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Association between diabetes mellitus and adverse characteristics of breast cancer at presentation

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ABSTRACT

Type 2 diabetes mellitus is associated with increased incidence and inferior outcome of various malignancies. The aim of this study was to explore the impact of type 2 diabetes on breast cancer characteristics at presentation. The study population included 79 diabetic and 158 age-matched non-diabetic patients. Parity, country of birth, co-morbidity other than diabetes, and mode of diagnosis were similar in both groups. Mean body mass index (BMI) was higher among diabetic patients. Tumour stage and size were higher among diabetic patients and the differences remained significant after adjustment for BMI. Moreover, after adjustment for BMI, breast cancer among diabetic patients was more often hormone receptor negative. Our results show that diabetes mellitus is associated with negative prognostic factors at breast cancer presentation.

1. Introduction

Type 2 diabetes mellitus is a major health problem, affecting more than 6.5% of the adults and up to 15% of the elderly population in the United States.[1] Type 2 diabetes mellitus, which accounts for 95% of diabetes cases, is a high insulin state, caused by insulin resistance in fat and muscle tissues, which leads to increased production of insulin. β Cells could decompensate and low insulin levels may occur, but only in the late stages of the disease. The main risk factors for type 2 diabetes mellitus are genetic predisposition, older age and obesity.[2] Diabetes mellitus is associated with increased risk, as well as worse outcome, of various malignancies, including endometrial, colon and pancreatic cancers.[3–6]

Breast cancer is another common disease, affecting one of every eight women during her lifetime.[7] Up to 16% of older breast cancer patients also suffer from diabetes.[8] An association between type 2 diabetes mellitus and an increased risk of breast cancer has been suggested by some, but not all, studies.[9–11] We recently conducted a meta-analysis of published studies and found the association to be significant although modest.[12] Three mechanisms may operate in both diabetes mellitus and breast cancer: altered endogenous sex-hormone

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regulation, activation of the insulin-like growth factor (IGF) signalling pathway and activation of the insulin-signalling pathway.[2,12,13] Obesity, the major risk factor for type 2 diabetes, is also associated with significantly increased risk of breast cancer incidence, presumably due to activation of these three mechanisms.[14] In addition to the biological mechanisms connecting diabetes to breast cancer, diabetes has also been associated with inadequate use of screening mammography and administration of therapy not consistent with consensus guidelines.[15–17]

The association between diabetes mellitus and the clinical and pathological characteristics of breast cancer are currently unexplored. In this study, we have investigated the association between type 2 diabetes mellitus on the clinical and pathological characteristics of consecutive diabetic breast cancer patients who were treated at the oncology institute of Sheba Medical Center, Tel Aviv, Israel between 1999 and 2002.

2. Patients and methods

2.1. Study population

The study population included all consecutive type 2 diabetic female patients, newly diagnosed for invasive breast cancer, that were treated at the oncology institute of Sheba Medical Center, Tel Aviv, Israel between 01/1999 and 10/2002. If patients were not treated by insulin or oral hypoglycemic therapy, the diagnosis of type 2 diabetes mellitus was confirmed, according to the definitions of the American Diabetic Association, by the presence of fasting glucose levels of above 126 mg/dl in routine laboratory evaluation.[18] Each diabetic patient was matched to two non-diabetic female breast cancer patients who were diagnosed at the closest date of diagnosis with age ±2 years (control group). Patients were excluded from the study if they had a diagnosis of another concomitant malignancy or type 1 diabetes.

2.2. Data collection

Patients' charts were reviewed and clinical data, including age, country of origin, parity, family history of breast cancer, height and weight were collected, as well as diabetes diagnosis and treatment details. The charts were also reviewed for type of surgery, radiation therapy, hormonotherapy and chemotherapy. All pathology reports were reviewed for tumour histology, size, lymph node involvement, grade, and oestrogen receptor (ER), progesterone receptor (PR) and Her-2 status. Stage was defined according to the 1997 American Joint Committee on Cancer Staging System for Breast Cancer.[19] Body mass index (BMI) was calculated as weight (kg)/height^2 (m). Co-morbidity was evaluated by the Charlson's co-morbidity score, which consists of 19 parameters regarding major classes of diseases and functional impairments. The score is a simple, well-validated tool and is often used in the research of breast cancer.[20] Mode of diagnosis was categorized as screening (either by screening mammography or routine physical examination), or by symptoms (e.g., mass palpated by the patient, pain and nipple discharge).

2.3. Data and statistical analysis

The distribution of all categorical variables by study group was tabulated. Univariate conditional logistic regression was used to examine the difference in the distribution of patients' characteristics as well as clinical and tumour characteristics, where the stratum variable was the unique number identifying each matched set. In the multivariate analysis, conditional logistic regression was performed to predict the influence of several variables on diabetes adjusting for BMI.

3. Results

3.1. Patients' characteristics

Of 1448 newly diagnosed breast cancer patients admitted during the study period, 79 diabetic breast cancer patients who met the study criteria were identified and matched to 158 non-diabetic breast cancer patients. The majority of the diabetic patients were treated by oral hypoglycemic agents ($n = 49$, 62%), and the rest by either diet ($n = 20$, 25%) or insulin ($n = 10$, 13%).

Patients' characteristics are presented in Table 1. The mean age at diagnosis was 64.9 ± 10 years for both groups, (range 31–90 years). Only 5% of the patients were younger than 50 years, and 15% were older than 75 years (data not shown). The groups were well balanced for country of origin, parity and family history of breast cancer among first-degree relatives. The crude co-morbidity score, as measured by the Charlson's co-morbidity score, was significantly higher among the diabetic patients ($P < 0.001$), but when adjusted for diabetes, the corrected score (excluding the category of diabetes mellitus) showed no difference between the groups. About half of the patients in both groups were diagnosed following the appearance of symptoms, mainly self-palpation of a breast mass, and only 26% were diagnosed following screening. As expected mean BMI was significantly higher (29.7 vs. 26.9, $P < 0.001$) among the diabetic compared to the non-diabetic patients.

3.2. The association between diabetes mellitus and breast cancer stage at diagnosis

Significant differences in the distribution of tumour stage were noticed between the study groups (Table 2). While almost half of the non-diabetic patients were diagnosed with stage I disease, only 24% of the diabetic patients were diagnosed at that stage (overall P value for differences in stage between the groups 0.002). Analysis of stage by early (T1/2, N0/1 and M0) versus advanced disease (T3/4, N2 or M1)[19,21] revealed that significantly more diabetic patients were diagnosed with advanced disease compared to the non-diabetic patients (18% vs. 8%, $P = 0.03$).

T stage was significantly higher among the diabetic patients, mainly due to differences in T1 and T2 disease (32% vs. 54% and 52% vs. 36%, respectively, overall $P = 0.028$). Compared to the non-diabetic patients, more diabetic patients had lymph node involvement, however, this difference was not statistically significant ($P = 0.32$). No differences were noticed

Table 1 – Distribution of patients' characteristics at diagnosis by study group

	DM[a] N = 79	Non-DM[b] N = 158	Overall P
Age (years) (mean ± SD)	64.9 ± 10.4	64.9 ± 10	0.96
Parity (N, %)			
0	5 (6)	12 (8)	0.64
1	10 (13)	20 (13)	
2	22 (28)	57 (36)	
3	22 (28)	40 (25)	
4+	20 (25)	29 (18)	
Country of origin (N, %)			
Europe/America	32 (40)	81 (51)	0.4
Asia/Africa	25 (32)	37 (23)	
Israel	19 (24)	35 (22)	
Unknown	3 (4)	5 (4)	
Family history (N, %)[c]			
Positive	9 (11)	24 (15)	0.41[d]
Negative	59 (75)	126 (80)	
Unknown	11 (14)	8 (2)	
Co-morbidity score	1	0.32	<0.001
Corrected co-morbidity score[e]	0.33	0.32	0.88
Method of diagnosis (N, %)			
Symptoms	37 (47)	73 (46)	0.95
Screening	21 (26.5)	45 (29)	
Unknown	21 (26.5)	40 (25)	
BMI[f] (mean ± SD)	29.7 ± 4.5	26.9 ± 4.1	<0.001
Obesity[g]	24 (41)	24 (20)	0.01

a DM, diabetic breast cancer patients.
b Non-DM, non-diabetic breast cancer patients.
c Excluding diabetes.
d N = 58 (74%) and 118 (74%) for DM and controls, respectively.
e Obesity is defined as BMI > 30.
f First-degree relative with breast cancer.
g Calculated without unknowns.

in the percentage of patients diagnosed with stage IV disease; however, the number of patients with stage IV disease was small in both study groups.

3.3. *The association between diabetes mellitus and biological characteristics of tumours*

The biological characteristics of tumours are shown in Table 3. No significant differences in the distribution of histology, grade and hormones' receptor status were noted. Her2/neu status was similar in both groups but was examined in less than 40% of the patients.

3.4. *Adjustment of diabetes mellitus effects for BMI*

As BMI is a major confounding variable, we conducted a multivariate analysis and calculated the odds ratios for selected study variables comparing diabetic to non-diabetic breast cancer patients, adjusted for BMI (Table 4). A positive association with higher stage and T status was noticed in the diabetic patients compared to the control group. This association reached significance when comparing stage II vs. I ($P = 0.026$), as well as T2 vs. T1 ($P = 0.023$). Importantly, breast cancer among diabetic patients was more often ER negative ($P = 0.04$) and PR negative ($P = 0.06$) compared to non-diabetic patients. The presence of diabetes was not associated with the mode of diagnosis.

3.5. *The effects of diabetes mellitus on treatment allocation*

No significant differences were found in any of the treatment modalities between the groups (data not shown). Breast conserving surgery was performed in the majority of the patients 89% and 93% in the diabetic patients and the control group, respectively, and 66% and 73% had adjuvant radiation treatment. Hormonotherapy, generally tamoxifen, was given to about 80% of the patients; 94% of them had positive hormone-receptors status. Chemotherapy was given to almost 40% of the patients in both groups.

4. Discussion

In this study, we investigated the association between type 2 diabetes mellitus and breast cancer characteristics at diagnosis, as well as differences in therapeutic modalities provided

Table 2 – Distribution of tumour stage at diagnosis by study group

Variable	Category	DM[a] N = 79		Non-DM[b] N = 158		Overall P
		N	(%)	N	(%)	
Stage	1	19	(24)	75	(48)	0.002
	2	46	(58)	70	(44)	
	3	8	(10)	8	(5)	
	4	6	(8)	5	(3)	
Stage[c]	Early	65	(82)	145	(92)	0.03
	Advanced	14	(18)	13	(8)	
T	1	25	(32)	85	(54)	0.028[d]
	2	41	(52)	57	(36)	
	3	6	(8)	7	(4)	
	4	2	(3)	4	(3)	
	X	5	(6)	5	(3)	
N	0	53	(67)	118	(75)	0.32[d]
	1	22	(28)	33	(21)	
	2	4	(5)	5	(3)	
	Unknown	0	(0)	2	(1)	
M	0	73	(93)	153	(97)	0.13
	1	6	(8)	5	(3)	

a DM, diabetic breast cancer patients.
b Non-DM, non-diabetic breast cancer patients.
c Early disease: T1/2, N0/1 and M0, advanced disease: T3/4, N2 or M1.
d Calculated without the unknowns.

Table 3 – Distribution of histology and tumour biological characteristics by study group

	DM[a] N = 79		Non-DM[b] N = 158		Overall P
	N	(%)	N	(%)	
Histology					
IDC	70	(90)	133	(84)	0.36
Other	9	(10)	25	(16)	
Grade					
1	8	(10)	16	(10)	0.98[e]
2	37	(47)	65	(41)	
3	19	(24)	37	(24)	
Unknown/not applicable	15	(19)	40	(25)	
ER[c] status					
Positive	59	(75)	125	(79)	0.64[e]
Negative	16	(20)	30	(19)	
Unknown	4	(5)	3	(2)	
PR[d] status					
Positive	35	(44)	83	(53)	0.42[e]
Negative	33	(42)	65	(41)	
Unknown	11	(14)	10	(6)	
Her2/neu status					
Positive	9	(11)	18	(11)	0.57[e]
Negative	16	(20)	45	(29)	
Unknown	54	(68)	95	(60)	

a DM, diabetic breast cancer patients.
b Non-DM, non-diabetic breast cancer patients.
c ER, oestrogen receptor.
d PR, progesterone receptor.
e Calculated without unknowns.

for these patients. The comparison of consecutive 79 diabetic with 158 matched non-diabetic breast cancer patients showed that the diabetic group presented with a larger tumour size at diagnosis and thus with a more advanced stage. These results remained significant after adjustment for BMI was performed. Moreover, after adjustment for BMI, breast

Table 4 – Odd's ratio (OR) and 95% confidence interval (CI) for predicting major study variables by study group, adjusted for BMI[a]

Variable	OR	95% CI
Stage		
2 vs. 1	2.89	1.14–7.33*
3 vs. 1	2.61	0.34–19.91
4 vs. 1	4.33	0.61–30.95
3 + 4 vs. 1 + 2	1.8	0.49–6.6
2–4 vs. 1	2.99	1.22–7.34*
T		
2 vs. 1	2.72	1.15–6.46*
3 vs. 1	3.47	0.55–21.8
4 vs. 1	95.41	
Histology		
IDC vs. non IDC	1.59	0.47–5.39
Grade		
3 vs. 1 + 2 + 9	0.95	0.33–2.76
ER[b] status		
Positive vs. negative	0.37	0.15–0.96*
PR[c] status		
Positive vs. negative	0.47	0.21–1.05**
Method of diagnosis		
Symptoms vs. Screening	0.96	0.64–1.45

This analysis is based on 58 DM and 118 non-DM patients and the number of matched sets was 54 for Stage and histology, 51 for T, 52 for ER and grade and 47 for PR.
a BMI, body mass index.
b ER, oestrogen receptor.
c PR, progesterone receptor.
* $P < 0.05$.
** $P = 0.06$.

cancer among diabetic patients was more often ER and PR negative. Analysis of mode of treatment revealed that similar treatment was given to diabetic and non-diabetic breast cancer patients.

Diabetes can change breast cancer characteristics and outcome either directly through biological mechanisms or indirectly, by influencing screening utilization and treatment allocation. Biological mechanisms that may contribute to the direct adverse effects of diabetes mellitus on breast cancer include; altered endogenous sex-hormone regulation, activation of the IGF signalling pathway and activation of the insulin-signalling pathway.[12] Post-menopausal obesity, a frequent finding among diabetes patients, is associated with increased adipocytes production of estradiol together with decreased liver production of sex-hormone binding globulins.[13] These changes result in high circulating levels of free estradiol, which is strongly associated with breast cancer risk.[22] Similar changes of sex hormones and sex hormone-binding globulin levels are found in diabetic women and remain significant even after adjustment for obesity.[23] As diabetes was associated with low expression of ER and PR, other pathways, such as the IGF and the insulin pathway, may also play an important role in the pathogenesis of breast cancer among diabetic patients. High circulating levels of IGF-1 is a known risk factor for breast cancer.[24] However, as IGF-1 is mainly associated with pre-menopausal breast cancer and as IGF-1 and 2 are not elevated in type 2 diabetes, the contribution of the IGF pathway to the effects of diabetes on breast cancer is probably small.[25,26] On the other hand, recent data suggest an important role for the insulin pathway in the pathogenesis of breast cancer. Insulin is able to directly affect proliferation of breast cancer cells,[27] insulin receptor content is high in human breast cancer[28] and insulin receptor expression is associated with worse prognosis among breast cancer patients.[29] While high insulin receptor content was found to be associated with expression of ER, most ER-negative tumours also express high levels of it.[28] In a recent study, Goodwin and colleagues showed that serum insulin levels were correlated with BMI and both were associated with worse outcome in 512 early-stage breast cancer women.[30] Importantly, insulin remained associated with worse outcome even after adjustment for BMI.[30] Thus, high insulin levels may be the major link between type 2 diabetes mellitus and breast cancer and may explain the association between diabetes and low expression of hormone receptors, as found in this study.

Several studies have shown that older age and co-morbidity reduce the likelihood of breast cancer patients to receive standard of care.[17,31–33] In our study, both groups received overall similar treatment which was in accordance with accepted guidelines[34]: 94% of all ER/PR positive patients were treated with adjuvant hormone therapy, more than 60% had breast conserving surgery and 40% of the patients were treated with chemotherapy.

Data regarding breast cancer screening utilization was not collected in this study. However, as all Israeli women aged 50–70 are invited to attend a free breast cancer screening mammography, regardless of co-morbidity, and, as no differences in mode of diagnosis were noted between the study groups, mode of diagnosis is also probably not a major confounding factor in this study. These results are in accordance with those of a study from the UK, in which diabetes mellitus did not affect the attendance to a free and invited breast cancer screening program.[15] In another study, from the United States, diabetic patients were less likely to use mammography as a diagnostic procedure.[16] However, in this study the screening was neither invited nor free of charge.[16]

As the diagnosis of diabetes mellitus was obtained retrospectively from medical records, and as the diagnosis of diabetes was based on patients' history, it is possible that some diabetic patients were misclassified as non-diabetes. However, such misclassification, if occurred, could only decrease the differences between both study groups. No differences in age, parity, country of origin and co-morbidity other then diabetes were noted between the study groups. Moreover, the rate of older patients (>65 years) in our study was similar to that of the general Israeli breast cancer patients' population (15% vs. 16%, respectively; Israel National Cancer Registry) and the co-morbidity scores were similar to those reported in the literature.[20]

Thus, our results indicate that type 2 diabetes mellitus may adversely alter the presentation of breast cancer and is associated with negative prognostic factors. Moreover, these biologic associations between diabetes mellitus and breast cancer seem to be independent of obesity. Better insight into the biological processes that are involved in breast cancer arising in diabetic patients may help us understand the

possible role of insulin in breast tumorigenesis and may lead to an improved therapeutic strategy.

Conflict of interest statement

The authors have no conflict of interest to disclose.

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