FDG PET: Elevated Plasma Glucose Reduces Both Uptake and Detection Rate of Pancreatic Malignancies

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The aim of the study was to evaluate the effects of elevated plasma glucose levels on tumor detection. **Methods:** One-hundred and seventy-one fasted patients (100 malignant pancreatic tumors, 46 chronic pancreatitis and 25 patients with other benign pancreatic lesions) were studied with ^{18}F-fluorodeoxyglucose (FDG) PET before planned resective pancreatic surgery. Nineteen of 171 patients had elevated plasma glucose levels above 130 mg/dl, and 24 of 171 had diabetes mellitus. Standard uptake values (SUVs) with and without glucose correction, tumor-to-muscle ratios and tumor-to-liver ratios were measured of the pancreatic lesion respective of the area with the highest uptake within the pancreas. The original qualitative PET reports concerning the dignity of the pancreatic lesion were translated into a five-point malignancy scale. Tumor detection rates and SUVs were compared according to plasma glucose levels above and below 130 mg/dl, the presence of diabetes and by using receiver operating characteristic (ROC) analysis. **Results:** The detection rates (and mean SUVs) for pancreatic malignancies were 86% and 42% (4.2 and 2.3) if fasted plasma glucose levels were below and above 130 mg/dl, respectively. The sensitivities (and mean SUVs of malignant tumors) were 83% and 69% (3.3 and 2.5) for patients without and with known diabetes. Areas under ROC curves were nearly equal for glucose corrected SUV and visual qualitative results (0.86 and 0.85), followed by uncorrected SUV (0.83), tumor-to-liver ratios (0.80) and tumor-to-muscle ratios (0.79). SUVs for chronic pancreatitis, muscle and liver had a tendency to increase with elevated plasma glucose levels. **Conclusion:** Negative PET results of patients with elevated plasma glucose should be interpreted with caution.

Key Words: fluorine-18-fluorodeoxyglucose; plasma glucose; pancreatic tumors

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The fact that a large variety of malignant tumors have increased glucose metabolism and the relatively straightforward production of the glucose analog ^{18}F-fluorodeoxyglucose (FDG) for PET imaging are reasons why FDG is becoming the mainstay tracer of oncologic PET. However, some tumor entities have diminished FDG uptake with elevated levels of plasma glucose (1–3). In a study on bronchial carcinoma by Langen et al. (1), tumoral FDG uptakes were almost halved with doubled plasma glucose levels. A similar phenomenon was observed by Lindholm et al. (2) on head and neck tumors. The feasibility of FDG PET to differentiate benign from malignant pancreatic masses has been demonstrated by our group and others (4–9). Even though a possible dependency of FDG uptake on glucose and/or the presence of diabetes mellitus has been presumed by previous authors, a dependency of tumoral FDG uptake and detection rate of pancreatic carcinoma from plasma glucose levels has not yet been assessed. We, therefore,

reanalyzed PET data of 171 patients that were examined to differentiate benign from malignant pancreatic masses. We compared the detection rate of malignancy as well as tumor and nontumor uptakes for patients with and without elevated fasted plasma glucose levels and with and without history of diabetes mellitus.

MATERIALS AND METHODS

Patients

Between April 1992 and August 1995, 334 patients attended the department of surgery for first-time resective surgery of the pancreas. Of these, 189 received FDG PET after written consent. The remaining 145 patients were not examined due to limited availability of PET or because the initial work-up (clinical exam, transabdominal sonography) resulted in a clear diagnosis of advanced disease alleviating surgery. Of the 189 patients receiving PET, 18 patients either had no histological proof of their diagnosis or were either lost in the follow-up period (e.g., 11 patients moved to unknown address), had misplaced plasma glucose measurement results (4 patients) or had damaged transmission or emission files hindering quantitative evaluation (3 patients). With the remaining 171 patients, 128 patients had histological or cytological verification of disease. Forty-seven patients had ductal pancreatic carcinoma, stages according to Unione Internationale contre le Cancer (UICC) (UICC I–IV: 17%, 11%, 53%, 19%, respectively), 11 patients had papillary carcinoma (UICC I–IV: 27%, 27%, 36%, 9%, respectively), 6 had carcinoma of the common bile duct, 5 had other rare tumors of the pancreas or the adjacent tissues and 1 had metastases from the kidney. Fifty-eight proven benign pancreatic conditions comprised 46 with chronic pancreatitis, 6 with various kinds of adenoma and 6 with other benign lesions. With the remaining 43 patients, the extent of the lesions and associated diseases were prejudicial against surgical exploration. Family physicians of all patients were telephoned between 14 mo and 54 mo after the PET exams. Patients who at that time did not have histologic verification of disease were considered to have benign disease if no sign or symptoms of malignant pancreatic disease were reported by the family physician for at least 18 mo (13 patients). Patients were classified to have malignant pancreatic disease when the family physician reported a rising tumor marker CA 19–9 associated with clinically malignant disease and death of the patient or a progressive pancreatic mass combined with clinical signs of malignant disease follow by the death of the patient (30 patients).

PET Imaging

All PET imaging was performed with a commercially available scanner (CTI ECAT 931–08-12, Siemens, Knoxville, TN) that allows simultaneous acquisition of 15 contiguous slice in one bed position. Patients fasted for at least 12 hr before the study. Diabetic patients did not recieve oral antidiabetic or insulin therapy on the day of the exam because they were fasting. Transmission imaging for attenuation correction was performed before FDG administra-

TABLE 1
Detection Rates Depending on Plasma Glucose and History of Diabetes Mellitus*

	Plasma glucose < 130 mg/dl	Plasma glucose ≥ 130 mg/dl	No history of diabetes	History of diabetes	History of diabetes and plasma glucose < 130 mg/dl
Sensitivity (%)	86	42	83	69	88
Specificity (%)	78	86	77	91	86
Plasma glucose (mg/dl)	88 ± 16	186 ± 59	92 ± 28	137 ± 69	95 ± 16
History of diabetes (%)	10	47	0	100	100
Number of patients	152	19	147	24	15

*Tumor stages did not vary significantly for those patients with tumors and plasma glucose levels < or > 130 mg/dl. The relative distribution (%) for UICC Stages I to IV was 12, 14, 43 and 31 for 78 patients with known stage and glucose levels < 130 mg/dl and 18, 0, 36 and 45 for 11 patients with glucose ≥ 130 mg/dl. The prevalence of malignant tumors in these gorups was 58% and 63%, respectively.

tion with a ^{68}Ge/^{68}Ga ring-source in at least three bed positions starting at the liver dome. Acquisition time was 10 min per bed position for both the transmission and the emission scan. FDG was synthesized according to standard procedures (10). Before FDG administration, 20 mg of furosemide was injected intravenously to reduce artifacts due to high radioactivity in the renal collecting system, the history of diabetes mellitus was taken and plasma glucose level was measured using venous blood and electronic measuring (Accutrend alpha; Boehringer Mannheim, Mannheim, Germany). Beginning about 1 hr after intravenous injection of 85–448 MBq FDG (median 266 MBq) emission scans were recorded. Image reconstruction was performed with an iterative reconstruction algorithm (11).

Patient Evaluation

For comparison of results, patients were divided into six groups: those who stated to have diabetes, those who denied diabetes, those with plasma glucose levels above or equal and below 130 mg/dl and those patients with diabetes and high/low glucose levels. While the normal range for plasma glucose is considered 60–120 mg/dl in our laboratory, a cutoff of 130 mg/dl was chosen for the following reason: the patients with high plasma glucose levels had mean glucose levels two times those levels of the remaining patients (Table 1). At qualitative visual analysis, any intense focal increased FDG uptake in the pancreatic region was considered malignant. For quantitative interpretation a region of interest (ROI) analysis using mean values was performed of the most intense focal uptake found within the pancreas. Circular ROIs had a 2 cm diameter. The ROI data were used to calculate standard uptake values (SUVs) (SUV = activity concentration divided by injected dose/body weight). These values were not corrected for partial volume effect. Additional SUVs were measured of the erector spinae muscles bilateraly using two circular ROIs of 2 cm diameter and of a nondiseased segment of the liver with a ROI of 4 cm in diameter. The original preoperative PET reports were scored from 1–5 as follows: 1 = no sign of malignant pancreatic disease; 2 = probably without malignant pancreatic disease; 3 = indecisive concerning malignant pancreatic disease; 4 = probable malignant disease of the pancreas; and 5 = definite malignant pancreatic disease. All reports were scored by two readers. In cases of discrepant scoring (9 patients) a consensus was reached after discussion. Receiver operating characteristics (ROC) analysis was performed using the CORROC2 program (University of Chicago Medical Center, Chicago, IL) (12). This program is applicable to correlated inherently categorical rating scale data and calculates the area under the ROC curve and gives the statistical significance of the difference between the two estimated ROC curves using an univariate z-score test of the difference between the areas under the two ROC curves. Significancy was assumed if the probability (p) was < 0.05.

RESULTS

Patients with an average plasma glucose level of 186 mg/dl (Table 1) had SUVs for malignant pancreatic lesions of 2.3 ± 0.7 compared to 4.2 ± 1.7 of patients with average glucose levels of 88 mg/dl (Fig. 1). On the contrary, SUVs of liver, muscle and benign tumors were slightly higher with elevated glucose (not significant). The detection rate of pancreatic malignancies (sensitivity) was also lower with elevated plasma glucose levels (Table 1). The difference was not as evident with history of diabetes versus no history of diabetes. Also, the detection rate of malignancies was not reduced with those 15 patients who had diabetes and a plasma glucose level < 130 mg/dl. There were only 9 diabetic patients with plasma glucose levels ≥ 130 mg/dl (average 207 ± 65 mg/dl). Five of these 9 patients turned out to have malignant pancreatic tumors. Only 2 of those were detected with PET. Interestingly, specificity of the test was not significantly affected by plasma glucose levels or the presence of diabetes. The distribution of SUVs of malignant tumors graphed according to plasma glucose levels is illustrated in Figure 2. It shows that while with low plasma glucose levels (e.g., <130 mg/dl) FDG affinity of tumors might be either high or low, FDG uptake was never high with marked elevated glucose levels. Figure 3 shows ROC curves of visual and quantitative results. Visual reading ranked highest, but it was not significantly superior to SUV. If the SUV was multiplied by plasma glucose (SUV × glucose), the area under the curve was slightly higher (not significant). Tumor-to-liver (T/L) and tumor-to-background (T/B) ratios had significantly smaller values compared to visual analysis.
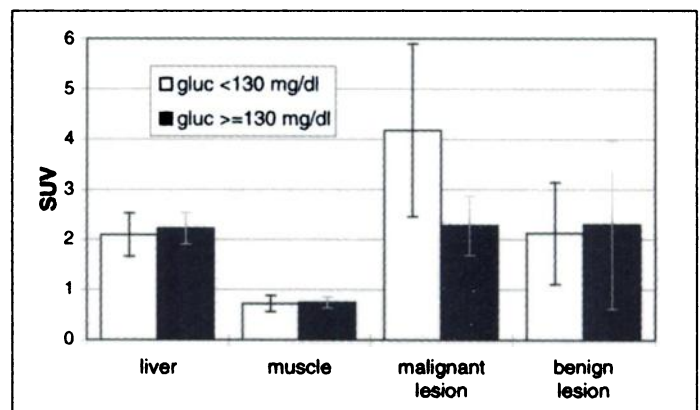
FIGURE 1. Mean standard uptake values (SUVs) with s.d. for liver, muscle, malignant pancreatic lesions (n = 100) and benign pancreatic lesions (n = 71) graphed according to nearly normal (n = 152) and marked elevations of plasma glucose (n = 19).
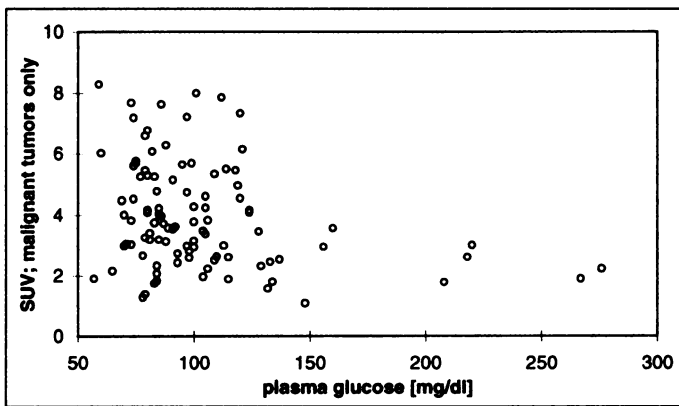
FIGURE 2. Distribution of standard uptake values (SUVs) of malignant tumors graphed according to plasma glucose levels.

DISCUSSION

FDG uptake in malignant pancreatic tumors was greatly reduced when elevated plasma glucose levels and/or diabetes mellitus were present. However, FDG PET sensitivity was not reduced in our study with 15 known diabetics that had low fasted glucose levels (Table 1). Possibly, the history of diabetes is an imprecise parameter. Patients might not have been fully informed about their possible diabetes, and a new onset diabetes might not have been fully worked up at the time of the PET exam. Patients who had plasma glucose levels two times above normal presented with tumor SUVs, which were roughly half (Table 1, Fig. 1). This is well in concordance with the studies by Langen et al. (1) and Lindholm et al. (2), who have observed a similar finding with FDG uptake in bronchial and head and neck carcinoma. However, the patients of these studies were loaded with intravenous glucose while our patients presented with high glucose levels while fasted. A glucose-dependent FDG uptake in an animal study with mammarian carcinoma had been observed earlier (3). These findings as well as our findings support the hypothesis that this phenomenon is due to competitive FDG displacement and should be seen with a larger variety of tumors with a high glucose avidity. On the contrary, with elevated plasma glucose liver tissue, muscle and chronic pan-

creatitis return a higher FDG uptake. The difference is marginal and not statistically significant.

Both chronic pancreatitis and pancreatic carcinoma often present with a mild or severe endocrine pancreatic insufficiency. This explains the relatively high prevalence of elevated plasma glucose in our study (Table 1). This obviously imposes a diagnostic problem for FDG PET mirrored by low detection rates for tumor and low tumor SUVs. Low tumoral FDG uptake of patients with markedly elevated plasma glucose levels should therefore be interpreted with care, if not disregarded. Glucose plasma levels should also be considered with follow-up studies or studies performed for therapy monitoring, since varying SUVs caused by varying glucose could result in over- or underestimations of therapy response.

The SUV and SUV correction for glucose (SUV × glucose) did not significantly improve overall accuracy as shown in Figure 3. SUV results may have been more favorable if values had been corrected for partial volume. However, most pancreatic malignancies are relatively large and present with a T2 or T3 stage (93% of tumors in our patient selection). In all 3 of 6 T1/T in-situ lesions that were missed by PET, no focal uptake can be seen in retrospect. Therefore, in this patient selection, partial volume corrected SUVs would unlikely have resulted in a considerable improvement of overall results. Alternatively, kinetic evaluation may provide parameters less sensitive to changes of plasma glucose levels. However, kinetic studies currently are both labor intensive and time consuming. Insulin infusions with diabetic rats before FDG application did increase FDG uptake in tumors, supporting the hypothesis of competitive FDG displacement (13). However, FDG uptake was found decreased in experimental mammary tumors under conditions of hyperinsulinism combined with hypoglycemia (14). These mechanisms need to be evaluated further. In particular, the influence of insulin on FDG uptake not only in tumors of diabetic patients should be assessed, but also in tissues possibly responsible for false-positive findings, i.e., reparative changes or inflammatory infiltrates.

CONCLUSION

The determination of plasma glucose levels appears more important than the history of diabetes. Markedly elevated plasma glucose levels greatly impair the detection of pancreatic malignancies. Twice-normal plasma glucose levels lead to tumoral FDG uptakes that are roughly halved.
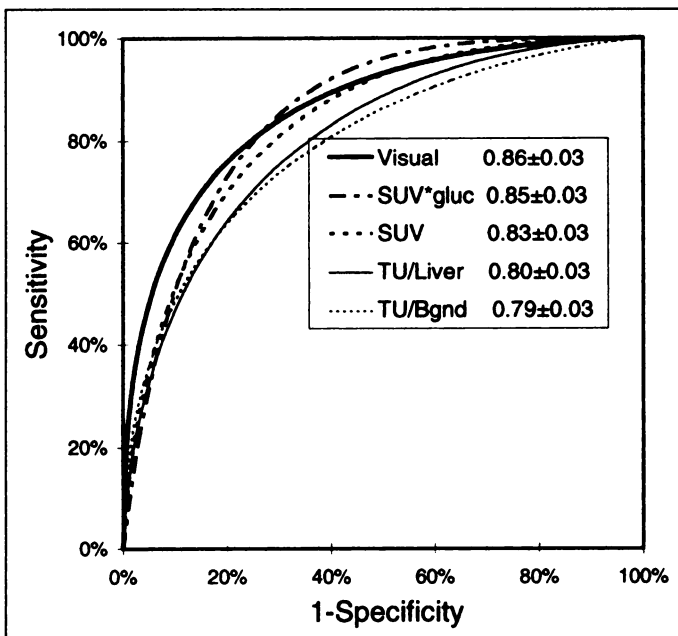
FIGURE 3. Interpolated receiver operating characteristics curves for all 171 patients. SUV = standard uptake value; gluc = glucose; TU = tumor; Bgnd = background.

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Bone Marrow Scintigraphy with Technetium-99m Anti-NCA-95 to Monitor Therapy in Malignant Osteopetrosis

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We report a case of a 2-mo-old girl with malignant osteopetrosis. Conventional radiological investigations of the skull and left hand showed the characteristic pattern of generalized sclerosis. Bone marrow immunoscintigraphy with ^{99m}Tc-labeled antibodies against nonspecific cross-reactive antigen (NCA) 95 was performed before and after bone marrow transplantation. Before transplantation, whole-body images showed bone marrow stores exclusively in the base of the skull. The rest of the skeleton did not reveal any hematopoietic activity. The liver and spleen showed increased antibody uptake as expected in extramedullary hematopoiesis. Repeat scintigraphy after bone marrow transplantation from her haploidentical father demonstrated an almost completely normalized tracer distribution corresponding to her clinical and hematological improvement. Bone marrow immunoscintigraphy appears to be an ideal complement to radiograph diagnostics in malignant osteopetrosis. In primary diagnosis, scintigraphy demonstrates the quantitative extent of bone marrow displacement. It also proves an ideal tool in monitoring the effectiveness of therapy after bone marrow transplantation.

Key Words: osteopetrosis; bone marrow immunoscintigraphy; anti-NCA-95 antibody; bone marrow transplantation

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O steopetrosis is a hereditary disorder of the skeleton, which is also known as Albers-Schönberg disease, osteosclerosis, osteopetrosis generalisata or marble bone disease. A relatively benign form transmitted autosomal dominantly can be distinguished from the autosomal recessive form also called malignant or infantile osteopetrosis (*1*). The disease is thought to result from a deficiency of osteoclasts, causing abnormally increased bone density as well as impaired bone remodeling and reabsorption of the calcified substantia spongiosa (*2,3*). During the course of the disease, the marrow spaces become obliterated leading to pancytopenia, which is complicated by infections, bleeding or death in severe cases. The adult form is characterized by less severe clinical presentations. Patients are often asymptomatic until osteosclerosis is discovered on radiographs obtained for pathologic fractures or cranial nerve palsy (*1*). Characteristic findings of conventional radiographs comprise increased bone density and poorly remodeled bones (*4*).

Bone scintigraphy in osteopetrosis demonstrates a diffuse increase in tracer uptake often combined with focal accumulation in fracture sites or areas of osteomyelitis.

For patient management, the grade of bone marrow displacement and the resulting hematopoietic dysfunction need to be known. Established methods for visualization of bone marrow alterations are MRI and bone marrow scintigraphy. We report on the value of bone marrow immunoscintigraphy with ^{99m}Tc-labeled monoclonal anti-NCA-95 antibodies (MAbs) in a case of malignant osteopetrosis before and after bone marrow transplantation (BMT).

CASE REPORT

A 2-mo-old girl was referred to the department of pediatrics in our hospital due to a discrete macrocephaly. She was the first child of related parents from Turkey. The pregnancy was normal, but birth was accomplished by cesarean section. The postpartum clinical course was complicated by findings of a tense fontanel, big skull and protrusion of the forehead. At the time of the third health care examination, the size of skull was above the 97th percentile. Except for an increased lactate dehydrogenase (LDH), all blood values and investigations were normal. A few weeks later, a rotavirus gastroenteritis occurred. At that time, hemoglobin and thrombocytes were decreased, which was considered to be a postinfectious alteration. At the age of 8 wk, the family pediatrician found a decreased blood count, a clear hepatosplenomegaly and increased size of the skull. During a second stay in hospital, physical examination revealed good general condition, but poor nutrition, a macrocephalus and a massive hepatosplenomegaly. Laboratory findings demonstrated a hemoglobin of 7.7 g/dl. White blood cell count was 21,740/ml (normal range 3000–15,000/ml) and thrombocytes 93,000/ml (100,000–400,000/ml). LDH was elevated to 2000 U/l (160–520 U/l) and triglycerides to 465 mg/dl (10–130 mg/dl). Repeated bone marrow aspiration was very difficult and demonstrated 26% atypical cells but no blasts.

Radiographic examinations of the skull and left hand showed a generalized sclerosis, which led to the diagnosis of osteopetrosis (Fig. 1).

The patient was referred to the department of nuclear medicine for bone marrow scintigraphy. We intravenously injected 15 µg anti-NCA-95 antibodies (MAb BW 250/183, Behring Marburg, recently distributed by CIS International, Dreirich, Germany) labeled with 30 MBq (0.8 mCi) ^{99m}Tc. Whole-body scans were obtained 4 hr after injection using a double-head gamma camera system equipped with low-energy, high-resolution collimators