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Original Article

Abnormal glucose metabolism in patients with malignant tumors

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Abstract: Our trial aimed to investigate the prevalence and characteristics of abnormal glucose metabolism in patients with malignant tumors to provide a basis for further intervention. A total of 1045 patients who had been diagnosed with malignant tumors and hospitalized were surveyed. The total prevalence of diabetes mellitus (DM) and impaired fasting glucose (IFG) was 39.1% (409/1045); that is, 16.4% (171/1045) for DM and 22.8% (238/1045) for IFG. The difference in the prevalence of abnormal glucose metabolism in different groups (i.e., age, sex, tumor type, chemotherapy cycle, and chemotherapy regimen) was statistical significance ($P<0.05$), especially that in the different chemotherapy cycle and regimen groups. The BMI, triglycerides, and total cholesterol in the DM and impaired glucose regulation groups were slightly higher than those in the normal glucose tolerance group; blood insulin was slightly lower. However, these differences were not statistically different ($P>0.05$). Age (B=1.52), chemotherapy (B=0.85), and tumor type (B=0.64) were incorporated into the equation for logistic multivariate analysis ($P<0.05$). High prevalence of abnormal glucose metabolism was observed in patients with malignant tumors, especially after multi-cycle, platinum-containing, or taxane-containing chemotherapy. Early intervention of abnormal glucose metabolism is important in treating malignant tumors. Age, chemotherapy regimen, and tumor type may be independent factors for abnormal glucose metabolism in malignant tumors.

Keywords: Malignant tumor, abnormal glucose metabolism

Introduction

Cancer is a high-wasting disease. Cancer patients suffer from lack of digestion and glucose absorption and from a glucose metabolism disorder, which is not conducive to nutritional support and rehabilitation. This glucose metabolism disorder is caused by a lack of insulin, leading to sugar, protein, and fat metabolism imbalance, causing many other complications, and severely impairing the patients' quality of life. The coexistence and interaction of malignant tumors and diabetes worsen prognosis and have thus drawn considerable attention [1, 2].

Glucose metabolism disorder (GMD) or abnormal glucose metabolism includes diabetes mellitus (DM) and impaired glucose regulation (IGR). IGR includes impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), both of which can predict the risk of type 2 diabetes. Patients with both IGT and IFG have the highest risk of type 2 diabetes. Diabetes increases the incidence of common human malignancies, such as colorectal [3-5], liver [6], pancreatic [7], breast [8], and endometrial cancer [9]. Saydah et al. [10] found that diabetes, especially in patients with IGT, increases the mortality rate of cancer, especially of colorectal and pancreatic cancer.

However, previous studies have the following limitations: First, these studies ignored the continuity of abnormal glucose metabolism, that is, the fact that pre-diabetes ultimately turns into diabetes and that the former is easy to prevent. Second, these studies have not confirmed whether cancer patients have a risk of abnormal glucose metabolism. Third, these studies focused on the relationship between a certain cancer and diabetes or on diabetes increasing the risk of a certain cancer but ignored the overall GMD trend in patients with malignant tumors. These studies were also mostly retrospective analyses with small sample sizes.

Table 1. Level of blood glucose, blood lipid and blood insulin in cancer patients ($\bar{x}$±s)

Item	$\bar{x}$±s
Age	56.3±15.9
BMI (kg/m^2)	22.4±3.9
Fasting blood glucose (mmol/L)	6.0 (4.8~9.6)
OGTT (2 h PG)	7.7 (6.3~12.6)
Triglyceride (mmol/L)	0.8±0.2
Total cholesterol (mmol/L)	4.1±0.4
High-density lipoprotein (mmol/L)	1.0±0.3
Low-density lipoprotein (mmol/L)	2.9±0.7
Fasting serum insulin (mU/l)	4.4±1.1

Note: The fasting plasma glucose, OGTT (2 h PG) with the median quartile, the restwith the $\bar{x}$±s. Body mass index: BMI; Oral glucose tolerance test: OGTT.

Consequently, the results of these studies are inconclusive. Therefore, we investigated the status and characteristics of abnormal glucose metabolism in 1045 cases of malignant solid tumors and compared the different effects of age, sex, tumor type, and treatment pattern on abnormal glucose metabolism.

Methods

Patients

A total of 1045 patients with a pathologically confirmed malignant tumor were selected from the First Affiliated Hospital of Xinxiang Medical College from June 2004 to April 2008. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of First Affiliated Hospital of Xinxiang Medical College. Written informed consent was obtained from all participants.

Data collection

Patient data were collected through a uniform questionnaire (i.e., common reporting format) created by systematically trained residents and graduate students and inspected by two supervisors (a postgraduate instructor of oncology and the deputy director of a hospital). The following data were collated and analyzed: 1) general data: age, sex, personal and family history of diabetes, pathology and clinical diagnosis, tumor stage, and treatment programs; 2) anthropometric data: height, weight, and body mass index (BMI, weight (kg)/height (m)^2); 3) oral glucose tolerance test (OGTT) results of non-diabetic patients with non-fasting blood glucose <7 mmol/L and patients who had undergone two, four, or six cycles of chemotherapy; and 4) other clinical laboratory test indicators: fasting blood glucose, blood lipids, and blood insulin.

Diagnostic criteria

1) Obese or overweight: Patients with BMI ≥25 kg/m^2 were considered overweight or obese. 2) Abnormal glucose metabolism: The history of diabetes of all patients was surveyed; the fasting blood glucose of the non-diabetic patients was checked the next day. Patients were diagnosed with diabetes if their fasting blood glucose was ≥7.0 mmol/L in two consecutive tests or their random blood glucose was ≥11.1 mmol/L. Otherwise, OGTT was performed. If the 2 h plasma glucose (PG) was ≥11.1 mmol/L, the diagnosis was diabetes; if the fasting plasma glucose (FPG) was <7.0 mmol/L and 2 h PG was ≥7.8 but <11.1 mmol/L, the diagnosis was IGT. If the fasting blood glucose was 6.1 mmol/L to 7.0 mmol/L and 2 h PG was <7.8 mmol/L, the diagnosis was IFG. 3) Age group classification: As indicated by World Health Organization standards, individuals aged ≥65 were considered elderly.

Chemotherapy proposals

Small-cell lung cancer: etoposide + carboplatin or cisplatin; non-small-cell lung cancer: cisplatin or carboplatin plus third-generation chemotherapy drugs, such as paclitaxel, gemcitabine, and docetaxel; breast cancer: anthracycline ± taxane, taxane ± gemcitabine, or Navelbine (in patients resistant to anthracycline); gastric cancer: fluorouracil + oxaliplatin or epirubicin regimens; colorectal cancer: FOLFOX (leucovorin + fluorouracil pyrimidine + oxaliplatin); ovarian and endometrial cancer: cyclophosphamide + cisplatin or Taxotere + cisplatin; malignant lymphoma: CHOP (cyclophosphamide + doxorubicin + vincristine + Strongpine); Liver cancer: mainly transcatheter arterial chemoembolization with doxorubicin, fluorouracil, and cisplatin. Dosage was determined according to National Comprehensive Cancer Network guidelines.

Lipids and blood insulin levels

Blood glucose, blood lipids, and blood insulin were detected through standard methods in

Table 2. Distribution of patients according to diabetes status (n/%)

Item	Number	n (%)			
		DM	IGR	DM+IGR	NGT
Age					
≥65 years	567	123 (21.7)**	178 (31.3)**	301 (53.1)**	266 (46.9)**
<65 years	478	48 (10.0)	60 (12.6)	108 (22.6)	370 (77.4)
Gender					
Male	599	106 (16.0)	140 (25.0)	246 (41.2)	353 (58.9)
Female	446	65 (14.6)	98 (22.0)	163 (36.5)	283 (63.5)
BMI					
Overweight	298	51 (17.1)	72 (24.2)	123 (41.2)	175 (58.7)
Obese normal	747	120 (16.1)	166 (22.2)	286 (38.3)	461 (61.7)

Note: **P<0.001. Body mass index: BMI.

Table 3. Distribution of DM+IGR according to type of the tumor (n/%)

Item	DM+IGR	
	Number	n (%)
Pancreatic cancer	15	8 (53.3)
Liver cancer	50	22 (44.0)
Colorectal cancer	104	44 (42.3)
Lymphoma	49	20 (40.8)
Lung cancer	206	84 (40.8)
Endometrial cancer	18	7 (38.9)
Intracranial tumor	24	7 (29.1)
Breast cancer	112	32 (28.6)
Esophageal cancer	186	50 (26.9)
Gastric cancer	110	29 (26.4)
Ovarian cancer	48	12 (25.0)
Nasopharyngeal cancer	42	10 (23.8)
Cervical cancer	23	5 (21.7)
Soft tissue sarcoma	52	10 (19.2)
Prostate Cancer	6	1 (16.7)

Diabetes mellitus: DM; Impaired fasting glucose: IFG.

the hospital central laboratory to ensure unified quality control.

Statistical analysis

SPSS 17.0 was used to process the data. The distribution characteristics of the continuous variables were described with $\bar{x}\pm s$. Any two groups were compared using t-test; single-factor ANOVA was used to make multiple comparisons. Variables with non-normal distribution were analyzed using the median (quartile range). The significance of discrete variable was determined by χ^2 tests.

Results

Basic information

A total of 1045 eligible cases of malignant tumor were included in the analysis; 599 of the patients were male, and 446 were female. The ratio of males to females was 1.3:1.0, and the average age was 56.3± 15.9 years (range: 27-83 years). The blood glucose, blood lipids, serum insulin, average BMI, and Carve-digit of the patients are shown in **Table 1**.

Illness characteristics

The prevalence of diabetes in the entire sample was 16.4% (171/1045); 58 of these cases were previously diagnosed, and 113 were newly diagnosed (66.1%). The IGR prevalence rate was 22.8% (238/1045), the overall prevalence rate of abnormal glucose metabolism was 39.1% (409/1045), and normal blood glucose tolerance (NGT) was 60.9% (636/1045). The prevalence rate of DM+IGR in the >65 age group (i.e., old-age cancer patients) was 53.1% (301/567); 21.7% (123/567) had DM, and 31.3% (178/567) had IGR. The incidence rate of DM+IGR in the <65 age group was 22.6% (108/478); 10.0% (48/478) of these patients had DM, and 12.6% (60/478) had IGR. The difference between both groups was statistically significant (χ^2=57.792, P<0.001). The differences in abnormal glucose metabolism between different sexes and between different BMIs were not statistically significant (P>0.05) (**Table 2**). Abnormal glucose metabolism varied with tumor type: pancreatic, liver, and colorectal cancer had high incidence, and soft tissue sarcoma and prostate cancer had low incidence (**Table 3**).

Chemotherapy

Of the 845 patients undergoing chemotherapy, only 835 were included in the analysis. Ten patients were excluded because they refused to undergo OGTT before chemotherapy. Eleven

Table 4. Influence of chemotherapy on abnormal glucose metabolism (n/%)

Item	Number	DM n (%)	IGR n (%)	DM+IGR n (%)
Chemotherapy				
Before	835	137 (16.4)	188 (22.5)	325 (38.9)*
After	835	198 (3.7)	231 (27.7)	429 (51.4)
Chemotherapy regimens				
Taxane-containing or platinum-containing	556	202 (36.3)	229 (41.2)	431 (77.5)**
Taxane-containing only	218	86 (39.4)	98 (45.0)	184 (84.4)
Platinum-containing only	242	75 (31.0)	87 (36.0)	162 (67.0)
Taxane-containing and platinum-containing	96	41 (42.7)	44 (45.8)	85 (88.5)
Other	279	29 (10.4)	47 (16.8)	76 (27.2)
Cycles				
≤3	278	47 (16.9)	80 (28.8)	127 (45.7)**
4~6	557	184 (33.0)	196 (35.2)	380 (68.2)

Note: *P<0.05, **P<0.01. Diabetes mellitus: DM; Impaired fasting glucose: IFG.

Table 5. Comparison of blood lipid and insulin in different groups

Item	Group			t	P
	DM	IGR	NGT		
Triglyceride (mmol/L)	0.8±0.2	0.7±0.1	0.7±0.1	0.362	>0.05
Total cholesterol (mmol/L)	4.8±0.7	4.7±0.8	4.2±0.8	0.996	>0.05
High-density lipoprotein (mmol/L)	1.4±0.3	1.2±0.3	1.2±0.4	0.992	>0.05
Low-density lipoprotein (mmol/L)	2.9±0.7	2.8±0.7	2.8±0.7	0.335	>0.05
Fasting insulin (mU/l)	4.3±1.1	4.2±1.2	4.2±1.2	2.996	>0.05

Diabetes mellitus: DM; Impaired fasting glucose: IFG; Normal blood glucose tolerance: NGT.

Table 6. Cox regression analysis of multi-factors for abnormal glucose metabolism

Item	Regression coefficient	P
Age	1.52	0.023
Chemotherapy	0.85	0.011
Tumor type	0.64	0.008

patients who refused to undergo OGTT after chemotherapy were included in the analysis, but only their fasting blood glucose levels after chemotherapy were analyzed. Fifty-one patients completed one cycle of chemotherapy, 38 completed two, 189 completed three, and the remaining cases completed four to six. Abnormal glucose metabolism before and after chemotherapy was significantly different. DM and IGR were significantly higher after chemotherapy than before (i.e., 78.8% (394/500) vs. 30.8% (154/500), χ^2=232.543, P<0.01). Abnormal glucose metabolism was significantly different in patients undergoing different chemotherapy regimens. The incidence of abnormal glucose metabolism was significantly higher in taxane- or platinum-containing programs than in other programs (χ^2=22.657, P<0.01) (**Table 4**).

Lipids and blood insulin levels

Triglycerides, total cholesterol, and low-density lipoproteins in the DM, IGR, and NGT groups were higher than those in the control group, whereas serum insulin and high-density lipoproteins were lower. The blood lipid levels increased with increasing abnormal glucose metabolism, although this increase had no statistically significant difference (P>0.05) (**Table 5**).

Multiple regression analysis

For logistic Cox regression multivariate analysis, we used DM+IGR or IGT as the dependent variable and possible influencing factors, namely, obesity, blood lipids, age, sex, chemotherapy, and tumor type as the independent variables. Age (B=1.52), chemotherapy (B=0.85), and tumor type (B=0.64) were incorporated into the equations (**Table 6**).

Discussion

Abnormal glucose metabolism increases the incidence and mortality rates of cardiovascular

and cerebrovascular diseases and has therefore received considerable attention [11, 12]. However, the relationship between abnormal glucose metabolism and cancer has only recently attracted research attention. Diabetes and IGT increase cancer risk possibly because they are associated with high fat, high-energy and -insulin diet, and imbalance of insulin-like growth factor-related cell growth regulators. Diabetes and abnormal glucose metabolism increase the risk of several cancers, and IGT in cancer patients also increases mortality [10, 13, 14]. However, several researchers argue that no relationship exists between abnormal glucose metabolism and malignancy [15]. This controversy may primarily be due to population selection, diagnostic criteria, methodological inconsistencies (such as nonstandard OGTTs or the use of fasting blood glucose alone), and abnormal glucose metabolism diagnosis (i.e., based only on fasting blood glucose without an OGTT). These factors cause a diagnostic error rate of 87.4% for IGR and 80.5% for diabetes [16]. In this study, the patients with malignant tumors were diagnosed with diabetes or pre-diabetes by measuring FPG and glucose tolerance (OGTT). We evaluated the prevalence of diabetes in such patients and other influencing factors. The prevalence of diabetes was 16.4%; 58 of these cases were previously diagnosed, and 113 cases were newly diagnosed (66.1%). The prevalence rate of IGR was 22.8%, and the overall prevalence rate of abnormal glucose metabolism was 39.1%; the prevalence of abnormal glucose metabolism in the >65 age group was higher than that in the <65 group. Abnormal glucose metabolism also varied with tumor type: patients with pancreatic, liver, or colorectal cancer had high abnormal glucose metabolism, whereas those with soft tissue sarcoma or prostate cancer had a low proportion. Yang [17] found that the prevalence of diabetes in adults is 11.66% and that of pre-diabetes is 15.19% (i.e., higher than the diabetes prevalence). In the present study, the prevalence of diabetes or pre-diabetes in cancer patients was higher than in the general population; however, differences in prevalence between the sexes were not observed probably because the study population was taken from different regions or economic statuses or because the sample was small. Zhan et al. [18] found that the DM+FPG rate in 2048 patients with malignant tumor was 28%. This rate is much lower than that in our study primarily because Zhan et al. diagnosed DM based on fasting blood glucose, whereas we used OGTT for diagnosis.

This study found that diabetes and IGT patients significantly increased after chemotherapy, especially after multi-cycle chemotherapy. The prevalence of DM and IGT in patients treated with platinum- or paclitaxel-containing regimens was significantly higher than that in patients treated with other programs, consistent with Wang et al. [19]. The possible reasons for this discrepancy include the following: 1) Cancer and diabetes are more common in the elderly. The elderly generally have low glucose tolerance, which chemotherapy may turn into overt diabetes. 2) Chemotherapy may damage pancreatic B cells and thus impair lower islet function. Barone et al. found that glucose metabolism disorders in male cancer patients are related to insulin resistance and decreased insulin secretions [20]. 3) Patients who consume high-energy diets or receive a large amount of glucose infusion in chemotherapy have high risk of diabetes given their potential IGT. 4) Using a large amount of glucocorticoid hormones in chemotherapy promotes gluconeogenesis and inhibits the oxidative phosphorylation of glucose to reduce glucose metabolism, thereby causing hyperglycemia. Using such an amount of hormones also inhibits the renal tubular reabsorption of glucose from urine. These effects are mostly reversible, but hidden diabetes may turn into overt diabetes. Dai et al. [21] found that abnormal blood glucose is common in cancer patients after chemotherapy, especially after taxane-containing regimens, resulting in secondary DM. 5) Chemotherapy causes drug-induced liver cell damage and thus affects glucose uptake and glycogen production in the liver. 6) Chemotherapeutic drugs inhibit three major enzymes in glycolysis (hexokinase, phosphofructokinase, and acetone kinase) and thus increase sugar consumption. 7) High-dose platinum-containing programs require furosemide, which increases blood sugar and thus causes IGT. 8) Fadini et al. [22] found that white blood cells or macrophage colony-stimulating factors induce diabetes. 9) Nausea and vomiting caused by chemotherapy results in the loss and lower intake of electrolytes from the gastrointestinal tract; the large amount of hydration and diuret-

ic potassium produced by platinum-containing chemotherapy and platinum-induced injury of the renal tubular reabsorption function commonly causes hypokalemia and hypomagnesemia. Long-term uncorrected hypokalemia and the large amount of intravenous fluid infusion used to correct it aggravate islet cell function and increase abnormal glucose tolerance [23].

Lipid changes in patients with malignant tumor and DM or IGR are more complicated than increases in blood lipids in diabetes [15]. In this study, total cholesterol and triglycerides in the IGT and DM groups increased. However, this increase was not statistically significant possibly because the patients in our study mostly had advanced cancer and lost weight. Moreover, abnormal glucose metabolism exists in patients with malignant tumors. In these cases, the body needs plenty of energy, but glucose metabolism is inefficient and thus increases protein breakdown and fat mobilization to provide adenosine triphosphate. These events cause weight loss and a negative protein and fat balance. This trend worsens as the disease develops [24].

In the multivariate analysis, the variables included in the regression equation were age, chemotherapy, and tumor type. These variables were independent prognostic factors for abnormal glucose metabolism in patients with malignant tumors. Whether these factors can be adjusted to reduce abnormal glucose metabolism in cancer patients warrants further prospective studies.

In summary, a high prevalence of abnormal glucose metabolism was observed in cancer patients, especially after multi-trip or platinum- or taxane-containing chemotherapy. Significant difference was found among tumor types and age groups. Therefore, abnormal glucose metabolism caused by the treatment of malignant tumors should be given adequate attention. About 40% of cancer patients die from malnutrition rather than the disease itself and treatment factors. Furthermore, nutrient deficiency may cause cancer and significantly promote tumor development. Diabetic patients have varying degrees of insulin deficiency, which causes abnormal sugar metabolism, negative protein and fat balance, and micronutrient deficiencies. Therefore, abnormal glucose metabolism in cancer patients should be given attention. Abnormal glucose metabolism should be detected early, proper diet guidance should be offered, and appropriate dosage of antidiabetic drugs should be provided to reduce the burden on pancreatic islet B cells, provide adequate energy and support treatment, and facilitate cancer treatment. The smooth implementation of cancer treatment is vital to improve the survival and quality of life of cancer patients.

Disclosure of conflict of interest

None.

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