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Research Article

Deep Cancers in Uncontrolled Diabetes and Weight Loss

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Abstract

An unexpected weight loss can be the first manifestation of deep cancers, more frequent in diabetes. How many are detected by a Thoraco-Abdominal-Pelvic Scanner (TAP)? From the register of TAP-scanners performed in our diabetology department from 2010 to 2019, we selected those indicated for unexplained weight loss. Binary logistic regression analysis was performed to identify clinical and biological characteristics related to cancer.

The 359 patients were mainly men (61%), 58±12 years old, BMI: 26.6±6.0 kg/m^2, with 8±11 years duration of diabetes, poorly controlled (HbA1c: 10.6±2.8%), with frequent vascular complications (62.2%). The scanner led to 22 (6.1%) diagnosis of cancers: 8 pancreatic, 7 pulmonary, 3 hepatic and 4 renal. As compared to cancer-free, these patients had greater weight loss: -21±12 kg vs. -15±11, p=0.02. They did not differ for other clinical and biological characteristics, except lower HbA1c and higher liver enzymes. Adjusted for age and gender, maximal weight losses more than -13 kg (HR: 3.28, 95%CI: 1.18-9.10) and abnormal Gamma-Glutaryl-Transferases (HR: 5.84, 95%CI: 1.64-20.81) were related to the detection of a cancer. No cancer was detected among the 63 patients with weight losses lower than 13 kg and normal GGTs. Among 359 patients admitted for uncontrolled diabetes and weight loss, the CT-scan detected 22 deep cancers (6.1%), especially in patients with important weight loss and abnormal GGTs.

Highlights

- Weight loss and deep cancers are more frequent in subjects with diabetes.
- In 359 subjects admitted for uncontrolled diabetes and weight loss, we performed a CT-scanner and found 22 deep cancers (6.2%): pancreas, lungs, liver and kidneys.
- The cancers were more frequent for important weight loss when Gamma-Glutaryl-Transferases were increased.

Keywords: Diabetes; Cancer; Weight loss; CT-scanner

Introduction

Cancer is the leading contributor to diabetes-related death [1]. Many cancers are more frequent among subjects with diabetes, especially deep cancers such as pancreatic and hepatocellular, with X2.5 relative risks [2]. Insulin resistance and hyperinsulinism may play an important role [3], however the risk is also increased in type 1 diabetes [4]. Despite these information's, the rates of cancer screening are lower among subjects with diabetes [5].

Deep cancers often develop without early clinical symptoms, and they are not easily detected by clinical examination, especially in obese subjects. They also challenge usual imaging techniques as ultrasounds. There may be a place for CT-scan imaging [6], interesting in cases of non-specific symptoms as unexplained weight loss [7]. Some abnormal blood tests can help to select weight losing subjects for CT-scan imaging [8].

However, in the general population, only 1.4% cancers are diagnosed during the 6 months after weight loss [9] that may be due to many other diseases than cancer, including diabetes itself [10]. Decreasing BMI trajectories are possible among subject with diabetes, they relate to a higher mortality after the age of 50 [11]. The intentionality of weight loss is surely critical: voluntary weight loss, relates to improved glycemic and blood pressure control [12], and to a better life expectancy [13]. The SOS study has shown that the incidence of cancers was reduced after participants with diabetes lost weight due to a bariatric surgery [14]. In case of unexpected weight loss, it is hard to distinguish metabolic alterations due to cancer vs diabetes [15].

We hypothesized that a CT-scanner may help to detect a deep cancer in such patients. From 2010 to 2019, we performed a CT-scanner in 359 subjects with diabetes, indicated for an unexpected weight-loss. How many cancers did we find? Did subjects with cancer exhibit characteristics that may reinforce our indication for the CT-Scanner?

Research Design and Methods

Subjects

We identified from our hospital registry all patients admitted in our diabetologic unit from 2010 to 2019, who had a CT-Scanner during their hospitalization. From these 461 subjects, we excluded 102 cases with specific indications for the Scanner: signs or symptoms outside weight loss and follow-up of already known tumors. Three hundred and fifty-nine patients were included. All were interviewed, had a clinical exam, blood and urinary samples. All subjects gave their informed consent to participate in the study, which was approved by the local ethic committee.

The following data were collected: age, gender, type (1, 2 or 3 in case of pancreatic diabetes) and duration of diabetes, past history of cancer, body weight (at inclusion, 3 months before, and maximum weight reached during their lifetime), height, tobacco and alcohol consumption and diabetes complications: retinopathy, neuropathy, history of foot ulcers, and macroangiopathy (myocardial infarction, stroke, and peripheral revascularization). The blood and urinary analysis included HbA1c, Albumin Excretion Rates (AER), and serum creatinine to estimate the Glomerular Filtration Rates (eGFR) calculated with the CKD-EPI formula, liver enzymes, serum albumin, calcium, C reactive protein, and blood count (total white cells, platelets, hemoglobin).

Outcomes

All the subjects had a contrast-injected CT-scanner with 64- or 128- multidetector row CT of the chest, abdomen and pelvis. Routine dataset reconstructions at 2.0 mm section thickness were performed in axial planes. CT scans were classified as positive if they led to the diagnosis of cancer after complementary explorations.

Statistical analysis

The results of the continuous variables were expressed as mean±SD or median (IQR). The categorical variables were presented as numbers (percentages). The subjects with cancer diagnostic were compared to the others by ANOVA or non-parametric tests for continuous variables, and by Chi-2 for categorical variables. A multivariable backwards stepwise logistic regression analysis was performed to analyze the clinical and/or biological parameters related to the diagnosis of cancer, adjusted for age and gender. A value of $p<0.05$ was considered as significant.

Results

Characteristics of the population (N=359)

The characteristics of the 359 patients are depicted in the table 1 (A Clinical and diabetes characteristics and B Biological parameters). They were mainly men, 58.8±12.6 years old, with 8.5±11.0 years duration of diabetes, poorly controlled: mean HbA1c at 10.6±2.8% (92±7 mmol/mol). Most of them (62.2%) had chronic diabetic complications: 38.1% had a neuropathy, 32.1% had a diabetic kidney disease, 16.0% had a diabetic retinopathy and 20.1% had a macroangiopathy. Their BMI was 26.0±6.0kg/m^2 at the inclusion and the maximal BMI during their life had been 32.5±7.3kg/m^2.

	Total	Cancer	No cancer	p
N	**359**	**22**	**337**	
Age (years)	58.8±12.6	63.8±10.4	58.5±12.6	0.054
Women, n (%)	140 (39.0)	8 (36.4)	132 (39.2)	0.794
History of previous cancer, n (%)	27 (7.5%)	4 (18.2%)	23 (6.8%)	0.072
Duration of diabetes (years)	8.5±11.0	8.6±8.2	8.5±11.2	0.972
Type of diabetes n (%)				0.269
Type 1	54 (15)	1 (4.5)	53 (15.7)	
Type 2	285 (79.4.0)	21(95.5)	264 (78.3)	
Type 3	20 (5.9)	0	20 (5.6)	
HbA1c at inclusion (%) mmol/mol	10.6±2.8 92±7	9.6±1.9 81±6	10.6±2.9 93±7	0.036
BMI at inclusion,(kg/m²)	26.6±6.0	27.1±5.0	26.6±6.0	0.651
Maximal BMI during life (kg/m²)	32.5±7.3	34.1±6.4	32.4±7.4	0.261
Weight loss during the previous 3 months,(kg)	-4.1±4.5	-3.7±3.2	-5.1±4.6	0.618
Weight loss from maximal weight, kg	-15.6 ±11.4	-21.7 ±12.4	-15.1±11.2	0.02
Diabetic retinopathy, n (%)	61 (17)	1 (4.5)	60 (17.8)	0.109
Diabetic Kidney Disease, n (%)	104 (32.4)	7 (38.9)	97 (32)	0.545
Macroangiopathy, n (%)	76 (21.2)	4 (19)	72 (21.4)	0.801
Neuropathy, n (%)	143 (40.1)	9 (42.9)	134 (39.9)	0.787
History of foot ulcer, (%)	18 (5)	1 (4.5)	17 (5)	0.917
Alcohol consumption, n (%)	147 (54.4)	11 (61.1)	136 (54)	0.557
Tobacco smoking, n (%)	205 (66.8)	15 (75)	190 (66.2)	0.418

Table 1A: Clinical characteristics of subjects with versus without Cancer.

	Total	Cancer	No cancer	p
N	**359**	**22**	**337**	
C-Reactive Protein (mg/dL)	9.68±26.1	9.60±12.3	9.68±26.7	0.988
Hemoglobin (g/dL)	13.6±1.6	13.3±1.4	13.6±1.6	0.373
White blood cells (G/L)	7.3±2.5	7.4±2.7	7.2±2.4	0.756
Platelets (G/L)	225±82	215±115	225±80	0.589
Calcemia (mmol/l)	2.34±0.14	2.33±0.12	2.34±0.14	0.973
Albumin (g/L)	37.6±5.1	37.8±4.7	37.6±5.2	0.850
ASAT (U/L)	36±35	40±29	36±36	0.587
ALAT (U/L)	38±34	54±50	37±32	0.016

PAL (U/L)	86±38	103±53	86±37	0.047
GGT (U/L)	83±140	204±378	73±103	<0.005
Elevated Gamma-GTs, n (%)	179 (52.6)	18 (81.8)	151 (50.6)	0.005

Table 1B: Comparison of biological parameters of subjects with versus without Cancers.

Cancer cases (N=22)

The CT-scanner led to the diagnosis of cancer in 22 patients (6.1%): 8 pancreas, 7 lung, 3 liver and 4 kidney. Four of them had a previous history of another cancer (18.2% vs 6.8% for others, p=0.072 by Fisher's exact test). The patients who had a new diagnosis of cancer mainly had type 2 diabetes: only one cancer among 54 type 1, and none among 20 pancreatic diabetes. They were older, their HbA1c were lower, negatively related to the recent weight loss (B = -0.305, p<0.001), and not to the long-term weight loss. They did not differ from others for the magnitude of recent weight loss, however they had lost more from their maximal weight: -21.7kg±12.4 vs -15.1kg±11.2 (p=0.02). Most of them had lost more than -13kg, the median for loss from maximal weight during their life in our population (p=0.043 by Chi-2). The rates of vascular complications of diabetes did not differ between cancer cases and others.

Serum albumin, calcium, C reactive protein, and blood count (total white cells, platelets, hemoglobin) did not differ between cancer cases and others, whereas liver enzymes (GGT, ALAT and Alkaline phosphatases) were higher among cancer cases: 81.2% of the patients with the diagnosis of cancer had gamma-GT upper than normal vs 50.6% in the others (p = 0.005).

Logistic regression analysis of variables related with the detection of cancer

In the multivariable logistic regression analysis including all the variables related to the diagnosis of cancer by univariate analysis (age, history of previous cancer, weight loss from maximal, HbA1c, and liver enzymes) two variables were significantly related to cancer: weight loss from maximal (HR: 1.05, 95%CI: 1.01-1.09) and GammaGTs (HR: 1.16, 95%CI: 1.01-1.34). Adjusted for age and gender, weight loss more than its median of -13kg (HR: 3.28, 95%CI: 1.18-9.10) and abnormal GGTs (HR: 5.84, 95%CI: 1.64-20.81) were related to the detection of a cancer. No cancer was found in the 63 subjects who lost less than 13 kilograms (median), and whose Gamma-GTs were normal, whereas 11/70 subjects (15.7%) who presented these two characteristics had a diagnosis of cancer.

Discussion

Among 359 patients admitted for uncontrolled diabetes and weight loss, the CT-scanner of the chest, abdomen and pelvis allowed the diagnosis of 22 cancers, an incidence of 6.1%. The patients with cancer had a similar magnitude of recent weight loss, but greater long-term weight loss and increased Gamma-GTs. No case of cancer was detected among the 63 subjects who had lost less than 13 kg and had normal GGTs.

The 6.1% rate of CT-Scanner-detected cancers is higher than the 1.4-2.4% rates of cancer explaining weight loss in the general population (8,16), and higher than a threshold of 3%, optimal positive predictive value recommended by National Institute for Health and Care Excellence [17]. It is lower than the 9.5% from the report of Damiano, et al who performed abdominal scanners to detect pancreatic cancers in 115 patients over 50 years with recently diagnosed diabetes requiring insulin [18]. Although weight loss was not the primary reason to perform a scanner in Damiano's study, it was the only significant difference between the tumor-bearers (-6.9±5.8 kg) and the others (-3.8±4.5 kg). Higher rates of cancers (28% to 36%) were reported in radiologic series using a CT-scanner in patients with unexplained weight loss, not selected for uncontrolled diabetes [9,19], probably due to additional localizing symptoms, anemia and elevated tumor markers in these series. The detection of a deep cancer on 6.1% of CT-Scanners shows that this exam should be considered in subjects with uncontrolled diabetes and an unexpected weight loss.

The most frequent localization of cancer in our patients was pancreas (8/22), the haunting of diabetology. Weight-loss has been related to 6-fold increased risk of pancreatic cancer in subjects with recent diabetes, but the risk is still 3-fold higher in longer standing diabetes [20]. As we recruited subjects hospitalized for uncontrolled, long-duration diabetes, our study cannot inform whether subjects with new-onset diabetes or impaired fasting glucose may have benefit from a CT-scanner to detect a pancreatic cancer, which is another important question. In subjects with known diabetes, most of pancreatic cancers occur more than 4 years after diabetes onset, and they are related to weight loss [21]. The second localization was lung, with 7 cases. Lung cancer is more frequent among subjects with diabetes, especially women [22], and our findings show that the CT-scanner must not only check the abdominal area for pancreas, liver and kidneys, but also the chest.

Weight loss was the primary reason to perform a CT-scanner in our patients, and loss from maximal weight were more pronounced among subjects with cancer. Recent weight loss did

not differ, and they were related to the HbA1c, which suggests that uncontrolled diabetes, rather than cancer, contributed to these recent weight loss. Weight loss is common among subjects with diabetes: in the NHANES cohort, the first disease associated with weight loss was diabetes (38%), before cancer, liver and cardiovascular diseases [10]. However, many weight losses among subjects with diabetes were intentional, due to favorable changes of diet and physical activity. Trying to lose weight has been related to a better life expectancy in type 2 diabetes [13], whose weight control improves the HbA1c trajectories [23]. We performed CT-scanners in subjects with unexpected, involuntary weight loss, which did not result in well-controlled diabetes.

Liver enzymes predict cancer in the general population [24], and this includes other localizations than liver cancer for GGTs, also related to pancreas and lung cancers [25]. High GGTs have been related to a higher cancer-related mortality in subjects with type 2 diabetes [26]. The relation between GGTs and some later cancers is stronger in subjects with hyperglycaemia [27]. The mechanisms underlying the association between GGTs and cancer are uncertain [28]. Due to Non Alcoholic Fatty Liver Diseases, abnormal GGTs are common among subjects with type 2 diabetes. The absence of CT-scanner detected cancer among our patients with moderate weight loss and normal GGTs seems an interesting information for practice, which will have to be confirmed.

Our study has some limitations. All the subjects had a CT-scanner, without a control group. In patients with idiopathic venous thromboembolism, Carrier et al. found 3.9% new cancers during a one-year follow-up [29]. They tested an extensive screening including a scanner of the abdomen and pelvis, to detect occult cancers, and they did not demonstrate a benefit compared to participants with a limited evaluation without a scanner. We do not state that the diagnosis of cancer from the CT-scanner modified the life expectancy for our 22 patients; however a later diagnosis based on specific symptoms would have led to regrets as they had been hospitalized for uncontrolled diabetes and weight loss. Chronic pancreatitis favors pancreatic cancer, however we did not detect any cancer in our 20 patients with pancreatogenic diabetes, a limited effective. A high BMI has been related to later mortality from cancer in type 2 diabetes [30], well-accorded with the higher maximal BMI during lifetime for our patients with cancer, however the +1.7 BMI difference did not reach significance for our limited effective.

Conclusion

Cancer was fortunately not the most frequent cause of weight loss in our patients: it is a sign of many other organic and psychiatric diseases, including diabetes itself due to insulin deficiency, high glycosuria, and some antidiabetic treatments. Clinical judgement is therefore crucial before prescribing a CT-Scanner to a weight-loosing subject with poorly controlled diabetes. Hyperthyroidism and monoclonal Gammopathy must be excluded, renal function must be checked, and glucose levels must be controlled, without Metformin, before the contrast injection.

The 6.1% rate of cancers as we detected suggests that the exam should be considered in patients with uncontrolled diabetes, unexpected weight loss and increased Gamma-GTs.

Disclosure

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Data are available from the authors, on reasonable request.

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