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Sex-Gender Differences in Diabetic Retinopathy

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ABSTRACT

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

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

INTRODUCTION

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

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

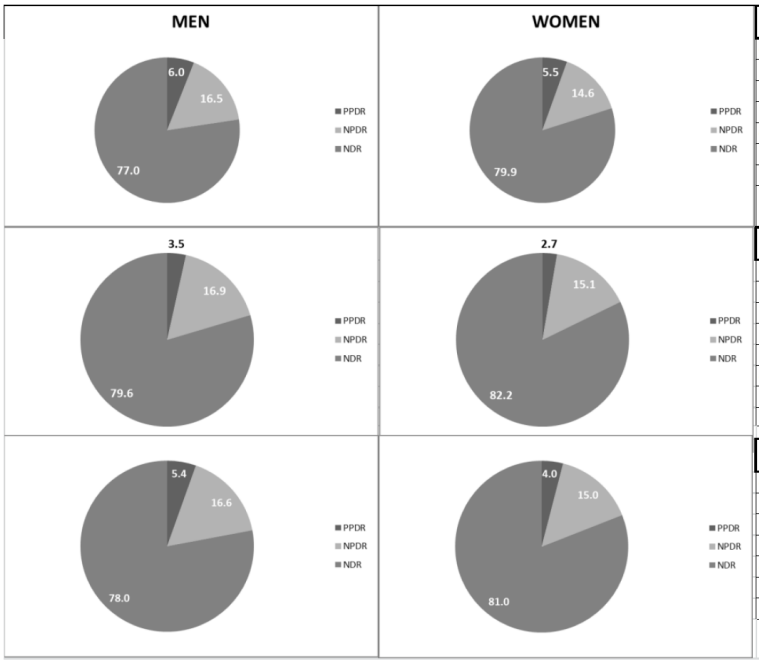
Differences between men and women both in type 1 and type 2 diabetes incidence and in the development of chronic complications are reported by several epidemiological studies [7-9 and cited literature]. Controversial results are available in literature regarding DR and sex-gender differences. Some studies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

As new therapies for diabetic retinopathy are available (from laser-based therapies to vitrectomy and intravitreal corticosteroids, anti-vascular endothelial growth factors and more advanced stem cells and ribonucleic acid interference technologies), it becomes demanding to evaluate all the risk factor for DR onset also from a gender perspective**.** Gender is generally considered a social construct that transforms a female in woman and a male in man, 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**. **S**o, 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

RESULTS

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



SET 1	NDR	NPDR	PPDR
Chi 2		10.5	6.81
MEN vs WOMEN	NS	P=0.0015	P=0.009
CORRECTED Chi 2		9.89	6.62
(Yates)	NS	P=0.017	P=0.01
MEN vs WOMEN			

SET 2	NDR	NPDR	PPDR
Chi 2			
MEN vs WOMEN	NS	4.64	4.44
		P=0.03	P=0.03
CORRECTED Chi 2		4.52	4.16
(Yates)	NS	P=0.033	P=0.04
MEN vs WOMEN			

SET 1 +2	NDR	NPDR	PPDR
Chi 2		14.68	9.94
MEN vs WOMEN	NS	P=0.0001	P=0.0016
CORRECTED Chi 2		14.53	9.74
(Yates)	NS	P=0.0001	P=0.0018
MEN vs WOMEN			

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

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

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

TABLE 1

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

	Number	**SEX**	**HbA1c ≤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%
•	• Chi 2* p=0.006 **p=0.007 • Corrected Chi2 =(Yates) * p=0.0000, ** p=0.0001				

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

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

TABLE 2

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

		NDR	NPDR	PPDR
Age (years)	MEN	68.1 ± 8.6	74.0±10.2₸	73.1±8.0₸
	WOMEN	68.8 ± 9.0	75.3±9.9 ₡	73.0±8.1 ₡
DD (years)	MEN	10.1 ± 5.4	17.0±9.9₸. ***	21±10 ₸
	WOMEN	10.4±5.4	20.3±10.7₡	22±10 ₡
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 ₸. *	7.8±1.1 ₸. *
	WOMEN	7.0 ±0.9	7.5±1.3 ₡	8.3±1.7 ₡
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 ₵	91.8±66.7 ₵
AER (mg/l)	MEN	32±108***	56±159 ₸. ***	85±178 ₸. *
	WOMEN	26 ±94	16±45	45±112
eGFR (ml/min/m2)	MEN	77±29	67±39	62±38 ₸
	WOMEN	71 ± 26	60±35	54±42 ₵

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

MEN vs WOMEN = *p<0.05,**p<0.01,***p<0.001; Within MEN vs NDR =₸p<0.001;

Within WOMEN vs NDR = ₵p<0.01,₡ p<0.001

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

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

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

TABLE 3

Data for associated pathologies: Hypertension (HT) and Chronic renal failure any grade (CKF) in the 5,362 T2DM of the Olbia operative Unit .Distribution of diabetic retinopathy and clinical 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

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

Results are given as % of subjects

Women had more hypertension in all DR classes, being significant in NDR and PPDR. Chronic renal failure (CRF) had a higher prevalence in NDR men in comparison with NDR women, while it was significantly higher in PPDR women than in PPDR men.

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

TABLE 4

Drug therapy for diabetes and associated pathologies in the 5,362 T2DM patients of Olbia operative 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

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

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

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

DISCUSSION

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

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

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

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

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

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

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

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

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

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

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

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

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

METHODS

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

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

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

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

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

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

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

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

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

CONCLUSIONS

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

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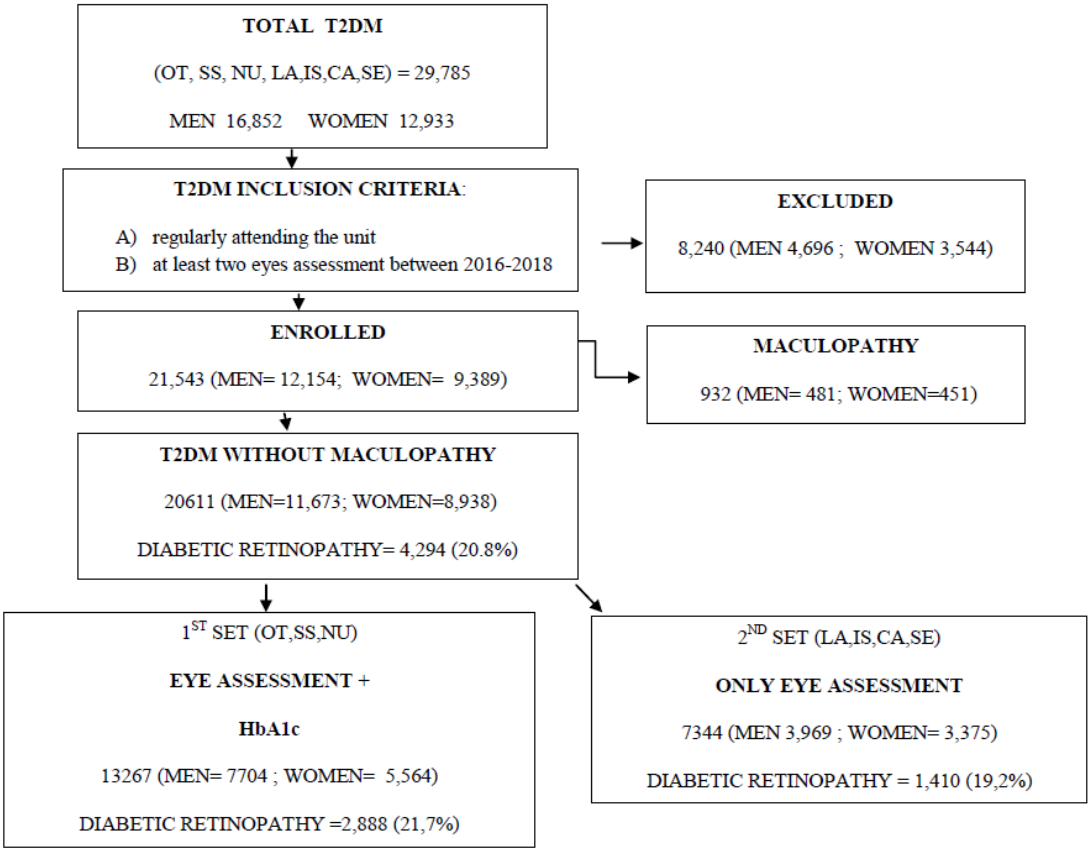
ADDITIONAL DATA: FLOW CHART OF THE STUDY



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