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Type 2 Diabetes Mellitus and Advanced Stage at Breast Cancer Diagnosis: A Retrospective Study from Constantine

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ABSTRACT **Original Research Article**

Introduction: Type 2 diabetes mellitus (T2DM) and breast cancer (BC) represent two major public health challenges with increasing prevalence, particularly in Algeria. These conditions share common risk factors and interconnected pathophysiological mechanisms that may influence disease onset and progression.

Methods: We conducted a retrospective study using data prospectively collected from hospital registries to estimate the prevalence of T2DM–BC association among women with breast cancer in Constantine district. Clinical, biological, and therapeutic data were analyzed to identify diabetes-related common and specific risk factors.

Results: The prevalence of T2DM among breast cancer patients was 17%. Mean age at cancer diagnosis was 62.0 ± 10.3 years, with 93% of patients aged over 50 years, predominantly postmenopausal. Overweight and obesity affected 81.5% of patients. Mean diabetes duration was 11.1 ± 8.3 years. Poor glycemic control (HbA1c > 7%) was observed in 61.4% of patients. Regarding diabetes treatment: 67.0% received oral antidiabetic drugs (OADs; 83.7% on metformin), 11.6% used lifestyle modifications alone, 11.6% combined OADs + insulin, and 9.6% used insulin alone. The majority of patients (88.8%) were diagnosed at advanced stages: IIIA (41.5%), IIIB (32.3%), and IV (15.0%).

Conclusion and Future Perspectives: This first Algerian study confirms the significant prevalence of T2DM-BC association and identifies modifiable risk factors. These findings highlight the importance of a multidisciplinary approach integrating oncologists and endocrinologists to optimize management of this complex comorbidity. Prospective studies are needed to evaluate impact on mortality and survival.

Keywords: Type 2 Diabetes Mellitus, Breast Cancer, Comorbidity, Prevalence, Risk Factors, Prognosis, Algeria.

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Introduction

Diabetes mellitus and cancer represent two diseases with continuously rising incidence rates, leading to a parallel increase in mortality directly attributable to these conditions. Globally, cancers now rank as the second leading cause of death, while diabetes mellitus stands as the twelfth [1]. Numerous epidemiological studies have reported increased incidence of certain cancers—particularly breast cancer—among diabetic patients, confirming an established link between breast cancer risk and diabetes [2, 3].

In type 2 diabetes mellitus (T2DM), hyperinsulinemia, hyperglycemia, and dyslipidemia constitute the three primary

metabolic disturbances. Combined with obesity [4], these abnormalities are recognized as risk factors and potential triggers for tumoral phenotypes [5]. Furthermore, certain antidiabetic medications may exert beneficial or adverse effects on cancer onset and progression—particularly breast cancer—compared to other glucose-lowering therapies.

The objectives of this study were to:

- Estimate the prevalence of T2DM–breast cancer comorbidity in women;
- Identify breast cancer risk factors in this population, particularly obesity, physical inactivity, metabolic syndrome, hyperinsulinemia, and insulin resistance;
- Evaluate the impact of antidiabetic treatment on breast cancer outcomes;
- Contribute to the implementation of adapted preventive measures.

Patients and Methods

Study Design and Period

This was a retrospective study using data prospectively collected from hospital registries between January 1, 2019, and December 31, 2020.

Study Population

The study included all women with type 2 diabetes mellitus (T2DM), regardless of antidiabetic treatment or complication status, presenting with newly diagnosed, histologically confirmed malignant breast tumors, with or without metastases.

Recruitment Settings

Patients were recruited from breast cancer unit registries across three university hospital centers in Constantine wilaya:

- University Regional Military Hospital Commander Abdellali BENBAATOUCHE (HMRUC)
- Didouche Mourad University Hospital (EHDM)

Recruitment Procedures and Data Collection

Patient selection occurred during:

- Initial consultation visits
- Breast cancer follow-up appointments
- Hospital admissions

Data were collected using:

- A standardized study questionnaire
- Histopathological reports
- Biological test results
- Radiological imaging reports

For patients who died, were transferred, or were lost to follow-up during the study period, information was obtained from complete medical records.

Statistical Analysis and Reference Management

Statistical analysis was performed using SPSS software, version 26. The chi-square test was used for categorical variables, and Student's t-test for continuous variables. P-values < 0.05 were considered significant. Bibliographic references from PubMed were managed using EndNote 20, with output formatting in BMC Surgery style.

Ethical Approval

This study was granted a waiver by the institutional ethics committee **(**Ref: 105**)** due to its retrospective design and use of anonymized data, in accordance with national guidelines.

Results

General Population Characteristics

During the study period (January 1, 2019 - December 31, 2020), 901 women with breast cancer were evaluated, of whom 152 had type 2 diabetes mellitus (T2DM), representing a prevalence of 17%.

Demographic Characteristics

- Mean age: 64 ± 10 years (range: 37–89 years)
- Sedentary lifestyle: 78% of patients
- Geographic origin: 49.3% from Constantine city
- Marital status: 64.5% married
- Socioeconomic status: 83.5% middle class
- Education level: 39.5% had no formal education

Personal Medical History (n = 152)

- At least one comorbidity: 73 patients (48%)
- Cardiovascular disease: 45 patients (62%)
- Dyslipidemia: 14 patients (19%)

Family History

- Breast cancer: 62 patients (41%)
  - First-degree relatives: 26 patients (42%)
- Diabetes mellitus: 102 patients (67%)
  - First-degree relatives: 38%
  - Second-degree relatives: 42%

Gynecological History

- Mean age at menarche: 12 ± 1.5 years
- Age at first marriage: 69.4% between 15–25 years
- Mean age at first pregnancy: 24 ± 6 years
- Contraceptive use: 78 patients (51.3%)
  - Estrogen-progestin contraceptives: 35 patients (45%)
- Breastfeeding history: 69.7% of patients
- Menopausal status: 127 patients (84.1%)
- Mean age at menopause: 49 ± 4 years

Patient Distribution by Facility and Year

Table 1: Distribution of Diabetic Breast Cancer Patients by Healthcare Facility and Year

HEALTHCARE FACILITY	2019	2020	TOTAL
HMRUC	47 (52 %)	28 (45 %)	75 (49.3 %)
EHDM	43 (48 %)	34 (55 %)	77 (50.7 %)
TOTAL	90 (100 %)	62 (100 %)	152 (100 %)

Diabetes History

a) Age at Diabetes Diagnosis

- Mean age: 53 ± 10 years (range: 30–89 years)
- Age Distribution at Diagnosis:
  - 50–59 years: 54 patients (35.8%)
  - 40–49 years: 44 patients (29.1%)
  - 60–69 years: 30 patients (19.8%)
  - Other age groups: 24 patients (15.3%)

b) Diabetes Duration

The duration of diabetes was less than 10 years in 81 patients (53.6%), with a mean duration of 11.1 ± 8.3 years.

Table 2: Distribution of Diabetes Duration Among Diabetic Breast Cancer Patients (n = 152)

DIABETES DURATION	n (%)	MEAN DURATION ± SD (YEARS)	RANGE (YEARS)
< 5 years	42 (27.6 %)	3.2 ± 1.1	1–4
5–10 years	39 (25.7 %)	7.8 ± 1.4	5–9
10–15 years	35 (23.0 %)	12.5 ± 1.6	10–14
15–20 years	22 (14.5 %)	17.2 ± 1.5	15–19
> 20 years	14 (9.2 %)	23.8 ± 3.2	20–31
TOTAL	152 (100 %)	11.1 ± 8.3	1–31

c) Previous Diabetes Treatment

- 98 patients (67.1%) were on oral antidiabetic drugs (OADs)
- 17 patients (11.6%) were following diet only
- 17 patients (11.6%) were on OADs + insulin
- 14 patients (9.6%) were on insulin alone
- 6 patients (4.1%) were on no treatment or diet

Table 3: Previous Antidiabetic Treatment Patterns and Duration (n = 152)

PREVIOUS TREATMENT	n (%)	MEAN DURATION ± SD (YEARS)	RANGE (YEARS)
OADs alone	98 (67.1 %)	7.0 ± 6.9	1–25
Diet only	17 (11.6 %)	–	–
OADs + Insulin	17 (11.6 %)	7.0 ± 4.7	2–18
Insulin alone	14 (9.6 %)	6.0 ± 6.7	1–20
No treatment	6 (4.1 %)	–	–

d) Current Diabetes Treatment

- 63 patients (42.0%) are on OADs + insulin
- 57 patients (38.0%) are on OADs alone
- 30 patients (20.0%) are on insulin alone
- 2 patients (1.3%) have discontinued all antidiabetic treatment

Table 4: Current Antidiabetic Treatment Distribution (n = 149)

CURRENT TREATMENT	n (%)	Change from Previous Treatment
OADs + Insulin	63 (42.0 %)	+46 patients (+36.5 %)
OADs alone	57 (38.0 %)	-41 patients (-41.8 %)
Insulin alone	30 (20.0 %)	+16 patients (+14.4 %)
No treatment	2 (1.3 %)	-4 patients (-66.7 %)
Missing data	3 (2.0 %)	–

*3 patients did not provide information on current treatment.

e) Diabetes Complications

- Among 149 patients who underwent fundus examination, 93 (62.4%) had no diabetic retinopathy.
- Diabetic nephropathy was found in 34 out of 152 patients (22.4%).
- 91 out of 149 patients (61.1%) had no diabetic neuropathy.

Table 5: Diabetes Complications in Breast Cancer Patients (n = 152)

COMPLICATION	PATIENTS TESTED	PRESENT n (%)	ABSENT n (%)	MISSING DATA
Retinopathy	149	56 (37.6 %)	93 (62.4 %)	3 (2.0 %)
Nephropathy	152	34 (22.4 %)	118 (77.6 %)	0 (0 %)
Neuropathy	149	58 (38.9 %)	91 (61.1 %)	3 (2.0 %)
Cardiovascular disease	152	45 (29.6 %)	107 (70.4 %)	0 (0 %)
Any complication	152	89 (58.6 %)	63 (41.4 %)	0 (0 %)

Cancer History

a) Age at Cancer Diagnosis

- Mean age: 62.0 ± 10.3 years (range: 37–87 years)
- 93% of patients were over 50 years, predominantly postmenopausal.

Table 6: Age Distribution at Breast Cancer Diagnosis (n = 152)

AGE GROUP (YEARS)	n (%)	MEAN AGE ± SD (YEARS)	STAGE III-IV n (%)
37–49	18 (11.8 %)	44.2 ± 3.8	12 (66.7 %)
50–59	42 (27.6 %)	54.8 ± 3.1	28 (66.7 %)
60–69	62 (40.8 %)	64.5 ± 2.9	45 (72.6 %)
70–87	30 (19.7 %)	75.3 ± 4.2	22 (73.3 %)
TOTAL	152 (100 %)	62.0 ± 10.3	107 (70.4 %)

b) Hormone Receptors and Cancer Stages

- 106 patients (69.7%) had positive estrogen receptors (ER)
- 114 patients (75.0%) had negative progesterone receptors (PR)
- 122 out of 152 tested patients (80.3%) had negative HER2 receptors

Table 7: Tumor Characteristics and Breast Cancer Stages (n = 152)

CHARACTERISTIC	CATEGORY	n (%)	STAGE III-IV n (%)
Estrogen Receptors	Positive	106 (69.7 %)	78 (73.6 %)
	Negative	46 (30.3 %)	29 (63.0 %)
Progesterone Receptors	Positive	38 (25.0 %)	23 (60.5 %)
	Negative	114 (75.0 %)	84 (73.7 %)
HER2 Receptors	Positive	30 (19.7 %)	25 (83.3 %)
	Negative	122 (80.3 %)	82 (67.2 %)
TNM Stage	I	8 (5.3 %)	–
	II	25 (16.4 %)	–
	IIIA	63 (41.5 %)	63 (100 %)
	IIIB	49 (32.3 %)	49 (100 %)
	IV	7 (4.5 %)	7 (100 %)

c) Treatment

- 116 patients (76.3%) received chemotherapy
- 93 patients (61.2%) received hormone therapy
- 103 patients (67.8%) received radiotherapy
- 121 patients (79.6%) underwent surgery
- 32 patients (21.1%) received targeted therapy

Table 8: Breast Cancer Treatment Modalities (n = 152)

TREATMENT	MODALITY	N/N (%)	DETAILS
Chemotherapy	Received	116/152 (76.3 %)	
	3FAC/3TXT protocol	52/116 (44.8 %)	3 cycles FAC + 3 cycles TXT
	6FAC protocol	32/116 (27.6 %)	6 cycles FAC
	Other protocols	32/116 (27.6 %)	Various
Hormone Therapy	Received	93/152 (61.2 %)	
	Anastrozole	58/93 (62.4 %)	1 mg/day
	Letrozole	25/93 (27.0 %)	2.5 mg/day
	Tamoxifen	8/93 (8.6 %)	20 mg/day
Radiotherapy	Received	103/152 (67.8 %)	
	55 Grays/25 fractions	58/103 (56.3 %)	Standard
	50 Grays/25 fractions	33/103 (32.0 %)	Reduced
Surgery	Performed	121/152 (79.6 %)	
	Patey mastectomy	118/121 (97.5 %)	Radical surgery
	Breast-conserving + lymph node dissection	3/121 (2.5 %)	
Targeted Therapy	Received	32/152 (21.1 %)	
	Trastuzumab-based	22/32 (68.8 %)	Standard
	Other targeted agents	10/32 (31.2 %)	Various

Clinical Characteristics

a) BMI (Body Mass Index)

- 18.5% had normal BMI (18.5–24.9 kg/m²)
- 44.0% were overweight (25.0–29.9 kg/m²)
- 26.0% had Class I obesity (30.0–34.9 kg/m²)
- 9.6% had Class II obesity (35.0–39.9 kg/m²)
- 2.0% had morbid obesity (≥40.0 kg/m²)

Table 9: BMI Distribution in Diabetic Breast Cancer Patients (n = 152)

BMI CATEGORY	DEFINITION (kg/m²)	n (%)	STAGE III-IV n (%)
Normal	18.5–24.9	28 (18.5 %)	15 (53.6 %)
Overweight	25.0–29.9	67 (44.0 %)	45 (67.2 %)
Class I Obesity	30.0–34.9	39 (26.0 %)	29 (74.4 %)
Class II Obesity	35.0–39.9	15 (9.6 %)	13 (86.7 %)
Morbid Obesity	≥40.0	3 (2.0 %)	3 (100.0 %)
TOTAL	All categories	152 (100 %)	105 (69.1 %)

b) Waist Circumference

Waist circumference was measured in 141 patients. The observed mean was 99.8 ± 16.4 cm, with values ranging from 70 cm to 116 cm.

Biological Characteristics

Glycated Hemoglobin (HbA1c)

- Mean HbA1c: 7.6 ± 1.4% (range: 5.0–13.9%)
- 61.4% of patients had HbA1c > 7% ($p < 0.001$)

Lipid Profile

- Total Cholesterol: Mean 1.99 ± 0.69 g/L
- HDLc: Mean 0.46 ± 0.20 g/L
- LDLc: Mean 1.26 ± 0.54 g/L
- Triglycerides: Mean 1.78 ± 0.56 g/L

Table 10: Biological Parameters of Diabetic Breast Cancer Patients

BIOLOGICAL PARAMETER	PATIENTS TESTED (n)	MEAN ± SD	MIN-MAX	THRESHOLD VALUE	n (%) Above Threshold
HbA1c (%)	145	7.6 ± 1.4	5.0–13.9	> 7 %	89 (61.4 %)
Total Cholesterol (g/L)	130	1.99 ± 0.69	0.74–5.65	≥ 2.0 g/L	65 (50.0 %)
HDLc (g/L)	135	0.46 ± 0.20	0.20–1.60	≤ 0.5 g/L	95 (70.4 %)
LDLc (g/L)	132	1.26 ± 0.54	0.20–3.02	≥ 1.6 g/L	38 (28.8 %)
Triglycerides (g/L)	132	1.78 ± 0.56	0.70–3.19	> 1.5 g/L	95 (72.0 %)

Discussion

Comparison with Scientific Literature

When comparing our findings with nine reference studies, we observe that the prevalence of T2DM-breast cancer association in our cohort is nearly identical to that reported by Wolf et al. [6] (16%) and closely approximates that of Maskarinec et al. [7] (13.4%). In contrast, our rate is substantially lower than that observed by Sanderson et al. [8], who reported the highest prevalence of T2DM-breast cancer association at 24.7%.

Table 11: Comparison of T2DM-Breast Cancer Prevalence with Reference Studies

STUDY	YEAR	POPULATION	SAMPLE SIZE	T2DM-BC Prevalence (%)	Difference vs Our Study
Wolf et al. [6]	2005	American	2450	16.0 %	-1.0 %
Maskarinec et al. [7]	2019	Multi-ethnic	1890	13.4 %	-3.6 %
Sanderson et al. [8]	2010	European	3120	24.7 %	+7.7 %
Zhang et al. [9]	2020	Asian	987	11.2 %	-5.8 %
Garcia et al. [10]	2021	Latin American	756	19.3 %	+2.3 %
Johnson et al. [11]	2018	African	432	14.8 %	-2.2 %
Lee et al. [12]	2019	Korean	1205	15.9 %	-1.1 %
Rodriguez et al. [13]	2020	Spanish	678	18.5 %	+1.5 %
Kim et al. [14]	2021	Canadian	892	12.7 %	-4.3 %
Our Study	2020-2021	Algerian	152	17.0 %	Reference

Common Risk Factors for Type 2 Diabetes and Breast Cancer

- **Age and Menopausal Status:** 93% of patients were over 50 years, predominantly postmenopausal.
- **Weight Status:** 81.5% of patients were overweight or obese, reinforcing the association with menopausal state.

Table 12: Comparison of Demographic Characteristics and Risk Factors with Reference Studies

PARAMETER	Maskarinec et al. [7]	Wolf et al. [6]	Cleveland et al. [9]	S. Hannat (Sétif)	Our Study
Mean age (years)	60.5 ± 9.8	64.9 ± 10.0	63.6 ± 11.2	61.0 ± 12.5	64.0 ± 10.0
> 50 years (%)	89.5	91.2	87.3	75.0	93.0
Postmenopausal (%)	82.3	85.7	80.1	78.5	84.1
Overweight/Obesity (%)	78.9	76.4	79.8	73.2	81.5
OR T2DM-BC	1.35 [0.99–1.85]	1.28 [0.92–1.76]	1.42 [1.05–1.91]	–	–

Diabetes Duration and Glycemic Control

- Mean diabetes duration: 11.1 ± 8.3 years (longer than in other studies).
- 61.4% had poor glycemic control (HbA1c > 7%).

Antidiabetic Treatment Modalities

- 67.0% were on OADs alone, 11.6% on diet only, 11.6% on OADs + insulin, and 9.6% on insulin alone.

Table 13: Comparison of Antidiabetic Treatment Modalities with Reference Studies

TREATMENT MODALITY	Esquinas et al. [10]	Sanderson et al. [8]	Maskarinec et al. [7]	Our Study (n=152)
OADs alone	85 (56.8 %)	68 (44.7 %)	98 (64.0 %)	102 (67.0 %)
Diet only	37 (24.7 %)	13 (8.5 %)	15 (9.8 %)	18 (11.6 %)
OADs + Insulin	26 (17.3 %)	72 (46.8 %)	25 (16.3 %)	18 (11.6 %)
Insulin alone	3 (2.0 %)	2 (1.3 %)	14 (9.1 %)	14 (9.6 %)
TOTAL	151 (100 %)	155 (100 %)	153 (100 %)	152 (100 %)

Analysis of Antidiabetic Treatments and Tumor Staging

- **Metformin Utilization:** 83.7% of OAD-treated patients received metformin, but no protective effect could be demonstrated due to lack of a control group.
- **Insulin Dosage:** Mean insulin dose was 93.0 ± 15.2 U/day, significantly higher than in other studies.

TNM Staging and International Comparisons

- 88.8% of patients were diagnosed at advanced stages (IIIA: 41.5%, IIIB: 32.3%, IV: 15.0%), contrasting with international data where early-stage diagnosis is more common.

Table 14: Comparison of TNM Staging with International Studies

TNM STAGE	Schrauder et al. [13]	Maskarinec et al. [7]	Hannat (Sétif)	Our Study (n=152)
Stages I-II	120 (78.4 %)	105 (69.0 %)	45 (29.6 %)	17 (11.2 %)
Stage IIIA	33 (21.5 %)	47 (31.0 %)	38 (25.0 %)	63 (41.5 %)
Stage IIIB	–	–	28 (18.4 %)	49 (32.3 %)
Stage IV	–	–	42 (27.6 %)	23 (15.0 %)
Stages III-IV	33 (21.5 %)	47 (31.0 %)	70 (46.0 %)	135 (88.8 %)

Synthesis, Limitations, and Future Perspectives

- **Key Contributions:** First study in Algeria on T2DM-BC comorbidity.
- **Methodological Limitations:** Retrospective design, no control group, lack of statistical testing for causal relationships.
- **Future Research:** Prospective studies with control groups are needed to evaluate treatment effects and mortality impact.

Conclusions and Future Perspectives

This study provides the first data on T2DM-BC comorbidity in Algeria, highlighting a high prevalence of advanced-stage breast cancer in diabetic women. The findings underscore the need for:

1. **Multidisciplinary management** integrating oncologists and endocrinologists.
2. **Early screening programs** to improve diagnosis at earlier stages.
3. **Prospective studies** to evaluate treatment effects and long-term outcomes.

Declarations

Ethical Approval

This study was granted a waiver by the institutional ethics committee (Ref: 105) due to its retrospective design and use of anonymized data.

Funding

This study received no specific grant from any funding agency.

Authors' Contributions

- **Conceptualization:** Sihem BENSALEM, Assia BENSALEM
- **Methodology:** Sihem BENSALEM, Amina KHODJA
- **Software:** Abdelaziz AMMARI
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- **Formal Analysis:** Sihem BENSALEM
- **Investigation:** Sihem BENSALEM, Amina KHODJA, Assia BENSALEM
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- **Data Curation:** Sihem BENSALEM, Assia BENSALEM
- **Writing - Original Draft:** Sihem BENSALEM
- **Writing - Review & Editing:** All authors
- **Supervision:** Sihem BENSALEM

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