was started and the patient was still alive at the time of the manuscript (Figure 3).

Case 3

A 78-year-old non-smoking woman was diagnosed with T2DM within 1 month before her enrolment. Her BMI was 35.5 kg/m^2. She scored 2 points (new-onset DM, age) on our risk-estimating system. Her aspecific symptoms, such as weakness and weight loss was tought to be the consequences of diabetes. Two weeks after the diagnosis of T2DM and her joining the

study US identified a 45x29x26 mm hypoechoic lesion in the tail. CT examination revealed a diffuse enlargement of the tail, with a 56x31x43 mm hypodensity in it. The liver was inhomogeneous, with multiple metastases 8-25 mm in size. Histological examination of the US-guided biopsy proved ductal adenocarcinoma. Chemotherapy was started, but unfortunately the patient died only a few weeks after the diagnosis of PaC (Figure 4).

The general incidence of PaC in our study was 2.78% (3/108) and the person-time incidence was 2%. The value of SIR was 198.6 (95% CI=6.25-46.9).

The efficacy of the diagnostic modalities used in this study for the screening of PaC is presented in Table 2. The serum CA 19-9 level was elevated in 10 patients, but none of them had PaC. Two patients with PaC had a normal serum marker level.

The US examination clearly revealed the pancreatic mass in 2 out of the 3 patients. In the remaining 105 negative cases, the possibility of false-negative findings was excluded as a result of the follow-up.

CT was performed in 18 of the 108 patients (i.e. 1 patient with a positive US finding, 10 with an elevated CA 19-9 level, 4 with incomplete US examinations and 3 with symptoms not suggestive of pancreatic diseases). CT revealed a pancreatic mass in all 3 PaC cases.

DISCUSSION

The early detection of PaC in an operable stage, requires the screening of asymptomatic subjects for the disease. Since the incidence of PaC is low, screening should be restricted to subjects at high risk of PaC (5). A recent meta-analysis demonstrated that individuals with new-onset (< 4 years) DM had a 50% greater risk of PaC as compared with individuals who had had DM for > 5 years (OR 2.1 vs. 1.5, P=0.005) (9). Several studies have noted that DM is prevalent even in early-stage PaC (8, 10). Our prospective study has demonstrated that the incidence of PaC among newly diagnosed T2DM patients is 198.6-fold higher than in the normal population. New-onset T2DM can therefore be classified as a high-risk group for PaC. Damiano et al. (29) reported a similar incidence (5.2%) of PaC in patients hospitalized for new-onset DM (shorter than 30 days) because the instability of the DM necessitated insulin treatment.

Our study has provided evidence that screening is beneficial for the detection of PaC in asymptomatic new-onset T2DM. However, our results were also discouraging, since all 3 PaC

cases diagnosed in our screening programme were in an advanced inoperable stage. An earlier retrospective study demonstrated that the mean interval between the onset of DM and the diagnosis of PaC was 10 months (range 5-29 months) (30). The average time between the diagnosis of T2DM and the enrolment of the patients in our study was 3.5±4.4 months in the screened population and 3.7±4 months in the patients finally diagnosed with PaC. The fact that advanced cases were diagnosed in our study can not therefore be explained by a prolonged interval between the onset of DM and inclusion in the study.

The prospective screening of PaC by endoscopic retrograde pancreatography in new-onset DM patients revealed a very high incidence (13.9%) of PaC. However, most of the diagnosed PaC cases were unresectable, similarly as in our study (31). The duration from the onset of DM in that investigation was longer (9.2 months). A decrease of the time of diagnosis of PaC after the diagnosis of DM or a more aggressive diagnostic approach may be of benefit.

Unfortunately, it seems that our protocol is not yet able to diagnose PaC in an early, still resectable stage, despite the results based on extremely high SIR values indicating that the patients with new-onset DM are an appropriate risk group for the screening of PaC. Thus, to identify a higher proportion of cases with resectable PaC, the risk group of newly diagnosed DM patients should be, i.e. signs present in the asymptomatic stage should be sought for a more certain distinction of DM with PaC from T2DM. Mizuno et al. found that a loss in weight and exacerbation of the DM could be seen in DM patients, 12 months prior to the diagnosis of PaC. The time of the weight loss distinguishes two groups: patients with DM caused by PaC have already lost weight at the time of the diagnosis of the DM and they continue to lose weight until the diagnosis of the cancer, while T2DM patients have already gained weight at the diagnosis of DM, after which the weight stagnates or increases further (32). Moreover, DM diagnosed in individuals aged (> 55 years) tends to be the DM caused by PaC, whereas diagnosis at a younger age is indicative of T2DM (32,33), as in our study Gupta et al. came to the opposite conclusion: younger age is a risk factor for PaCDM (34).

At least one additional PaC risk factor, such as age, the family history and obesity, was present in our patients with diagnosed PaC. A recent study demonstrated that obesity and T2DM are independent risk factors for PaC (35). Our results suggest that consideration of the above factors may increase the yield of a screening programme for PaC.

The combination of serum CA 19-9 measurement and the use of transabdominal US as a screening tool in PaC was studied retrospectively earlier, and the possibility of determinating neoplastic lesions in patients already diagnosed with PaC was investigated. That study

revealed that these tools together identify ductal adenocarcinoma of the pancreas with 85.4% sensitivity, which means that this combination is suitable for the non-invasive screening of PaC (36).

CA 19-9 would be an ideal method for screening: it is easy to carry out, widely available, repeatable, reliable, verified and cost-effective. However, we have revealed that CA 19-9 determination is not of value in screening for PaC in new-onset DM. Both the sensitivity and the positive predictive value of CA 19-9 were zero and the false positive rate was 9% in our study. The average of elevated CA 19-9 levels was only 52.613±23.13 U/mL in our study.

However, the optimal cut-off value of CA 19-9 to differentiate between benign and malignant pancreatobiliary diseases was demonstrated to be 70.5 U/mL (82.1% sensitivity, 85.9% specificity, 81.3% positive predictive value and 86.5% negative predictive value) (37). Furthermore, CA 19-9 in diabetics may be considered as the indication of exocrine pancreatic dysfunction and a higher cut-off value of CA 19-9 was proposed to differentiate benign and malignant pancreatic disease (38).

The serum level of CA 19-9 can be elevated not only in PaC, but also in biliary, hepatocellular, gastric, colon and non-gastrointestinal tumours and in liver diseases and jaundice, leading to false-positive results (39). However, such diseases were not detected in any of our patients who gave false-positive CA 19-9 results. Our findings are inconsistent with those of Kim et al. (40), who reported that CA 19-9 is appropriate alone for the identification of PaC among patients with new-onset DM. Our results are rather in line with those of Zubarik et al. (41), who demonstrated that the positive predictive value of Ca 19-9 in patients with a positive family history of PaC was only 3.7%.

Abdominal US would likewise be an ideal method for screening: it is easy to carry out, widely available and cost-effective (42). The low sensitivity of US in our study, however suggests that it is not effective for screening. Furthermore, in view of a possible need for a prolonged screening programme, a CT scan is not recommended because of the risk associated with radiation exposure.

If it is accepted that DM in PaC is a paraneoplastic sign caused by the tumour itself, a search for diabetogenic factors (43) produced by the tumour and their utilization as screening tools is needed. This may improve the success of our strategy to use new-onset DM as a screening tool for the identification of subjects with asymptomatic PaC.

One limitation of our study is the small number of cases, and we therefore plan to continue with this study.

In conclusion, the prevalence of PaC is significantly higher in patients with new-onset T2DM than in the general population and screening is beneficial for the detection of PaC in this patient population. CA 19-9 and US are not effective, whereas CT is a reliable screening modality for PaC screening in this population.

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