



1 **Sex-Gender Differences in Diabetic Retinopathy**

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13 **ABSTRACT**

14 Diabetic retinopathy (DR) is one of the main causes of visual loss in individuals aged 20-64
15 years old. The aim of this study was to investigate, in a multicenter retrospective
16 cross-sectional study, sex-gender difference in DR in a large sample of type 2 diabetic
17 patients (T2DM). 20,611 T2DM regularly attending the units for the last three years were
18 classified as having: a) No DR (NDR), b) non proliferative DR (NPDR), c)
19 pre-proliferative/proliferative DR (PPDR). DR of all grade was present in 4,294 T2DM
20 (20,8%) with a significant higher prevalence in men as compared to women (22,0% vs 19,3%
21 $p<0.0001$). Among DR patients both NPDR and PPDR were significantly more prevalent in
22 men vs women ($p=0.001$ and $p=0.0016$, respectively). Women had similar age and BMI, but
23 longer diabetes duration, worse glycemic metabolic control and more prevalence of
24 hypertension and chronic renal failure (CRF) of any grade vs. men. No significant
25 differences between sexes were evident in term of drug therapy for diabetes and associate
26 pathologies. **Conclusion:** In this large sample of T2DM, men show higher prevalence of DR
27 vs. women, in spite of less represented risk factors, suggesting that men sex per se **might be**
28 a risk factor for DR development.

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30 Key words: diabetes complications, type 2 diabetes, microvascular complications

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32 INTRODUCTION

33• Diabetic retinopathy (DR) is one of the main causes of visual loss in diabetic subjects of age
34 between 20 and 64 years [1]. Diabetic retinopathy can be classified as **non proliferative**
35 **(NPDR), usually mild with the walls of the blood vessels in retina weaken with tiny**
36 **bulges (microaneurysms) protruding from the vessel walls of the smaller vessels,**
37 **sometimes leaking fluid and blood into the retina far away from the macula. NPDR can**
38 **progress to a more severe type, sometimes named as pre-proliferative, characterized by**
39 **leaking fluid and /or blood closely to the macula, which is a prelude to the more**
40 **advanced form of proliferative diabetic retinopathy. In proliferative diabetic**
41 **retinopathy damaged blood vessels close off, causing the growth of new, abnormal**
42 **blood vessels in the retina, and can leak into the clear vitreous, possibly ending in visual**
43 **loss[1].**

44 Careful control of glycaemia and blood pressure can reduce the risk of developing DR and
45 delay its progression [2]. Higher HBA1c level, diabetes duration, hypertension, and chronic
46 renal failure are globally recognized risk factors for the development of DR [3-6].

47 Differences between men and women both in type 1 and type 2 diabetes incidence
48 and in the development of chronic complications are reported by several epidemiological
49 studies [7-9 and cited literature]. Controversial results are available in literature regarding
50 DR and sex-gender differences. Some studies report an higher risk of DR among men
51 [10-14], while others suggest that women might have a higher prevalence of DR than men
52 [15-17]. A clinic-based retrospective longitudinal study with Japanese type 2 diabetes
53 mellitus patients indicated female sex as an independent risk factor for the development of
54 DR, with female sex showing higher prevalence of proliferative DR at baseline [18]. Only
55 few old reports do not show significant gender difference [19]. Moreover, DR progresses
56 during pregnancy [20, 21], suggesting a possible role of sex hormones in retinal damage in
57 diabetes [22, 23]. The controversial results on gender differences in DR might be related to
58 ethnic differences, population selection with sometimes mixed T1DM and T2DM subjects or
59 otherwise not well specified, low number of observations and differences in drug treatment
60 for diabetes or associated pathologies between sexes.

61 As new therapies for diabetic retinopathy are available (from laser-based therapies to
62 vitrectomy and intravitreal corticosteroids, anti-vascular endothelial growth factors and more
63 advanced stem cells and ribonucleic acid interference technologies), it becomes demanding
64 to evaluate all the risk factor for DR onset also from a gender perspective. Gender is
65 generally considered a social construct that transforms a female in woman and a male in man,
66 whereas sex is considered as the biological aspect of femininity and masculinity. Sex and

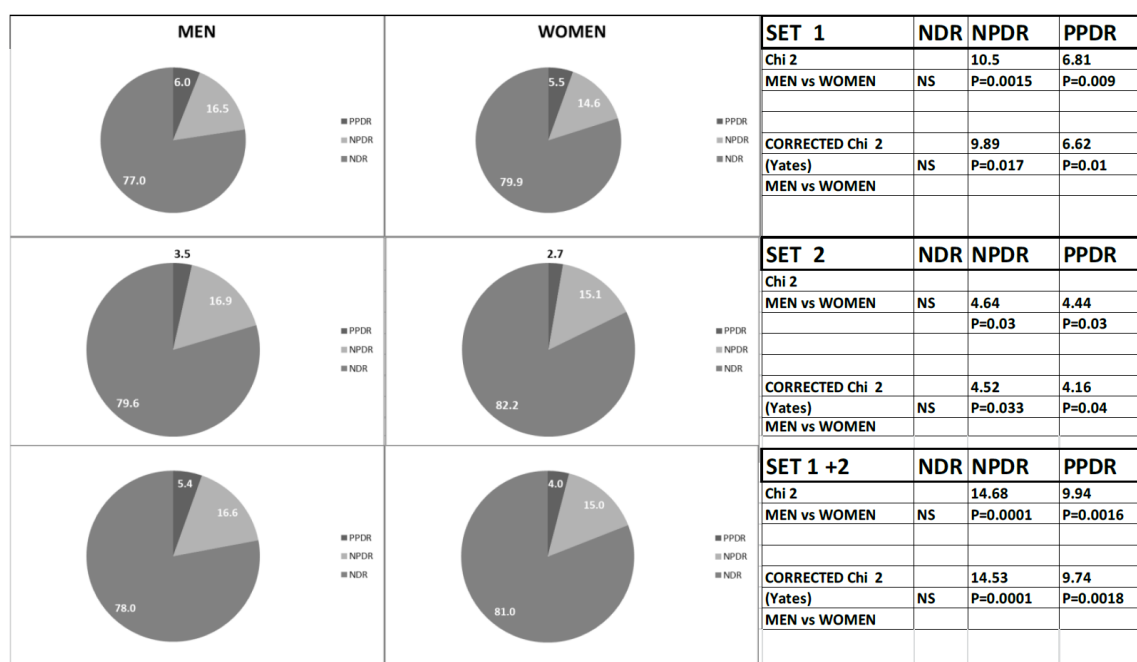
67 gender have numerous interactions [24], **and sometimes it is difficult to divide sex from**
68 **gender** thus it is preferable to adopt “sex-gender” terminology that strongly suggests that the
69 two concepts are jointed, **in fact, differences and inequalities in health status often derive**
70 **from both biological differences and social, cultural and political arrangements in**
71 **society.** So, we will use this term through this paper.

72 The aim of this study was to investigate possible sex-gender differences in DR in a large
73 cohort of Sardinian type 2 diabetes (T2DM) patients in a retrospective cross sectional study.

74

75 **RESULTS**

76 All selected patients attended the outpatient clinics regularly without significant differences
 77 between males and females. Nine hundred thirty-two T2DM patients had **maculopathy**
 78 (MAC: 481 men and 451 women) with no significant sex-gender differences. In set 1 (7,704
 79 men and 5,563 women), DR of any grade was significantly more represented in men (NPDR
 80 16.5% vs 14.6% p=0.0017 and PPDR 6.5% vs 5.5% p=0.01), indicating men having more
 81 DR than women (Fig 1).



82 **Figure 1** Percentage of DR in T2DM patients divided for sex and DR grade [No DR (NDR); Non proliferative DR (NPDR), and pre-proliferative/proliferative DR (PPDR)] in set 1, set 2 and in Set 1+2, respectively. Tables represents the results of Chi 2 analysis

83 This data was confirmed in the independent analysis performed in set 2 (3,969 men and 3,375
 84 women) with a significant prevalence of DR in men (NPDR 16.9% vs 15.1% p=0.03 and
 85 PPDR 3.5% vs 2.7% p=0.04, fig 1). When data from set one and two were joined (11,673
 86 men and 8,938 women) men confirmed having a significantly higher rate of DR of any
 87 grade (p<0.0001) and also individually for NPDR (p = 0.001) and PPDR p=0.0018) in
 88 comparison to women (fig 1). **Since premenopausal women represented 2.6% of the**
 89 **women sample (144/5563 in set 1 and 81/3375 in set 2) no attempt to stratify women in**
 90 **pre e post menopausal status was done.**

91 Table 1 report data for T2DM patient of set 1 divided for DR class and HbA1c $\leq 7\%$, $>7\%$ or
 92 $>8\%$: women consistently showed in all classes of DR higher prevalence of subjects with
 93 HbA1c over 7 or over 8%, being significantly in the NPDR group, indicating a general worse
 94 metabolic control in the women group.

95 **TABLE 1**

96 T2DM patients of set 1 (OL,NU,SS = 13,267 T2DM) divided for sex (MEN, WOMEN),
 97 diabetic retinopathy grade and HbA1c $\leq 7\%$, $>7\%$ or HbA1c $> 8\%$.

	Number	SEX	HbA1c $\leq 7\%$	HbA1c $>7\%$	HbA1c $>8\%$
NRD	5936	MEN	51,9%	48.1%	14.0%
	4443	WOMEN	48,8%	51.2%	14.8%
NPDR	1269	MEN	42,0%	58.0%*	18.8% **
	813	WOMEN	33,9%	66.1% *	25.2 % **
PPDR	499	MEN	27,9%	72.1%	29.1%
	307	WOMEN	25,4%	74.6%	29.4%
•	<ul style="list-style-type: none"> • Chi 2* p=0.006 **p=0.007 • Corrected Chi2 =(Yates) * p=0.0000, ** p=0.0001 				

98 No diabetic retinopathy (NDR) Non proliferative diabetic retinopathy (NPDR) ,pre
 99 proliferative/proliferative diabetic retinopathy (PPDR).Data are reported as %.

100

101 Clinical data were available for T2DM patients of OT unit (5,362 T2DM patients: men 3,003
 102 and women 2,359). Also in this additional subset men showed higher prevalence of DR as
 103 compared to women (NPDR p=0.041, PPDR p= 0.033). In these patients, subjects with
 104 NPDR and PPDR were older, showed a longer diabetes duration, worse metabolic control
 105 and lower eGFR in comparison to NDR (Table 2).

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113 **TABLE 2**

114 Data from the 5,362 T2DM (WOMEN 2359, MEN 3003) of the Olbia operative Unit : Distribution
 115 of diabetic retinopathy and clinical parameters divided for sex (MEN, WOMEN) and diabetic
 116 retinopathy grade

		NDR	NPDR	PPDR
Age (years)	MEN	68.1 ± 8.6	74.0±10.2 $\bar{\tau}$	73.1±8.0 $\bar{\tau}$
	WOMEN	68.8 ± 9.0	75.3±9.9 \mathcal{C}	73.0±8.1 \mathcal{C}
DD (years)	MEN	10.1 ± 5.4	17.0±9.9 $\bar{\tau}$. ***	21±10 $\bar{\tau}$
	WOMEN	10.4±5.4	20.3±10.7 \mathcal{C}	22±10 \mathcal{C}
BMI (kg/m2)	MEN	29.4 ± 3.7	29.0±6	30.0±5.2
	WOMEN	29.8 ±4.7	31.1±12	31.4±6.8
HbA1c (%)	MEN	6.8 ± 0.9*	7.3±1.4 $\bar{\tau}$. *	7.8±1.1 $\bar{\tau}$. *
	WOMEN	7.0 ±0.9	7.5±1.3 \mathcal{C}	8.3±1.7 \mathcal{C}
Total cholesterol(mg/dl)	MEN	162 ± 27***	163±35	156±38
	WOMEN	174 ± 27	168±39	160±39
HDL(mg/dl)	MEN	44 ± 9***	45±12***	42±9.9**
	WOMEN	51± 10	51±16	49±13
LDL(mg/dl)	MEN	115±62	96±46***	100±50
	WOMEN	114 ±4	110±66	118±42
TG(mg/dl)	MEN	105±32***	116± 31	90±28
	WOMEN	104 ± 31	116±30	92±38
Creatinine(μmol/l)	MEN	88.0±32.4***	96.0± 46***	103.5±44.9
	WOMEN	74.0 ± 31.0	82. 8±44.1 \mathcal{C}	91.8±66.7 \mathcal{C}
AER (mg/l)	MEN	32±108***	56±159 $\bar{\tau}$. ***	85±178 $\bar{\tau}$. *
	WOMEN	26 ±94	16±45	45±112
eGFR (ml/min/m2)	MEN	77±29	67±39	62±38 $\bar{\tau}$
	WOMEN	71 ± 26	60±35	54±42 \mathcal{C}

117 No diabetic retinopathy (NDR) Non proliferative diabetic retinopathy (NPDR) ,pre proliferative/
 118 proliferative diabetic retinopathy (PPDR).

119 MEN vs WOMEN = *p<0.05,**p<0.01,***p<0.001; Within MEN vs NDR = $\bar{\tau}$ p<0.001;

120 Within WOMEN vs NDR = \mathcal{C} p<0.01, \mathcal{C} p<0.001

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122 Women showed significantly higher values, in comparison with men, for diabetes duration
 123 (p<0.001 in NPDR), HbA1c (p<0.05 in all classes), HDL – cholesterol (p<0.01 in all
 124 classes) and LDL-cholesterol (p<0.001 in NPDR), while BMI, total cholesterol and TG were
 125 similar in men and women in the different groups without significant differences.
 126 Creatinine was higher in men, but no differences in calculated eGFR was evident between
 127 men and women. In the different classes (NDR, NPDR and PPDR) in both sexes eGFR

128 decreased constantly while diabetes duration and age increased, again without significant
 129 differences between men and women. Albumin excretion rate (AER) was somehow
 130 significantly higher in men in all groups.

131 Finally, associated pathologies were analysed for T2DM patients of OT unit (Table 3).

132 **TABLE 3**

133 Data for associated pathologies: Hypertension (HT) and Chronic renal failure any grade (CKF) in
 134 the 5,362 T2DM of the Olbia operative Unit .Distribution of diabetic retinopathy and clinical
 135 parameters divided for sex (MEN, WOMEN) and diabetic retinopathy grade.

	NDR MEN=2331 WOMEN=1912		NPDR MEN=504 WOMEN= 344		PPDR MEN=168 WOMEN=103	
	HT	CKF	HT	CKF	HT	CKF
MEN %	20.3	6.1	30.3	6.6	14.8	11
WOMEN %	27.3	4.7	33.7	8.9	20.1	22.5
Chi2	P=0.0000	p=0.002	ns	ns	ns	P=0.0000
Corrected Chi2	P=0.0000	P=0.002	ns	ns	ns	P=0.0000

136 No diabetic retinopathy (NDR) Non proliferative diabetic retinopathy (NPDR) ,pre proliferative and
 137 proliferative diabetic retinopathy (PPDR).

138 Results are given as % of subjects

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143 Women had more hypertension in all DR classes, being significant in NDR and PPDR.

144 Chronic renal failure (CRF) had a higher prevalence in NDR men in comparison with NDR
 145 women, while it was significantly higher in PPDR women than in PPDR men.

146 No significant difference between men and women were present in drug therapy for diabetes
 147 or for antihypertensive drugs or lipid lowering drug use. Among antihypertensive drugs no
 148 significant differences in Angiotensin Converting Enzyme Inhibitors (ACEI) or Angiotensin
 149 II Receptor Blockers (ARB) use was present between men and women as well as in the use of
 150 statins (Table 4).

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153 **TABLE 4**

154 Drug therapy for diabetes and associated pathologies in the 5,362 T2DM patients of Olbia operative
 155 unit divided for sex (MEN, WOMEN) and diabetic retinopathy grade.

SEX	MEN	WOMEN
N (%)	3003 (56)	2359 (44)
DIABETES THERAPY (%)		
DIET	6.5	5.8
DIET/OHA	61.9	59.3
OHA +I	12.7	15.2
I	18.9	19.7
OTHER DRUG THERAPY %		
ANTI HYPERTENSIVE	62	59
ACEI/ARB USE	51.8	52.2
LIPID LOWERING	48	48
STATIN USE	94.1	92.5

156 No diabetic retinopathy (NDR) Non proliferative diabetic retinopathy (NPDR) ,pre
 157 proliferative/proliferative diabetic retinopathy (PPDR). OHA = Oral Antidiabetic Drugs, OHA+I= =
 158 Oral Antidiabetic Drugs +Insulin, I= Insulin, ACEI/ ARB = Converting Enzyme Inhibitors /
 159 Angiotensin Receptor Blockers .

160 Data are reported as %..No significant differences between Men and Women

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162 The logistic regression analysis performed in the Olbia patients indicate sex as the only
 163 significant variable.

164 **DISCUSSION**

165 DM is associated to an excess risk of cardiovascular mortality and, in this context,
 166 there are evidences highlighting the fact that diabetic women are at a higher risk than their
 167 counterpart, particularly in postmenopausal period [27]. While sex-gender differences in
 168 macrovascular complications are well established, less is known about microvascular
 169 complications in T2DM.

170 In our population, the prevalence of DR was 20.8%, slightly lower than described in
 171 other sets [28-32]. Although our prevalence seems lower than described in other sets, we
 172 have to remember that in the other realities, diabetic operative units deal mainly with
 173 complicated T2DM patients, while in Sardinia more than 95% of the diabetic population
 174 attend a diabetic operative unit. This data is also important to define a better epidemiologic

175 DR rate among T2DM patients, which in our Sardinian population appears to be in the order
176 of 20.8%.

177 Sex-gender differences in diabetes and in some diabetic complications are well
178 defined, but in DR these differences are less evident, due to the heterogeneity of the
179 published studies in term of ethnic origin of the population studied, number of patients
180 analysed and selection bias. Male is generally, but not always, considered an independent
181 risk factor for DR. Besides what already discussed before in the introduction, several
182 studies give in any case controversial results on sex-gender difference in diabetic
183 retinopathy. A large-scale study performed in the United States revealed that in diabetic
184 patients over the age of 40 years, men show a 50% higher prevalence of diabetic
185 retinopathy than women [17]. On the other hand, the LALES study [33] showed no
186 statistically significant difference in the incidence of DR between the two sexes and so was
187 in other different studies that found no statistically significant associations between DR and
188 sex [1,34, 35-37]. The UKPDS 50 study [38] also found no difference in prevalence
189 between the two sexes ($P=0.67$), with women showing anyway a lower rate of progression
190 of DR than men do. In addition, data from a large clinical register in Denmark, show no clear
191 sex-gender differences in DR rate but men have a higher risk for reaching sight threatening
192 DR [39].

193 Male seems to be a risk factor for diabetes in adults as well as in juveniles, at least for
194 the western countries [40-42], while it is quite the opposite in countries where the population
195 is of non-European origin, in which the prevalence of diabetes seems to be higher in women
196 [43]. Among our patients women represented the 43% of the sample. In some studies that
197 found male as a risk factor for DR, men showed also higher HbA1c levels and higher systolic
198 and diastolic blood pressure values than women. Since these are risk factors for progression
199 of DR [44], it could explain the sex-gender difference in the progression rate of DR found in
200 men as an increased presence of additional risk factors for DR. The imbalanced distribution
201 of risk factors among genders could be caused by differences in lifestyle [39], although sex
202 hormones might have a role. DR often progresses during pregnancy which is associated with
203 higher estrogen and progesterone levels [45, 46]. However it has been demonstrated that

204 women following a tight metabolic control regimen during pregnancy, do not show an
205 elevated risk for progression of DR, although the risk often increases again in the
206 post-partum period since this tight metabolic regimen frequently is no longer followed.
207 [45-47].

208 Mortality and disability after a first vascular event is higher in women and there are
209 evidences reporting that women receive less medical care regarding cardiovascular
210 complications even in presence of diabetes, or, in any case reach less frequently the targets.
211 From published studies, appears clear that: 1) WOMEN come later and in worse clinical
212 conditions to diagnosis of diabetes, 2) WOMEN are more obese at diagnosis and reach
213 guideline target goals for glycated haemoglobin , LDL- cholesterol or blood pressure control
214 in a much lesser extent [48]; 3) WOMEN have a lesser chance of receiving all the diagnostic
215 and therapeutic measures than diabetic men, even if it is well known that mortality after a
216 first cardiovascular event is more elevated in diabetic WOMEN [49,50]; 4) finally, some
217 anti-aggregating and anti-hypertensive drugs seem to be less efficacious in diabetic
218 WOMEN, while side effects of some hypoglycaemic agents seem to be more frequent,
219 reducing treatment compliance. In a recent ongoing prospective study, side effects of
220 metformin have the same incidence in men and women, with the latter showing greater
221 intensity and duration of these side effects, conditioning the compliance to drug treatment
222 (preliminary personal observation). Studies focused on sex-gender differences in diabetic
223 microvascular complications are indeed scarcely represented, either at preclinical or clinical
224 level, mainly due to the well-known limitations of inclusion criteria in trials, but also due to
225 the difficulty of dissecting genetic and environment interactions. Certainly, the lack of our
226 capacity to target directly the mechanism initiating the disease, instead of the
227 epiphenomenon, is the cause of the partial failure in the control of diabetic microvascular
228 complication and this is true in sex-gender oriented medicine as well. Neuroretinal
229 dysfunction can be used to predict the location of future retinopathy up to three years before
230 it is manifest and recently, in adult type 2 diabetic patients, an abnormal local neuroretinal
231 function as been shown in men as compared to women [51]. If confirmed, this might be an
232 alternative explanation relative to the higher prevalence of diabetic retinopathy in men

233 subjects we found in spite of the fact that women had more risk factors for diabetic
234 retinopathy onset and progression.

235 In this large set of Sardinian T2DM patients, we show that women and men are equally
236 receiving drug therapy for diabetes and associated pathologies (mainly hypertension and
237 hypercholesterolemia), but women have more prevalence of hypertension and chronic renal
238 failure and show worse **glycemic** metabolic control, as known in literature [9, 8]. The less
239 satisfactory results of drug therapy obtained in women can be determined by factors that
240 disregard gender inequalities in the assistance and therapeutic approach, they are perhaps
241 more related to a different physiological response in the two sexes to the drugs (eg the
242 statins), or difference in adverse drug reactions explaining less compliance to the treatment,
243 as already said above.

244 RAAS modulators, mainly ACEI and ARB, may reduce onset and progression of DR in
245 normotensive Type 1 diabetic patients [52,53] and these drugs are able to make the
246 regression of a mild DR in normoalbuminuric Type 2 diabetic patients [54]. A recent
247 meta-analysis pointed out that RAAS modulators (ACEI more than ARB) might indeed
248 reduce onset and progression of DR in normotensive diabetic patients [55]. In the OT subset
249 of patients, no difference in ACEI/ARB use was evident between men and women excluding
250 this possible confounding data in our results.

251 **Finally the role of sex hormones on retinal disorder must be considered. Recently the**
252 **argument has been reviewed [56]. Indeed it appears that estrogens, androgens, and**
253 **progesterone receptors are present throughout the eye and that these steroids are**
254 **locally produced in ocular tissues. Estrogenic cycle might have beneficial effect on**
255 **neuroretinal function with estrogens, by a vasodilator effect on retinal perfusion being**
256 **protective, while testosterone, and progesterone, by a vasoconstrictive effect might be**
257 **cause of progression. Although interesting the role of sex hormone on retina and their**
258 **contribution to retinal disorders remain to be proved.**

259 A limitation of this study is that is not a longitudinal study able to detect, in a gender oriented
260 manner, who might have more rapid progression to DR. A longitudinal prospective study is
261 starting now with these patients and hopefully in the next years we will **clarify** this aspect.

262 There are some strengths in this paper : 1) the big sample size of enrolled patients, 2) the
263 multicenter design with the enrollment done in seven different operative units and the
264 replication of the results in two different sets, 3) more than 98% of T2DM patients in Sardinia
265 refer to a diabetes operative unit , allowing to have a clear picture of the real prevalence of
266 retinopathy in T2DM patients, 4) comprehensive data on potential confounders variables
267 in 5,362 T2DM patients.

268 **METHODS**

269 A multicentre observational retrospective cross sectional study was carried out on T2DM
270 patients from 7 diabetes care units located in different areas of Sardinia: **Olbia (OT), Sassari**
271 **(SS), Nuoro (NU), Lanusei (LA), Isili (IS), Cagliari (CA), Selargius (SE).**

272 The study was approved by the “Comitato di Bioetica” ATS Sardegna on Jan 27th 2015.

273 We selected patients with established diagnosis of T2DM regularly attending the Unit from
274 more than 3 years with at least 2 coincident eye examination in the period 2016-2018.
275 Diagnosis of **type 2** diabetes was done according to the presence of fasting blood glucose
276 more than 126 mg/dl, **glycated** haemoglobin more than 6.5% or blood glucose more than 200
277 mg/dl at 120' of an 75 gr Oral Glucose Tolerance test or blood glucose more than 200 mg/dl
278 at any time with symptoms. Out of a total 29,785 T2DM (16,852 men and 12,933 women),
279 8,242 did not fulfilled the enrolment criteria (T2DM diagnosis criteria, not regular attendance
280 to the operative Unit, no or not coincident eye examination in the period 2016-2018
281 available) and were excluded. From the remaining 21,543 T2DM patients (12,154 men and
282 9,389 women) enrolled, 932 had maculopathy, in the remaining 20,611 patients the
283 prevalence of DR of any grade was 20.8%.

284 These 20,611 T2DM subjects were divided in two sets: Set 1: patients with HbA1c
285 aggregation data and eye examination (13,267: 7,704 men and 5,564 women) these patients
286 were enrolled in the OT, SS and NU diabetes care unit; Set 2: patients with only eye
287 examination (7,344: 3,969 men and 3,375 women) these patients were enrolled in the LA, IS,
288 SE and CA diabetes care units. Set 2 was selected to confirm/deny the results of a different
289 rate of DR between men and women eventually found in set one.

290 In addition, full clinical data extracted from the clinical database of the Olbia operative unit
291 (OT) were available for 5,362 T2DM patients (3,003 men and 2,359 women). HbA1c, body
292 mass index (BMI), creatinine, urinary albumin excretion rate, total and HDL cholesterol,
293 triglycerides (TG) were extrapolated from the database and the mean of the data for any
294 single patient in the last available year was used. Estimated glomerular filtration fraction
295 (eGFR) was calculated with the MDRD equation [25], LDL cholesterol was calculated with
296 the Friedewal formula [(total cholesterol – HDL-Cholesterol) /triglycerides]. Chronic renal
297 failure of any grade was defined from eGFR < 60ml/min/m² in two consecutive occasions at
298 least one month apart and hypertension as blood pressure >140/90 mmHg in three different
299 occasions or antihypertensive drug use.

300 DR was classified after full midriatic eye observation by an ophthalmologists as :a) no signs
301 of DR (NDR), non-proliferative mild to moderate DR (NPDR),
302 pre-proliferative/proliferative DR (PPDR) and maculopathy (MAC) [26]. **Definition of**
303 **pre-proliferative diabetic retinopathy has been given in the introduction.**

304 Primary endpoint was the evaluation of sex-gender differences in the different grades of DR,
305 while secondary endpoints included the association between DR and clinical and
306 biochemical parameters in T2DM men and women as well as the sex-gender differences in
307 DR associated diseases and therapies.

308 Numerical variables were represented as mean ± standard deviation (SD), categorical
309 variables were presented as frequencies and percentages. Bivariate analysis was performed
310 using Student t test for continuous variables and chi 2 test for categorical variables. Statistical
311 significance was set at 5% level. P-value of <0.05 was deemed statistically significant.

312 Logistic regression analysis was performed in the 5,362 T2DM patients of the Olbia Unit
313 to identify independent risk factors for diabetic retinopathy using sex as categorical variable
314 and, blood pressure, diabetes duration, triglycerides and HbA1c as continuous variables.

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319 **CONCLUSIONS**

320 In conclusion, in our large sample of T2DM patients women, **although having the same**
321 **drug treatment of men**, show a clear worse **glycemic** metabolic control, higher prevalence
322 of hypertension and chronic renal failure, **all well established risk factors for DR**, but men
323 show higher prevalence of DR of any grade suggesting a more independent sex-gender
324 effect. **If male sex is cause of the development of diabetic retinopathy or female sex is**
325 **protective remain to be proven.**

326

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ADDITIONAL DATA: FLOW CHART OF THE STUDY

