ORAL ANTIDIABETICS AND INSULINS DO NOT INCREASE CANCER RISK

YUSUF AYDIN, MÜCAHIT ERDEN[1], FATIH ERMIS[2], ALI KUTLUCAN[1], ERTUGRUL KAYA[3], LEYLA YILMAZ AYDIN[4], ELIF ÖNDER[1], GÖKHAN CELBEK[1]

[1]Department of Endocrinology, Duzce University Faculty of Medicine, Duzce - [2]Department of Gastroenterology, Duzce University Faculty of Medicine, Duzce - [3]Department of Pharmacology, Duzce University Faculty of Medicine, Duzce - [4]Department of Chest Diseases, Duzce University Faculty of Medicine, Duzce

ABSTRACT

Aims*: To determine the effects of diabetes mellitus (DM) treatment regimens on malignancy.*

Methods*: Six hundred fifty-five DM patients were enrolled. Patients receiving diabetes therapies for at least one year were retrospectively assessed with physical examination, detailed medical, habits, demographic characteristics and laboratory tests, and divided into two groups according to the diabetes treatment type (using oral agent or insulin and using metformin or not). Insulin users were grouped according to insulin regimens (intensive, basal and mixed) and to the insulin type (glargine, detemir, human insulin, biphasic analogue). Cancer cases were identified at the first visit.*

Results*: Among 655 DM patients 13 (2%) were Type 1 DM, 642 (98%) were Type 2 DM; 379 (58%) were female, 276 (42%) were male. Thirty-six cancers and 76 benign tumors were observed. Patients with and without a cancer were compared for diabetes treatment regimens and types of agents. No significant differences were observed between groups using oral agent or insulin (p=0.429) and using metformin or not (p=0.119). There were no significant differences between groups according to insulin regimens (p=0.059) and the insulin type (p=0.418).*

Conclusion*: There was no significant difference in terms of cancer risk between different types of pharmacological treatments of diabetes (including analog insulins).*

Key words*: Diabetes mellitus, cancer, insulin, insulin glargine, metformin, oral antidiabetics.*

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Introduction

Diabetes mellitus (DM) and cancer are diseases which are increasing globally. High morbidity and mortality rates, on the other hand high medical expenses and loss of manpower cause a large burden on the patient and community[1-3].

Number of patients diagnosed with diabetes, and cancer has been increased significantly in the last decades. Some researchers have emphasized the epidemic nature of diabetes and it is estimated that there will be 320 million patients with diabetes around the world in 2025. Cancer is also increasing rapidly and approximately 12.4 million new cancer cases were diagnosed in 2008[3-5].

Epidemiological data had showed that cancers were associated both with diabetes and with certain risk factors for diabetes. Liver, pancreas, endometrium, colon, rectum, breast and bladder cancers were seen more frequently in patients with diabetes, prostate cancer is less shown but there isn't a clear relationship with other types of cancer. In addition, recent observational studies suggested that some antidiabetic drugs could be related with an increase or decrease in risk of cancer. Especially there are some publications related with metformin and insulin glargine. According to these, metformin prevented the cancer but insulin glargine was associated with its development[6,7].

Presence of common risk factors both for diabetes and cancer, diabetes duration, antidiabetic drugs role in the development of cancer and pathophysiological mechanisms of diabetes possible role in cancer development still retain the complexity.

Large scaled studies are needed to enlighten the relationship between diabetes and cancer[7,8]. In this perspective we reviewed admitted patients to our hospital who use antidiabetics in order to investigate the possible relationship between diabetes and cancer.

Materials and methods

This retrospective study is conducted in Duzce University, Faculty of Medicine between January 2010 and January 2011. Patients referred to Endocrinology and Diabetes outpatient clinic and inpatient, due to any illness, diabetics who use antidiabetic drugs at least for one year were enrolled in the study. Diabetes was diagnosed according to American Diabetes Association (ADA) 2010 diagnostic and classification criteria. 655 patients' records were evaluated retrospectively.

The study, named as "The effects of antidiabetic agents on the development of cancer", has been approved by the ethical committee with the application file number 2011/145 and conducted by the Endocrinology Department.

Patients age (years), gender, height (cm), body weight (BW) (kg) and body mass index (BMI) (kg/m^2) were noted. Alcohol consumption was questioned and alcohol use more than two glasses in a day was defined as alcohol dependence. Smoking was evaluated as pack-years. Patients' occupations were questioned and they were defined in three groups as fixed income (government official, employee, fixed income workers in private institutions), non-salaried employees (tradesman, farmer), jobless (unemployed, housewife). First diagnosis date, type of diabetes and beginning of treatment were recorded.

Comorbid diseases were questioned. Hypertension, coronary artery disease, congestive heart failure, cerebrovascular diseases were grouped in cardiovascular system diseases. Chronic obstructive pulmonary disease, asthma, interstitial lung diseases and occupational lung diseases were grouped in respiratory system diseases. Thyroid, parathyroid, pancreas, pituitary, hypothalamus, adrenal, and endocrine metabolic disorders were grouped in endocrinologic diseases. Liver, spleen, stomach, small bowel, large bowel and anal disease were grouped in gastrointestinal tract diseases.

Operations that patients had had before enrolling were noted as pelvic, abdominal, thoracic and breast surgery. Family histories of the patients' were queried about presence both diabetes and cancer. The most recent HbA1c values that had been measured within the last 3 months were recorded.

Antidiabetic agents used in the treatment were inquired and patients were divided into two groups as oral antidiabetic (OAD) and insulin users. OAD users were divided into 5 subgroups as sulfonylurea (SU); metformin; pioglitazone; SU and metformin; SU, metformin and pioglitazone users. In addition, according to the treatment protocol, patients were also divided into 2 groups as metformin users and non-users. Durations of antidiabetic use were recorded as years. Insulin using patients were divided into 3 subgroups as basal insulin, mixture insulin and intensive insulin therapy. Patients were also divided into 4 different groups according to types of insulin they had used as analog mixture insulin, human insulin, insulin glargine and insulin detemir. Durations of insulin use were recorded as years. Daily used insulin dosage was determined as IU/day. Changes in antidiabetics, transition from OAD to insulin, changes in type of insulin and dosage were determined. Treatment forms before diagnosis of cancer and benign tumors were noted.

Patients with a history of antidiabetic treatment at least one year from the date of diagnosis of DM were assessed by anamnesis, detailed physical examination, routine laboratory tests and posterior-anterior (PA) chest X-rays taken within 3 months. Patients were questioned about presence of cancers and benign tumors.

Gastroscopy, colonoscopy, mammography and other imaging methods for diagnosis were performed for further assessment of patients with suspected cancer. Consultations were requested from relevant departments for final diagnosis. Operation and pathology results were obtained and type and date of diagnosis of cancers and benign tumors were noted from hospital information system. Pathological results and if any operations, chemotherapy and radiotherapy procedures performed for patients who had diagnosed or treated in other hospitals before or patients who have ongoing treatments in other hospitals were obtained and cancer type and date of diagnosis were recorded.

Cancers or benign tumors that had been diagnosed before diabetes, cancers or benign tumors that had been diagnosed in the first year of diabetes diagnosis, patients who didn't get regular antidiabetic treatment at least one year after diabetes diagnosis, patients who can't provide official documented information of their disease although they had can-

cers or benign tumors were excluded from the study.

Statistical Analysis

The analysis was performed with Statistical Package for the Social Sciences (SPSS) computer software (version 17.0, SPSS Inc, Chicago, IL, USA). Descriptive characteristics of patients were given as mean, median and percent (%). One-way analysis of variance (ANOVA) test was performed to determine the differences between different groups. Spearman's correlation analysis was used to determine the relationship between variables. Chi Square test was performed to determine the relationship between categorical variables. In determining the relationship between categorical variables, chi square test was performed on two-way tables. Statistical significance was accepted when $p<0.05$.

Results

The study consisted a total of 655 patients with diabetes. Three hundred seventy-nine (58%) were women, while 276 (42%) were male. Mean age of the patients was 57.16±11.44 years. Six hundred forty-two (98%) patients were type 2 DM while 13 (2%) were type 1 DM. Mean BMI was 30.23±5.87kg/m2. 333 (50.8%) patients had a family history of diabetes and 133 (20.3%) patients had a family history of cancer. It is known that 12 (1.8%) patients have used alcohol and average smoking rate was 6.72±13:43 pack/years. The mean duration of DM, 8.53±6.60 years, mean HbA1c was 7.95%±7.90%. Two hundred twenty-nine (34.9%) patients have been using insulin therapy while 426 (65.1%) patients have been using OADs (Table 1). Mean OAD usage time was 6.77±5.33 years. Among patients under insulin treatment, 22 (9.6%) patients with diabetes have used basal insulin, 133 (58.1%) patients with diabetes used mixture insulin and 74 (32.3%) of them used intensive insulin therapy. Insulin preparations used in the treatment were as follows: 111 (48.4%) mixed insulin analogue, 26 (11.3%) human insulin, 60 (26.2%) insulin glargine and 32 (13.9%) were insulin detemir. The mean duration of insulin use was 4.93±4.26 years with a daily average dose as 50.80±26.10 IU (Table 1).

Number of detected cancers were as follows: 5 (13.9%) breast, 5 (13.9%) thyroid, 4 (11.1%) colon/rectum, 4 (11.1%) larynx, 4 (11.1%) prostate, 4 (11.1%), bladder, 3 (8.3%) lymphoma/leukemia, 2 (5.5%), hepatocellular, 1 (2.8%) lung, 1 (2.8%) biliary tract, 1 (2.8%) endometrial/cervical, 1 (2.8%) renal, and 1 (2.8%) was metastatic cancer of unknown primary (Table 2). Characteristics of patients with malignancy were shown in Table 3.

	n (%)
Gender (Female/Male)	379/276 (58/42)
DM Type (Type 1/2)	13/642 (2/98)
Alcohol (use/not use)	12/643 (1.8/98.2)
Additional disease	
Cardiovascular disease	354 (54.0)
Respiratory disease	22 (3.3)
Endocrine disease	64 (9.7)
Gastrointestinal disease	17 (2.5)
Family history of DM (Yes/No)	333/322 (50.8/49.2)
Family history of cancer (Yes/No)	133/522 (20.3/79.7)
Occupation	
Fixed income	178 (27.1)
Non salaried employees	108 (16.4)
Jobless	369 (56.3)
Treatment type (OAD/Insulin)	426/229 (65.1/34.9)
OAD group	
SU	37 (8.7)
Metformin	123 (28.9)
Pioglitazone	4 (0.9)
SU+Metformin	200 (46.9)
SU+metformin+Pioglitazone	62 (14.6)
Insulin treatment type	
Basal	22 (9.6)
Mixed	133 (58.1)
Intensive	74 (32.3)
Insulin Type	
Analog mixed	111 (48.4)
Human insulin	26 (11.3)
Insulin glargine	60 (26.2)
Insulin detemir	32 (13.9)

Table 1: General characteristics of patients with DM (n=655).
DM: diabetes mellitus; SU: sulfonyurea OAD: oral antidiabetics

	n (%)
Breast cancer	5 (13.9)
Thyroid cancer	5 (13.9)
Colon/Rektum cancer	4 (11.1)
Larynx cancer	4 (11.1)
Prostate cancer	4 (11.1)
Bladder cancer	4 (11.1)
Lymphoma/Leukemia	3 (8.3)
Liver cancer	2 (5.5)
Endometrial/Cervical cancer	1 (2.8)
Biliary tract cancer	1 (2.8)
Lung cancer	1 (2.8)
Renal cell cancer	1 (2.8)
Carcinoma of unknown primary	1 (2.8)
Total	36 (100)

Table 2: The distribution of cancer cases detected in patients with Type 2 DM.

Patients with cancer were all type 2 DM consisting of 20 (55.5%) male and 16 female (44.5%). Non-cancer group consisted of 606 type 2 DM and 15 with type 1 DM. 255 (41.2%) were male and 364 (58.8%) were female patients. There wasn't any difference between two groups in terms of types of DM (p=0.386) and gender (p=0.064). There wasn't any difference in terms of BW (p=0.163), BMI (p=0.071), presence of additional disease (p=0.927), family history of cancer (p=0.354), family history of diabetes (p=0.43), either. The average age of cancer group was 63.54±11.35 years and average smoking rate was 11.89±16.15 pack / years while as non cancer group had an average age of 56.80±11.35 years with an average smoking rate as 6.43±13.19 pack/years. Patients with cancer were statistically significant older (p=0.001) with a much more smoking rate (p=0.019). In cancer group, mean duration of diabetes was 8.6±5.2 years with an average duration of OAD and insulin use were 7.12±5.54 and 6.03±3.77 years, respectively. In non-cancer group mean duration of diabetes was 8.5±6.6 years with an average duration of OAD and insulin use were 6.75±5.32 and 4.88±4.28 years, respectively. Although duration of OAD and insulin use were longer in the cancer group, there was no statistically

	Age(years)	Gender	DM duration (years)	HbA1c	Cancertype	Smoking (pack/year)	Treatment type	OAD type	Insulin type
Patient 1	56	F	7	9.5	Breast	-	OAD	Glic	
Patient 2	47	F	3	10	Breast	-	Insulin		NPA/Asp
Patient 3	58	F	10	6.3	Breast	10	OAD	Metf	
Patient 4	58	F	6	11.6	Breast	-	OAD	Metf+Glic	
Patient 5	78	F	8	8.4	Breast	-	OAD	Glim	
Patient 6	61	F	10	13	Thyroid	-	Insulin		Asp+Det
Patient 7	69	F	6	8.6	Thyroid	-	OAD	Metf +Glim	
Patient 8	83	F	3	7.6	Thyroid	30	OAD	Metf+Glic	
Patient 9	69	F	2	6	Thyroid	-	OAD	Metf+Glic	
Patient 10	54	F	11	7.7	Thyroid	-	OAD	Metf+Glic+ Pio	
Patient 11	41	M	6	6.1	Rectum	-	OAD	Glic	
Patient 12	57	M	9	7.4	Colon	-	OAD	Metf+Glic	
Patient 13	74	M	5	7.5	Colon	-	OAD	Glic	
Patient 14	65	M	14	7.6	Colon	-	OAD	Glic	
Patient 15	78	M	15	7.8	Bladder	-	OAD	Metf +Glim	
Patient 16	47	M	20	8.5	Bladder	-	OAD	Metf+Glic	
Patient 17	67	M	11	13.3	Bladder	-	OAD	Glim+Pio	
Patient 18	46	M	4	6.2	Bladder	15	OAD	Glic	
Patient 19	78	M	12	7.1	Prostate	-	Insulin		Det
Patient 20	73	M	2	6.3	Prostate	-	OAD	Glic	
Patient 21	66	M	12	10	Prostate	45	Insulin		Asp+Glar
Patient 22	68	M	15	7	Prostate	-	Insulin		Det
Patient 23	66	M	12	10.6	Larynx	45	Insulin		Asp+Glar
Patient 24	63	M	9	11	Larynx	-	Insulin		Glar
Patient 25	73	M	2	7.8	Larynx	30	OAD	Nate	
Patient 26	86	M	3	6.1	Larynx	34	OAD	Metf+Glic	
Patient 27	61	F	2	8.1	Lymphoma	-	OAD	Metf+Glim	
Patient 28	54	M	10	8	Lymphoma	20	OAD	Metf+Glim	
Patient 29	63	F	22	8	Lymphoma	-	OAD	Metf+Glim	
Patient 30	62	M	7	4.7	Liver	30	Insulin		Regl+NPH
Patient 31	73	F	9	9.2	Liver	-	Insulin		NPA/Asp
Patient 32	67	F	16	7.2	Lung	-	Insulin		NPA/Asp
Patient 33	51	F	10	7.1	Cervical	-	OAD	Metf	
Patient 34	51	M	4	13.2	Renal	20	OAD	Metf+Glic	
Patient 35	52	M	6	11	Biliary tract	-	OAD	Metf+Glic	
Patient 36	75	F	8	8	Primer X	-	Insulin		NPA/Asp

Table 3: Detailed characteristics of detected cancer cases.

F: female; M: male; Primer X: carcinoma of unknown primary; Glic: gliclazide; Metf: metformin; Glim: glimeprid; Nate: nateglinide; Pio: pioglitazone; NPA: neutral protamine aspart; Asp: aspart; Det: detemir; Glar: glargine; Regl: regular

difference between two groups in terms of duration of DM (p=0.937), OAD (p=0.737) and insulin use (p=0.418), respectively. In cancer group mean HbA1c value was 8.2%±2.3% and daily average insulin dose was 48.60±29.50 IU/day. In non-cancer group HbA1c value was 7.88%±1.9% and daily average insulin dose was 50.90±26.0 IU/day. Although mean HbA1c value was determined higher in the cancer group, there wasn't statistically difference in terms of HbA1c value (p=0.354) and daily average insulin dose (p=0.786) between two groups (Table 4).

	Cancer (n=36)	Without cancer (n=619)	P
DM duration (years)	8.6±5.2	8.5±6.6	0.937
Age(years)	63.54±11.35	56.80±11.35	0.001
Gender (male/female)	20/16	255/364	0.064
Weight (kg)	79.03±11.95	82.81±15.75	0.163
BMI (kg/m²)	28.48±3.88	30.32±5.95	0.071
Smoking (pack/years)	11.89±16.51	6.63±13.19	0.019
HbA1c (%)	8.2±2.31	7.88±1.93	0.354
OAD duration (years)	7.12±5.54	6.75±5.32	0.737
Duration of ınsulin use (years)	6.0±3.77	4.88±4.28	0.418
Daily dose of insulin (IU/day)	48.60±29.50	50.90±26.0	0.786
Additional disease	25	432	0.927
Family history of cancer	5	128	0.354
Family history of DM	12	321	0.43

Table 4: Comparison of patients with and without cancer.

DM: diabetes mellitus; BMI: body mass index; OAD: oral antidiabetics.

Both groups were assessed in terms of antidiabetic treatment. In cancer group 11 (30.5%) patients were using insulin and 25 (69.4%) patients were using OAD. In non-cancer group, 218 (35.2%) patients were using insulin and 401 (64.7%) patients were using OAD. There wasn't any statistically difference in terms of treatment type between two groups (p=0.429). Patients were evaluated for the use of metformin. In cancer group 16 (44.4%) patients were using metformin while 357 (57.6%) non-cancer patients were using this drug (p=0.119) (Table 5).

	Cancer		P
	With, n (%)	**Without, n (%)**	
	36 (5.49)	619 (94.5)	
DM treatment type			
Insulin	11 (30.5)	218 (35.2)	0.429
OAD	25 (69.4)	401 (64.7)	
Metformin			
Use	16 (44.4)	357 (89.1)	0.119
not use	20 (55.5)	44 (10.4)	
Insulin group			
Basal	3 (27.2)	20 (9.1)	0.059
Mixed	4 (36.3)	128 (58.7)	
Intensive	4 (36.3)	70 (32.1)	
Insulin type			
Analog mixed	4 (36.3)	108 (49.5)	0.438
Human insulin	1 (9.0)	24 (11.4)	
Insulin glargine	3 (27.2)	57 (26.1)	
Insulin detemir	3 (27.2)	29 (13.3)	

Table 5: Agents used to treat diabetes in patients with cancer and their relationship with cancer.

Both groups were assessed in terms of insulin types and treatment strategies. In cancer group 3 (27.2%) patients were using basal insulin, 4 (36.3%) patients were using mixture insulin and 4 (36.3%) patients were using intensive insulin therapy. In non-cancer group 20 (9.1%) patients were using basal insulin, 128 (58.7%) patients were using mixture insulin and 70 (32.1%) patients were using intensive insulin therapy.

Both groups were assessed in terms of insulin types. In cancer group 4 (36.3%) patients were using analogue mixed insulin, 1 (9%) patient was using human insulin, 3 (27.2%) patients were using insulin glargine and 3 (27.2%) patients were using insulin detemir. In non-cancer group 108 (49.5%) patients were using analogue mixed insulin, 24 (11.4%) patients were using human insulin, 57 (26.1%) patients were using insulin glargine and 29

(13.3%) patients were using insulin detemir. There was no statistically significant difference in terms of insulin treatment strategies (p=0.059) and forms of insulin (p=0.418) between two groups (Table 5).

Diabetes treatment types and different antidiabetic agents used in the study were evaluated in terms of development of cancers and benign tumors. Among 655 patients with diabetes a total of 112 tumors were detected. 36 were cancers and 76 of them were benign tumors. Distribution of benign tumors were as follows: 32 (42.1%) benign prostatic hyperplasia, 21 (27.6%) myoma uteri, 6 (7.9%) endometrial polyps, 3 (3.9%) parathyroid adenomas, 3 (3.9%) meningioma, 2 (2.6%) thyroid adenoma, 2 (2.6%) pituitary adenoma, 2 (2.6%) vocal cord nodules, 2 (2.6%) colon polyps and 1 (1.3%) breast fibroadenoma.

A total of 76 (11.6%) patients with benign tumors were evaluated in terms of their antidiabetics use. 25 (32.8%) patients were using insulin and 51 (67.1%) patients were using OAD therapy. In non-cancer group 203 (35.1%) patients were using insulin, and 376 (64.9%) patients were using OAD therapy. There was no statistically significant difference between in benign tumor group and non-tumor group in terms of insulin and OADs use (p=0.709) (Table 6).

	Benign tumor		P
	Yes, n (%) 76 (11.6)	**No, n (%)** 579 (88.3)	
DM treatment type			
Insulin	25 (32.8)	203 (35.1)	0.709
OAD	51 (67.1)	376 (64.9)	
Metformin			
Use	35 (46.0)	338 (58.3)	0.041
not use	41 (53.9)	241 (41.6)	
Insulin group			
Basal	3 (12.0)	20 (9.8)	0.858
Mixed	15 (60.0)	116 (57.1)	
Intensive	7 (28.0)	67 (33.0)	
Insulin type			
Analog mixed	13 (52.0)	98 (48.2)	0.588
Human insulin	4 (16.0)	21 (10.3)	
Insulin glargine	4 (16.0)	56 (27.5)	
Insulin detemir	4 (16.0)	28 (13.7)	

Table 6: In benign tumor group, diabetes treatments and agents and their relationship with benign tumor.

Patients were assessed about metformin use. In benign tumor group 35 (46%) patients were using metformin while 338 (58.3%) patients were using the same drug in non-tumor group. There were more patients in non-tumor group and difference was statistically significant (p=0.041).

Patients were assessed about insulin treatment strategies and different insulin types. In benign tumors group 3 (12%) patients were using basal insulin, 15 (60%) patients were using mixture insulin, 7 (28%) patients were using intensive insulin therapy. In non-tumor group 20 (9.8%) patients were using basal insulin, 116 (57.1%) patients were using mixture insulin and 67 (33%) patients were using intensive insulin therapy.

In benign tumors group 13 (52%) patients were using mixed insulin analogue, 4 (16%) patients were using human insulin, 4 (16%) patients were using insulin glargine and 4 (16%) patients were using insulin detemir. In non-tumor group 98 (48.2%) patients were using mixed insulin analogue, 21 (10.3%) patients were using human insulin, 56 (27.5%) patients were using insulin glargine and 28 (13.7%) patients were using of insulin detemir. There was no difference between two groups in terms of both insulin treatment strategies (p=0.858) and insulin types (p=0.588) (Table 6).

	Insulin Glargine, n (%) n=60	Other insulins, n (%) n=169	P
Total tumor, n=112	7 (3.0)	29 (12.6)	0.360
Cancer, n=36	3 (1.3)	8 (3.5)	0.787
Benign tumor, n=76	4 (1.7)	21 (9.1)	0.214

Table 7: Comparison of insulin glargine and other insulins in terms of cancer, benign tumor and total tumor.

Two hundred and twenty-nine (34.9%) patients were using insulin among 655 patients with diabetes in the study. Subgroup analysis was performed of patients who used insulin therapy. Patients who used insulin glargine and insulin detemir were compared with other insulins users in terms of the development of cancers and benign tumors. Sixty (26.2%) patients were using insulin glargine while 169 (73.8%) of them were using other types of insulin. Three (1.3%) out of whom cancer detected 36 patients were using insulin glargine and 8 (3.5%) of them were using other types of insulin (Table 7). 4 (1.7%) out of whom benign tumor detected 76 patients were using

insulin glargine and 21 (9.1%) of them were using other types of insulin. There wasn't statistically significant difference in terms of cancer (p=0.787) and benign tumor (p=0.214) between insulin glargine using group and other insulin groups.

	Insulin Detemir, n (%)	**Other insulins, n (%)**	**P**
Total tumor, n=112	7 (3.0)	29 (12.6)	0.269
Cancer, n=36	3 (1.3)	8 (3.5)	0.137
Benign tumor, n=76	4 (1.7))	25 (10.9)	0.760

Table 8: Comparison of insulin detemir and other insulins in terms of cancer, benign tumor and total tumor.

Discussion

Thirty-six malignancy and 76 benign tumor cases were determined throughout 655 patients with diabetes who have used OADs and insulins at least one year in this study. Malignancy detected patients with diabetes were all type 2 DM and there wasn't a relationship between malignancy and the medications they had used. Benign tumors were statistically significant less in metformin using patients than others. Advanced age, and smoking were identified as the most important risk factors for malignancy in patients with diabetes. There wasn't any difference between all different types of insulin and OADs.

Hyperglycemia, hyperinsulinemia, inflammation and obesity which are common risk factors both for diabetes and cancer have been advocated as possible mechanisms for the increase in cancer risk in individuals with diabetes[9,10]. The relationship between cancer and duration of cancer isn't known clearly and multi-drug regimens in diabetes treatment further complicate the relationship between diabetes and cancer[4-6]. Relationship between both diseases may be associated with concomitant risk factors like advanced age, obesity, diet, smoking, familial predisposition, comorbid diseases[7,11]. Risk of many types of cancer is higher in patients with higher BMI[12,13].

Thirty-six cancer patients were found to be obese. However there wasn't any statistically significant difference between non-cancer patients with diabetes and cancer patients in terms of BW and BMI. Both diseases' prevalence increase with obesity and that was compatible with our findings. Cancer group was older and smoking more than non-cancer group and the differences were found to be statistically significant. Cancer incidence increased with age and many types of cancer were related with smoking. These were compatible with our findings[4,14].

Although limited number of studies about the relationship between antidiabetics and cancer suggested some ideas, the results are inconsistent and still seem to be insufficient for a conclusion.

Monami et al. evaluated 195 patients with diabetes and found decreased cancer risk with metformin and gliclazide, increased cancer risk with glibenclamide. In his study insulins, pioglitazone, and acarbose were found to be unrelated with cancer development. Different sulfonylureas could be related with different types of cancer[15]. Currie et al.[16] examined the effects of antidiabetics on solid tumor development in 2009. A total of 62,809 patients were divided into four groups according to whether they received monotherapy with metformin or sulfonylurea, combined therapy (metformin plus sulfonylurea), or insulin. Insulin users were grouped according to treatment with insulin glargine, long-acting human insulin, biphasic analogue and human biphasic insulin. Patients under metformin monotherapy were associated with a lower cancer risk when compared with other groups. In subgroup analyses metformin was associated with lower colon and pancreatic cancer risk but found to unrelated with prostate and breast cancer risk (16). Rosiglitazone was also found to be unrelated with cancer development in Monami et al's study which was composed of 12522 participants[17].

Decensi et al. examined 4042 cancer-related patients in their meta-analysis, which consisted of 11 epidemiological studies up to May 2009[18]. According to their study metformin was found to be 31% lower risk of pancreatic and hepatocellular cancer when compared with other antidiabetics but there wasn't any significant decrease in colon, breast and prostate cancer. Also in our study, we found that OADs and insulin were not related with cancer and benign tumor development. When we compared metformin users with non-users cancer rate was less in the metformin group but the difference wasn't statistically significant. In subgroup analyses benign tumors were statistically less in metformin group.

It is difficult to determine each antidiabetic agent's effect on development of different types of cancer and benign tumor. Some drugs can reduce

while others may increase or no effect on cancer risk. Combination therapies are usually used and clinical experience of some drugs isn't enough for a conclusion[19]. Studies are performed in specific populations and some areas are known to be endemic for some types of cancer. All of these factors could be reason of inconsistencies between different studies. There are publications about exogenous insulins if they had increased cancer risk. Rosenstock et al. couldn't find difference between insulin glargine and neutral protamine Hagedorn (NPH) insulin on cancer development throughout 1017 type 2 DM patients[20]. Colhoun et al. compared insulin glargine with other insulins throughout 36254 type 2 DM patients between 2002-2005 but couldn't find difference in terms of cancer risk[21]. According to Jonasson et al. study which was performed on 114841 insulin using patients between 2005-2007 insulin glargine was found to be more related with breast cancer but there wasn't significant difference between insulin glargine and others in terms of other types of cancer development[22]. According to Manucci et al. study which was performed on 1340 insulin using patients high dose insulin glargine usage was found to be related with cancer development while other insulins were not[23]. Chang et al. also recently reported that insulin glargine use did not increase the risk of overall cancer incidence as compared with human insulin[24].

In our study, we did not find basal insulin, mixed insulin and intensive insulin usage related with development of cancers, benign tumors or overall tumors. When we examined different types of insulins we also couldn't find any significant relation between analog insulin, human insulin, insulin glargine and insulin detemir with development of cancers, benign tumors or overall tumors. In subgroup analyses insulin glargine and insulin detemir were compared with other insulins separately. Both types of insulins were found to be unrelated with development of cancers, benign tumors or overall tumors. Insulin detemir was also found unrelated with tumor development when compared with all other insulins.

Relationship between diabetes treatments and cancer is considered for a short time. Although some recent studies suggest relationship between insulin glargine with cancer development, many studies are performed relatively short and cross-sectional when compared with chronic, progressive course of both diabetes and cancer[16,22].

Diabetes treatment is a dynamic process and antidiabetic drugs are changed continuously. Patients with diabetes are exposed to high levels of endogenous insulin secretion in long-term and this could affect the process of tumor development. All of these could be reason of why insulin glargine had not been related with cancer in our study and inconsistent results of some other studies[22-24].

It's known that diabetes is associated with some types of cancers. Common risk factors between two diseases, possible connections of specific antidiabetics with different types of cancer progression and effect of DM make difficult to determine the real etiologic factor in increased cancer risk[25,26].

The only independent predictor of cancer was age in patients with diabetes in our study. Increased prevalence of diabetes and cancer with age was compatible with our findings. But it is difficult to find out how each risk factor effected diabetes and cancer relation. It's also difficult to compare specific antidiabetics effect on cancer with patients without any medication.

In this study we couldn't find a statistically significant relation between different types of insulins and OADs with cancer development. There were less benign tumors in the metformin group and this suggested the use of metformin might be associated with a lower risk of tumor development.

Relationship between diabetes and cancer keeps it's complexity because of the shared common risk factors. Cancer patients were older and more smoked individuals in our study. Prolongation of diabetes duration may be associated with increased cancer risk by pathophysiological mechanisms of diabetes regardless of antidiabetics. In drug choice for diabetes treatment due to lack of data increased cancer risk should not be a determining factor.

As a conclusion large number of population based, long-term researches were needed in order to examine relationship between diabetes and cancer and also antidiabetic mechanisms if it were a possible relation with cancer development.

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