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ORIGINAL PAPER

Female Sexual Dysfunction in Subjects with Type 2 Diabetes Mellitus

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Abstract

The correlation of female sexual dysfunction (FSD) with the degree of glycemic control, the duration and complications of diabetic disease and cardiovascular risk factors are not so clear. The aim of this study was to assess the prevalence of FSD in a sample of females with type 2 diabetes mellitus (T2DM), and to identify factors involved in its pathogenesis. We enrolled 81 females who have T2DM. We administered the female sexual function index (FSFI), self-rating anxiety scale (SAS) and self-rating depression scale (SDS) questionnaires. We also estimated anthropometric parameters, glyco-metabolic control, comorbidities, autonomic nervous system assessment, some adipocytokines and ongoing therapy. 87% of participants were affected by FSD. There was evidence of an inverse correlation between the total score of the FSFI questionnaire and the mean of the values of HbA_{1c} in the previous years. There was an inverse correlation with the duration of diabetes and homeostasis model assessment of insulin resistance index in participants not affected by FSD. Participants with FSD have a higher prevalence of anxiety ($p=0.043$) and participants with depression and ischemic heart disease scored less on the FSFI questionnaire ($p=0.005$ and $p=0.010$, respectively). Homocysteine and E-selectin values were higher in participants with FSFI ($p=0.002$, and $p=0.017$, respectively). Most of the enrolled females with T2DM had FSD. Glycemic control, ischemic heart disease, endothelial dysfunction, autonomic neuropathy, and psychological conditions, such as anxiety and depression, seem to have a close correlation with FSD. An early diagnosis of FSD can help to improve not only participants' quality of life, but also to early identify and treat risk factors related not only to FSD, but also to cardiovascular risk. Therefore, we highly recommend that clinicians have a high index of suspicion for FSD in females with T2DM.

Keywords Females · Italy · Sexual dysfunction · Type 2 diabetes mellitus

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Introduction

Female sexual dysfunction (FSD) is a multifactorial medical problem affecting both biological and psychological areas [1]. A link between type 2 diabetes mellitus (T2DM) and sexual dysfunction has been known since the 10th century when the Persian physician and philosopher Avicenna spoke of "collapse of sexual function" as a complication of diabetic pathology. However, the search for this connection did not start until about 1950, and the studies were conducted mainly in the male gender. Studies about the FSD were neglected until 1971, when Kolodny published a first work on this issue [2]. Like males, females with T2DM are equally likely to develop complications of the disease, including sexual dysfunction. There is evidence that male erectile dysfunction is an early sign of silent coronary artery disease [3]. For this reason, we hypothesize that FSD can be an early sign of coronary artery disease for females.

The prevalence of FSD is about 20–80% in females with T2DM compared to about 40% of the general female population [4].

Maiorino et al. [5] showed that a normal response to sexual stimuli requires the integrity of the sensory and autonomic nervous system, with consequent smooth muscle release and increased blood flow in the female genitals. Pathologically, T2DM leads to FSD through hyperglycemia, vasculopathy and neuropathy. Hyperglycemia leads to a reduction in the hydration of the membranes, including the vaginal tissues, with consequent reduction of lubrication and development of dyspareunia with infections [6]. Vascular alterations, caused by atherosclerosis and microangiopathy, cause endothelial dysfunction [7, 8]. Finally, diabetic neuropathy alters the normal perception of sexual stimuli and the consequent response [9].

However, the correlation between FSD and the degree of glycemic control, the duration and complications of diabetic disease and cardiovascular risk factors are not so clear. In literature, there is still a lack of evidence, with conflicting data on which parameter correlate [10], or not [11] with FSD. On this basis, the primary aim of this study was to assess the prevalence of FSD in a sample of females with T2DM. The secondary aim was to evaluate if there is a correlation between FSD, and glycemic control, ischemic disease, endothelial dysfunction, autonomic neuropathy, and psychological conditions.

Materials and Methods

Study Design

This observational study was conducted at the outpatient clinic for the cure of Diabetes and Metabolic Diseases of the Department of Internal Medicine and Therapeutics, University of Pavia, Pavia (Italy), and Fondazione IRCCS Policlinico San Matteo, Pavia (Italy).

All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all participants for being included in the study. Trial registration: ClinicalTrials.gov NCT01896648.

Participants

Participants were selected among females referred to our center and identified during routine visits and or through a search of the electronic database of our clinic. We enrolled 81 females aged ≥ 18 years affected by T2DM according to the European Society of Cardiology (ESC) and European Association for the study of Diabetes (EASD) guidelines criteria. Exclusion criteria was type 1 diabetes mellitus or latent autoimmune diabetes in adults (LADA), previous uterine and/ or ovarian surgery and use of hormone replacement therapy (HRT).

Assessments

Participants underwent an initial evaluation that included personal anamnesis and identification of the presence of factors associated with FSD including age, T2DM duration and its complications, glycemic control, hypertension and anti-hypertensive drugs, smoking status and alcohol use. Participants also underwent a physical examination to assess the presence of distal neuropathy and autonomic disorders. Then, these participants underwent the modified Neuropathy Disability Score (NDS), Neuropathy System Score (NSS) and several test such as lying to standing, Valsalva test, deep breathing, and orthostatic blood pressure measurement. We self-submitted participants the Female Sexual Function Index (FSFI) questionnaire to assess the presence of FSD and the evaluation of determinants of the sexual sphere (desire, excitement, lubrication, satisfaction, pain, and orgasm). We also administered the Self Rating Anxiety Scale (SAS) questionnaire and the Self Rating Depression Scale (SDS) questionnaire. All of these were validated in Italian language. We also assessed body weight and body mass index (BMI), waist, abdominal, and hip circumferences, systolic blood pressure (SPB), diastolic blood pressure (DBP), ankle brachial index (ABI), heart rate, glycated hemoglobin (HbA_{1c}) and its mean in the previous years, fasting plasma glucose (FPG), capillary pre- and post-prandial glycemia, fasting plasma insulin (FPI), homeostasis model assessment of insulin resistance index (HOMA-IR), total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), triglycerides (Tg), homocysteine, lipoprotein(a) [Lp(a)], plasminogen activator inhibitor-1 (PAI-1), soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), E-selectin, metalloproteinase 2 and 9, high sensitivity-reactive C protein (Hs-CRP). All blood parameters were determined after a 12-h overnight fast except for capillary post-prandial glycemia, determined 2 h after a standardized meal. Venous blood samples were taken for all participants between 08.00 and 09.00 and were drawn from an antecubital vein with a 19-gauge needle without venous stasis. We used plasma obtained by addition of Na2-EDTA, 1 mg/ml, and centrifuged at 3000 g for 15 min at 4 8 C. Immediately after centrifugation, the plasma samples were frozen and stored at −80 °C for no more than 3 months. All measurements were performed in a central laboratory. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Blood pressure measurements were obtained from each participant (using the right arm) in the seated position, using a standard mercury sphygmomanometer (GEIMA) (Korotkoff I and V) with a cuff of appropriate size. Blood pressure was measured by the same investigator, in the morning, after the participant had rested for ≥ 10 min in a quiet room. Three successive blood pressure readings were obtained at 1-min intervals, and the mean of the 3 readings was calculated. Capillary pre- and post-prandial

glycemia were measured using the FreeStyle Freedom Lite1 Blood Glucose Monitoring System (Abbott Laboratories, Abbott Park, Illinois, U.S.A.). For a description of how various laboratory parameters were assessed, see our previous work [12].

Questionnaires

The FSFI is a validated questionnaire of 19 items grouped in 6 domains: desire, excitation, lubrication, satisfaction, orgasm and pain to assess the presence of FSD. In the FSFI the score for each item ranges from 0, or 1, to 5 and a total score ≤ 26.55 is suggestive for FSD. The SAS questionnaire quantifies level of anxiety. SAS is a validated 20 item self-report assessment device which include measures of state and trait anxiety. Each question is scored on a scale of 1–4; a total score > 44 is suggestive for anxiety. The SDS questionnaire quantifies level of depression. There are 20 items that rate the four common characteristics of depression: the pervasive effect, the physiological equivalents, other disturbances, and psychomotor activities. Each question is scored on a scale of 1 through 4 and a total score > 49 is suggestive for depression.

Statistical Analysis

Quantitative data were expressed, if normally distributed, as mean and standard deviation (Shapiro test), median and interquartile range if not normally distributed. The qualitative variables were described as counts and percentage. The comparison of quantitative variables between two groups was performed with the Student *t* test; the *chi-square* test was used for comparisons among qualitative variables. The connection among quantitative variables were analyzed whit Pearson correlation coefficient [r]. All tests were two-tails, and the limit of significance was 5% ($p < 0.05$). Analysis was made using the software STATA (version 14.0) (Stata Corporation, 2016, 4905 Lakeway Drive, College Station, Texas 77,485, USA).

Results

Study Sample and FSD Prevalence

Of the 81 enrolled participants, 4 did not complete all the study scheduled procedures leaving 77 participants in the final analysis, 67 (87%) with FSD and 10 (13%) without FSD. The average age of the overall sample was 58.72 ± 9.73 years, 54.8 ± 9.18 years for the participants without FSD, and 59.31 ± 9.73 years for the participants with FSD.

Concomitant Diseases

Comparing the group with and without FSD, there was a significant difference regarding anxiety, with higher prevalence in the group affected by FSD ($p = 0.043$). There was no difference between two groups regarding depression or other diseases. However, when we stratified the sample according to the presence or absence of a certain disease and analyzed the general FSFI score obtained at the questionnaire, we noticed that participants affected

Table 1 Concomitant diseases

	Median FSFI score		*p* value
	Participants without the disease	Participants with the disease	
Obesity, [RI]	12 [4.20–21.70]	8.75 [3.60–25.50]	0.723
Hepatic steatosis, [RI]	9.70 [3.60–21.70]	9.30 [3.60–25.30]	0.400
Dyslipidemia, [RI]	17 [5.20–23.70]	9.30 [3.60–23.70]	0.611
Ischemic heart disease, [RI]	**13.70 [4.20–24.55]**	**3.60 [3.60–4]**	**0.010**
Hyperuricemia, [RI]	9.30 [3.60–23.60]	16.55 [7.25–26.45]	0.219
Hypertension, [RI]	20 [5–24.50]	7.70 [3.60–23.70]	0.183
Gastroesophageal reflux, [RI]	9.30 [3.80–22.85]	23.80 [3.40–26.40]	0.639
Chronic renal failure, [RI]	12.45 [3.60–23.75]	6.80 [4–8.20]	0.444
Microalbuminuria, [RI]	8.20 [3.60–23.90]	11.40 [4–22.45]	0.852
Diabetic retinopathy, [RI]	9.30 [3.50–23.40]	19 [4.20–25.50]	0.279
Neuropathy, [RI]	10.65 [3.60–23.80]	6.60 [4.40–22.60]	0.873
Arteriopathy, [RI]	8.75 [3.60–23.60]	16.70 [4–26.10]	0.394
Cerebrovascular diseas, [RI]	9.30 [3.60–23.80]	13.90 [3.40–22.60]	0.905
Menopause, [RI]	13.20 [5.20–25.20]	9.30 [3.60–23.60]	0.575
Alcohol, [RI]	9.30 [4–23.80]	12.75 [3.40–23.10]	0.597
Anxiety*, [RI]	**15.55 [4.50–23.85]**	**4.20 [3.40–12.90]**	**0.029**
Depression°, [RI]	**14.10 [4.20–25.20]**	**3.90 [2–7.70]**	**0.005**
Neuropathy§, [RI]	5.40 [3.20–23.60]	12.90 [4.20–23.80]	0.399
Neuropathy^, [RI]	7.55 [3.60–23.90]	12 [4.80–23.60]	0.420
Orthostatic hypotension, [RI]	13.7 [4.20–23.80]	4.20 [3.60–14.10]	0.135

Bold indicates statistical significance

Data are expressed as a median of the score obtained in the FSFI questionnaire

[RI]: interquartile range

*: determined by Self-Rating Anxiety Scale

°: determined by Self-Rating Depression Scale

§: determined by modified Neuropathy Disability Score

^: determined by modified Neuropathy Symptom Score

FSFI Female sexual function index

by anxiety, depression and ischemic heart disease obtained a lower FSFI score compared to participants not affected by the diseases (Table 1).

Concomitant Medications

Regarding the drugs taken chronically by the participants, we did not observe any differences when the sample was divided according to the presence or absence of FSD, in particular 60.00% of participants without FSD were taking oral anti-diabetic drugs versus 76.12 in participants with FSD ($p=0.275$); 40.00% of participants without FSD were taking insulin versus 20.90% of participants with FSD ($p=0.230$); 70.00% of participants without FSD were taking hypocholesterolemic agents versus 82.09% of participants with FSD ($p=0.398$). 20.00% of participants without FDS were taking vasodilatators versus

26.87% of participants with FSD ($p=1.000$); 40.00% of participants without FSD were in therapy with ACE-inhibitors versus 67.16% of participants without FSD ($p=0.156$). 20.00% of participants without FSD were taking beta-blockers, versus 32.84% of participants with FSD ($p=0.715$), 20.00% of participants without FSD were taking diuretics versus 35.82% of participants with FSD ($p=0.480$). Finally, 40.00% of participants without FSD, and 55.22% of participants with FSD were taking anti-thrombotic drugs ($p=0.501$). However, stratifying the sample on the assumption or not of a single therapy and evaluating the trend of the total score of the FSFI, we noticed that participants taking beta blockers had a worse performance at FSFI questionnaire with a lower score ($p=0.032$) (Table 2).

Anthropometric Variables

There were no differences in participants with or without FSD regarding anthropometric variables. However, conducting the analysis using the correlation coefficient of Pearson, there was a positive correlation between SBP (r = 0.476) and DBP (r = 0.652) in participants without FSD (Table 3).

Glyco-metabolic Control, Lipid Profile and Homocysteine

The mean values of HbA_{1c}, FPG, capillary pre- and post-prandial glycemia, and FPI were lower in the FSD group (Table 4). These differences were at the limit of significance for FPG, capillary pre- and post-prandial glycemia, and FPI, while the difference between HbA_{1c} values was significant ($7.49 \pm 0.71\%$ in females without FSD versus $6.86 \pm 0.88\%$ in females with FSD, $p=0.035$, respectively). No differences in lipid profile were observed between the group affected by FSD and the other one. Homocysteine value, instead, was higher in females with FSD compared to those without (17.75 ± 5.32 µmol/l versus 12.39 ± 1.98 µmol/l, $p=0.002$, respectively) (Table 4).

Table 2 Concomitant medications

	Median FSFI score		*p* value
	Participants NOT in therapy	Participants in therapy	
Oral anti-diabetic drugs, [RI]	15.50 [5–25.15]	8.20 [3.60–23.60]	0.218
Insulin, [RI]	8.20 [3.60–23.10]	15.95 [4–26.40]	0.300
Hypocholesterolemic drugs, [RI]	19 [5.20–25.20]	8.75 [3.60–23.60]	0.406
Vasodilatators, [RI]	13.90 [4.20–23.70]	4.90 [3.60–23.90]	0.252
ACE-inhibitors, [RI]	17.75 [4.60–24.50]	8.20 [3.60–22.30]	0.423
Beta-blockers, [RI]	**14.10 [4.20–23.90]**	**4.80 [3.20–18.55]**	**0.032**
Diuretics, [RI]	9.30 [3.60–23.70]	12.75 [3.60–23.90]	0.738
Anti-thrombotic drugs, [RI]	13.50 [4.20–23.80]	9.30 [3.06–23.60]	0.584

Bold indicates statistical significance

Data are expressed as a median of the score obtained in the FSFI questionnaire

[RI]: interquartile range

FSFI Female sexual function index

Table 3 Correlation between study parameters and FSFI questionnaire score

	Participants without FSD	Participants with FSD
Age (years)	0.317	−0.195
Duration of T2DM (years)	−0.227	−0.154
Duration of smoke(years)	−0.140	0,054
Weight (Kg)	−0.107	−0,135
Height (cm)	−0.119	−0,296
BMI (kg/m^2)	−0.029	−0.009
Waist circumference (cm)	0.268	−0.066
Abdominal circumference (cm)	0.160	−0.104
Hip circumference (cm)	0.398	−0.072
SBP (mmHg)	**0.476**	−0.200
DBP (mmHg)	**0.652**	−0.032
h (bpm)	0.334	0.201
Right ABI (n)	0.244	−0.026
Left ABI (n)	0.138	0.189

Bold indicates statistical significance

Data are expressed as correlation coefficient based on the score obtained in the FSFI questionnaire: 0–0.2 no correlation

0.2–0.4 weak correlation

0.4–0.75 good correlation

0.75–1 excellent correlation

FSD Female sexual dysfunction

BMI Body mass index, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *ABI* Ankle-brachial index, *T2DM* Type 2 diabetes mellitus

Extending the evaluation to a correlation analysis with the score of the FSFI questionnaire, we found an inverse correlation ($r = -0.413$) with the HbA_{1c} values in participants not affected by FSD; in the same group there were direct correlations with the values of TC ($r = 0.593$), LDL-C ($r = 0.586$) and HDL-C ($r = 0.541$) (Table 5). When evaluating the score of the FSFI questionnaire stratified by the desire, excitement, lubrication, and satisfaction domains, there was an inverse correlation with the values of HbA_{1c}, the duration of T2DM and HOMA-IR in participants not affected by FSD (Table 6)."

Adipocytokines

Participants with FSD had higher levels of E-selectin compared to participants without FSD. No other significant differences were recorded regarding PAI-1, sICAM-1, sVCAM-1, MMP-2, MMP-9, Hs-CPR (Table 7).

Table 4 Glycemic parameters trend and lipid profile parameters

	Participants without FSD	Participants with FSD	*p* value
HbA_{1c} (%)	7.49 ± 0.71	6.86 ± 0.88	0.035
FPG (mg/dl)	146.90 ± 41.20	134.15 ± 38.35	0.334
HbA_{1c} mean (%) 2016 (%)	6.75 ± 0.64	7.01 ± 0.91	0.582
HbA_{1c} mean (%) 2015 (%)	7.12 ± 0.63	6.95 ± 1.04	0.668
HbA_{1c} mean (%) 2014 (%)	**7.54 ± 0.53**	**6.73 ± 0.84**	**0.041**
HbA_{1c} mean (%) 2013 (%)	7.16 ± 0.62	6.94 ± 1.18	0.679
HbA_{1c} mean (%) 2012 (%)	6.68 ± 6.96	6.96 ± 1.08	0.583
Pre-prandial glycemia (mg/dl)	146.10 ± 51.38	126.31 ± 27.36	0.065
Post-prandial glycemia (mg/dl)	177.0 ± 56.19	156.07 ± 30.83	0.080
FPI (µU/ml)	22.70 ± 10.58	20.11 ± 20.40	0.069
HOMA-IR	7.40 [5.23–115]	4.13 [2.47–6.05]	0.234
TC (mg/dl)	166.50 ± 31.49	180.22 ± 44.73	0.353
LDL-C (mg/dl)	89.64 ± 16.70	97.22 ± 37.30	0.530
HDL-C (mg/dl)	47.80 ± 14.48	54.42 ± 17.14	0.250
Tg (mg/dl)	145.30 ± 62.74	141.36 ± 91.44	0.895
Lp(a) (mg/dl)	32.69 ± 17.36	46.51 ± 33.40	0.205
Homocysteine (µmol/l)	**12.39 ± 1.98**	**17.75 ± 5.32**	**0.002**

Bold indicates statistical significance

Data are expressed as median [interquartile range] or as mean ± standard deviation

FSD Female sexual dysfunction

HbA1c Glycated hemoglobin, *FPG* Fasting plasma glucose, *FPI* Fasting plasma insulin, *HOMA-IR* Homeostatic model assessment, index of insulin resistance, *TC* Total cholestero, *LDL-C* Low-density cholesterol, *HDL-C* High density cholesterol, *Tg* Triglycerides, *Lp (a)* Lipoprotein (a)

Neuropathy Parameters

Participants with FSD performed a lower score at deep breathing test ($p = 0.008$). There were no other differences in neuropathic variables (Table 8).

Discussion

Our data suggest a prevalence of FSD of about 87%, substantially in line with what reported in the literature: the published data, in fact, showed a prevalence of FSD from 20 to 80%. This wide range of prevalence is justified by the fact that the studies were conducted in different ethnic groups [13], and without univocal inclusion criteria [4]. Comparing our data with the study of Esposito et al. [11], carried out on an Italian sample and whose participants average age is similar to our sample (58.72 ± 9.73 vs. 57.9 ± 6.90 years), the prevalence is higher in our trial (87% vs. 53.4%). This difference can be justified by the fact that in the Esposito study a score < 23 was considered as a cut off for the FSF definition at the FSFI questionnaire, and not < 26.55, as performed by many Authors and to which we also conformed.

Regarding the etiology of FSD, previous studies suggested its multi-factorial genesis, with also a psychological involvement: in anxious females, as well as in males, the

Table 5 Correlation between various parameters and the score obtained in the FSFI questionnaire

	Participants without FSD	Participants with FSD
HbA_{1c} (%)	**−0.413**	0.138
FPG (mg/dl)	−0.178	−0.197
Pre-prandial glycemia (mg/dl)	−0.151	−0.101
Post-prandial glycemia (mg/dl)	−0.299	0.019
FPI (µU/ml)	−0.082	0.018
HOMA-IR	−0.301	−0.134
TC (mg/dl)	**0.593**	−0.153
LDL-C (mg/dl)	**0.586**	−0.035
HDL-C (mg/dl)	**0.541**	−0.154
Tg (mg/dl)	0.084	−0.041
Lp(a) (mg/dl)	0.269	−0.087
Homocysteine (µmol/l)	0.367	0.113

Bold indicates statistical significance

Data are expressed as correlation coefficient based on the score obtained in the FSFI questionnaire:

0–0.2 no correlation

0.2–0.4 weak correlation

0.4–0.75 good correlation

0.75–1 excellent correlation

FSD Female sexual dysfunction

HbA_{1c} Glycated hemoglobin, *FPG* Fasting plasma glucose, *FPI* Fasting plasma insulin, *HOMA-IR* Homeostatic model assessment, index of insulin resistance, *TC* Total cholesterol, *LDL-C* Low-density cholesterol, *HDL-C* High-density cholesterol, *Tg* Triglycerides, *Lp (a)* Lipoprotein (a)

Table 6 Correlation between glycemic parameters and the score obtained at the various area of FSFI questionnaire

	Desire	Excitation	Lubrication	Satisfaction
HbA_{1c} (%)	−0.162	**−0.433**	−0.358	−0.344
HbA_{1c} mean (%) 2015	−0.266	**−0.428**	**−0.423**	−0.282
Pre-prandial glycemia (mg/dl)	−0.127	−0.169	−0.094	−0.008
Post-prandial glycemia (mg/dl)	−0.033	−0.328	−0.248	−0.242
Duration of T2DM (years)	**−0.412**	−0.244	**−0.414**	−0.221
HOMA-IR	**−0.441**	−0.368	**−0.418**	−0.301

Bold indicates statistical significance

Participants not affected by FSD

Data are expressed as correlation coefficient based on the score obtained at the various dimensions of the sexual sphere examined in the FSFI questionnaire (expressed in column):

0–0.2 no correlation

0.2–0.4 weak correlation

0.4–0.75 good correlation

0.75–1 excellent correlation

HbA_{1c} Glycated hemoglobin, *T2DM* Type 2 diabetes mellitus, *HOMA-IR* Homeostatic model assessment, index of insulin resistance

Table 7 Adipocytokines

	Participants without FSD	Participants with FSD	*p* value
PAI-1 (ng/ml)	38.05 ± 7.63	48.89 ± 21.62	0.122
sICAM-1 (ng/ml)	232.06 ± 29.02	279.58 ± 82.84	0.077
sVCAM-1 (ng/ml)	477.29 ± 68.12	507.26 ± 115.58	0.428
E-selectin (ng/ml)	**29.15 ± 6.22**	**41.77 ± 16.20**	**0.017**
MMP-2 (ng/ml)	661.73 ± 98.84	718.43 ± 226.37	0.439
MMP-9 (ng/ml)	43.85 ± 4.87	54.42 ± 17.41	0.061
Hs-CRP (mg/l)	0.40 [0.11–1.33]	0.30 [0.1–0.87]	0.427

Bold indicates statistical significance

Data are expressed as median [interquartile range] or as mean ± standard deviation

FSD Female sexual dysfunction

PAI-1 Plasminogen activator inhibitor-1, *sICAM-1* Molecule-1 of soluble intercellular adhesion, *sVCAM-1* Soluble cell vascular adhesion protein-1, *MMP-2* Metalloproteinase-2, *MMP-9* Metalloproteinase-9, *Hs-CPR* High sensitivity C-reactive protein

Table 8 Neuropathy parameters

	Participants without FSD	Participants with FSD	*p* value
Deep breathing	**1.36 ± 0.15**	**1.22 ± 0.16**	**0.008**
Lying to standing	1.24 ± 0.09	1.21 ± 0.11	0.373
Valsalva	1.34 ± 0.15	1.35 ± 0.18	0.940

Bold indicates statistical significance

Data are expressed as median [interquartile range] or as mean ± standard deviation

FSD Female sexual dysfunction

increased sympathetic tone, and the higher levels of catecholamines generated by this condition could interfere with the smooth muscle release mechanisms, responsible for the correct responses to sexual stimulation of the erectile genital tissue [14].

In line with literature, our data showed a significant difference between participants with and without FSD regarding the prevalence of anxiety. Also, depression plays a leading role: there are many studies that correlate depression with FSD not only in general, but also in correlation with T2DM [11, 15]. The findings of our study support these data: in our study, participants with depression performed a lower FSFI score (3.9 vs. 14.1, $p = 0.005$).

Vascular dysfunction proved to be one of the main causes of erectile dysfunction in males [16]. The correlation between cardiovascular disease and FSD is debated and needs further study. Our data showed a statistically significant reduction of the total score to the FSFI questionnaire (13.7 [4.20–24.55] versus 3.6 [3.6–4.0], $p = 0.010$) for participants with ischemic heart disease, thus recognizing a close link between the two conditions.

Considering the main cardiovascular risk factors, we did not find any correlation with arterial hypertension; this is in line with previous literature [11]. This data is even emphasized by the finding of a direct correlation between the values of SBP and DBP and the

total score of the FSFI questionnaire in participants not affected by FSD (respectively r = 0.476, and r = 0.652), almost suggesting a protective effect; this mechanism could be explained by the fact that higher pressure values, within certain limits and for a first period, guarantee a more adequate perfusion overcoming initial vascular damage. Based on these aspects, it is not surprising that the means of the total score on the FSFI questionnaire of the participants examined is lower in ones taking beta-blockers (4.8 [3.2–18.55] versus 14.1 [4.2–23.9], $p = 0.032$), a data confirmed by Miocic et al. [17], and, transversely also in humans, by Burchardt et al. [18]. Differently from what reported by other authors [19], but in agreement with others [4], we did not observe significant differences in the prevalence of dyslipidemia between the two groups, probably because most of our participants (80.51%) were already treated with lipid-lowering drugs. Regarding the most debated aspect in literature, the correlation between FSD and the glycemic control, our data suggest a possible relationship between the two aspects. At a first glance, we observed an apparent contradiction: there was a lower mean of pre- and post-prandial glycemic values, and a lower HbA_{1c} value (6.86 ± 0.88 vs. 7.49 ± 0.71%, $p = 0.035$) in the group of participants with FSD, compared to the group without FSD, but we need to consider that these are the data collected at the time of enrollment. We must consider that, once developed, FSF led to a very important impact on quality of life [20, 21], this can motivate the patient and the physician to improve her lifestyle to gain a better glycemic control [22] with the improvement of HbA_{1c}. In fact, when we considered HbA_{1c} value trend in the years before the enrollment, we observed an inverse correlation between the total score of the FSFI questionnaire and the mean of the values of HbA_{1c}, confirming that a better glycemic control reduces the risk of developing FSD. We also observed an inverse correlation with the duration of diabetes and HOMA-IR in participants not affected by FSD, further underline that the alteration of these parameters may represent the prelude to the development of FSD.

Another important finding in our study is the higher value of homocysteine in participants with FSD compared to those not affected (17.75 ± 5.32 versus 12.39 ± 1.98 µmol/l, $p = 0.002$). It is known that hyperhomocysteinemia is a potent risk factor for early atherosclerosis [23], and that a moderate hyperhomocysteinemia is associated with an alteration of the endothelium-mediated arterial dilatation in humans [24]. The angiopathic effect throughout which hyperhomocysteinemia causes FSD is expressed in endothelial dysfunction with consequent altered dilatator effect of nitric oxide [25]. To support the hypothesis of a role of endothelial dysfunction, especially in the presence of increased oxidative stress and inflammatory conditions [26] in the pathophysiology of FSD, there was a higher value of E-selectin (41.77 ± 16.2 vs. 29.15 ± 6.22 ng/ml, $p = 0.017$) and, even if at the limits of significance, of MMP-9 (54.42 ± 17.41 vs. 43.85 ± 4.87 ng/ml, $p = 0.061$) in participants with sexual dysfunction. All these parameters showed a pro-inflammatory role in participants with T2DM [27–29].

Conclusion

The study showed a prevalence of FSD of 87% in a sample of females with T2DM attending our clinic, in line with literature. The factors involved in the development of FSD could be connected to psychological disorders such as anxiety and depression. There was also a correlation with glycemic control and ischemic heart disease; however, further data is needed to define whether, as for erectile dysfunction, FSD represents an early sign of coronary artery disease. Other important direct correlations were the one with autonomic

neuropathy and with endothelial dysfunction, supported by the detection of high levels of E-selectin and homocysteine in participants with FSD.

Authors' contribution Design and conduction of the study: GD and PM; data collection: all Authors; data interpretation and manuscript writing: GD, PM. All authors have reviewed the manuscript and agreed with the content.

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Data availability The authors confirm that the data supporting the findings of this study are available within the article.

Declarations

Conflict of interest The Authors declare that they have no conflict of interest.

Ethical Approval The study was performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments and the Good Clinical Practice Guidelines. The protocol was approved by the local Ethical Committee (ClinicalTrials.gov NCT01896648). Informed consent was obtained from all individual participants included in the study

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