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Excessive generalized and visceral adiposity is associated with a higher prevalence of diabetic retinopathy in Caucasian patients with type 2 diabetes

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Abstract *Background and aims:* Type 2 Diabetes Mellitus (T2D) has heterogeneous clinical phenotypes related to different risk of developing diabetes complications. We investigated the correlation between generalized and abdominal adiposity and the prevalence of both micro- and macrovascular complications in Caucasian patients with T2D.
Methods and results: We evaluated 769 individuals with T2D consecutively referred to our diabetes center. Body mass index (BMI), waist circumference (WC), waist to hip (W/H) ratio, glycated hemoglobin (HbA1c), systolic and diastolic blood pressure, lipid profile, smoking habit, diabetes therapy, and micro- and macrovascular complications were recorded. Patients were divided into three groups based on BMI and WC: non-obese with normal WC (nWC, n = 220), non-obese with excess of abdominal fat (AF, n = 260) and obese (Ob, n = 289). We found that nWC, compared with AF and Ob individuals, were predominantly males ($p<0.01$), had lower HbA1c ($p<0.01$), diastolic blood pressure ($p<0.01$), triglycerides ($p<0.01$), and showed a significantly lower prevalence of diabetic retinopathy (DR) ($p = 0.01$). The rate of proliferative DR was significantly higher in Ob (13.2 %) compared to the other groups ($p = 0.03$). Multivariate analyses showed a significantly decreased prevalence of DR in nWC compared to both AF (OR 0.58, 95 CI 0.34–0.96; $p = 0.03$) and Ob (OR 0.57, 95 CI 0.33–0.98; $p = 0.04$) individuals. Conversely, DR was associated, mainly in women, to higher WC and W/H ratio. The prevalence of the other diabetes-related complications was similar among the studied groups.
Conclusions: In our population, nWC subjects showed a lower prevalence of DR. An increased generalized and abdominal adiposity was associated to a higher prevalence of DR, especially among females.

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1. Introduction

Type 2 diabetes (T2D) is a heterogeneous and complex syndrome with multiple associated disabling comorbidities, which includes cardiovascular disorders, chronic kidney disease, peripheral neuropathy and diabetic retinopathy (DR) [1].

An increasing amount of evidence demonstrates that patients with T2D have a wide spectrum of clinical phenotypes related to a different level of risk of developing the above-mentioned diabetes complications [2]. Among others, overweight and obesity are well-recognized key determinants of T2D patient's phenotype, and, therefore, of their metabolic-related morbidity [3,4]. These conditions are common in the diabetic population with growing prevalence over time [5]. More specifically, visceral fat distribution (i.e. abdominal adiposity), strongly associated to insulin resistance and, thus, to cardio-metabolic impairment, is considered one of the major risk factors for macrovascular diabetes complications [6,7].

Beyond macrovascular risk, recent evidences, mainly derived from Asian studies, suggest a role of total and visceral fat in the development diabetes-related microvascular complications (e.g., retinopathy, nephropathy, and neuropathy) [8–12]. Although the pathophysiological mechanisms underlying this correlation are not fully understood, insulin resistance, inflammation, and oxidative stress are currently believed to play an important role in the pathogenesis of microvascular damage among overweight and obese T2D subjects [13].

Despite these preliminary findings, few and conflicting data are currently available on the association between fat mass chronic excess and the risk of microvascular disorders. Moreover, the differential role of either generalized or abdominal adiposity in microvascular damage is still debated.

The present study aimed to investigate the correlation between total and abdominal adiposity and the prevalence of chronic complications in a population of Caucasian T2D outpatients.

2. Methods

A cross sectional study was carried out in 769 Caucasian individuals with T2D (443 males, 326 females) consecutively referred to the Diabetes, Obesity and Dietetic Center of the Garibaldi-Nesima Hospital (Catania, Italy) between January 2020 and May 2021.

For all subjects, data concerning demographic characteristics, general and diabetes-related medical history, and smoking habit were collected from the electronic medical records routinely used at the Diabetes Center (Smart Digital Clinic 10.12.20, Meteda s.r.l.).

Body mass index (BMI), waist circumference (WC), waist to hip (W/H) ratio, systolic and diastolic blood pressure, smoking habits, lipid profile, glycated hemoglobin (HbA1c), and the diabetes therapy, were collected. The presence of microvascular (e.g., retinopathy, nephropathy, peripheral neuropathy) and macrovascular (e.g., myocardial infarction, stroke, carotid artery and lower limb atherosclerosis) diabetes-related complications was also recorded.

To explore the role of total and abdominal adiposity on the occurrence of diabetes complications, we distinguish patients into the following three groups on the basis of BMI (below or $\geq$30 kg/m^2) and WC (below or $\geq$ 102 cm for males and 88 cm for females): non-obese with normal WC (nWC), non-obese with excess of abdominal fat (AF) and obese (Ob, BMI $\geq$30 kg/m^2).

All procedures were in accordance with Declaration of Helsinki and its later amendments [14]. The local Ethics Committee (Catania 2, report 64/2019/CECT2) approved the study protocol. Clinical and laboratory data were retrospectively recorded on an anonymized database, thus, patient consent was not required.

2.1. Anthropometric measures assessment

BMI was calculated by dividing the weight in kilograms by height in square meters (kg/m^2). To estimate the abdominal fat, we measured WC at the superior border of the iliac crest using a non-elastic flexible tape. WC was considered abnormal when $\geq$88 cm in women and $\geq$102 cm in men [15,16]. W/H ratio was obtained by dividing WC (cm) by hip circumference (cm), and a value $\geq$ 0.85 for females and $\geq$0.90 for males was used to define an excess of abdominal fat [16].

2.2. Diabetes-related complications assessment

DR was defined as the evidence of any form of diabetes-related retinal alteration (e.g., microaneurysms, exudates, blot hemorrhages, retinal neovascularization, macular edema) at the eye examination (fundus oculi in mydriasis, fluorescein angiography or optical coherence tomography) performed at the Eye Center of the Garibaldi-Nesima hospital (Catania, Italy) [17]. Subjects were assigned, according to the classification of The International Clinical Disease Severity Scale for DR into the following three groups: NDR (subjects without DR), NPDR (subjects with non-proliferative DR), PDR (subjects with proliferative DR) [18,19].

Diabetic nephropathy was defined either as the evidence of an urine albumin to creatinine ratio (UACR) $>$ 30 mg/gr in random spot urine collection or the presence of an estimated glomerular filtration rate (eGFR) $<$ 60 ml/min according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula in a patient with a progressive decline eGFR and a kidney disease duration $>$3 months, [17,20]. Diabetic peripheral neuropathy was assessed by using the 10 gr Semmes-Weinstein monofilament (for tactile sensitivity) and biothesiometry (for vibration sensitivity). Three readings were obtained from each foot on the first metatarsal at different degrees of voltage increase and a mean was taken. A vibration perception threshold $>$25 V and/or an altered monofilament test were considered indicative of peripheral neuropathy [21]. The presence of documented myocardial

infarction (MI), ischemic or hemorrhagic stroke and arterial vessel disease (ultrasound evidence of carotid/lower limbs arterial vessel plaques), was also recorded.

2.3. Sample size and statistical analysis

Considering the study design and aims, we calculated that a sample size of at least 750 patients would have given 80 % power to detect at least 15 % between-groups difference in the prevalence of diabetes-related complications (assuming a mean prevalence of 25 % after 15 years since diagnosis) based on previously published studies aiming to investigate the correlation between adiposity and the prevalence of diabetes complications [22].

Comparisons have been conducted by Pearson χ^2 test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. Shapiro–Wilk and Kolmogorov–Smirnov tests to explore continuous variables distribution were used. Graphic analyses of histogram and Q–Q normality graph and asymmetry/standard error or kurtosis/standard error ratio supported the continuous variables distribution exploration [23,24].

Multivariate logistic regression models, accounting for possible confounders were applied to correlate patients' anthropometric characteristics to the prevalence of micro- and macrovascular damage. Hosmer–Lemeshow post-estimation test was used to assess the model performance. Adjusted odds ratios for the standardized predictive factors were calculated with 95 % confidence intervals [25].

Statistical analyses were carried out using the STATA 14.2 SE software (STATA Corp., College Station, Texas, USA).

3. Results

A total of 769 Caucasian patients affected by T2D were included in this analysis. Based on BMI and WC, we identified 220 nWC, 260 AF, and Ob 289 individuals.

Clinical and biochemical characteristics are summarized in Table 1. We found that nWC individuals, compared to the AF and Ob ones, were predominantly males (82.7 % vs. 46.5 % vs. 48.4 %, $p<0.01$), had a lower HbA1c (7.1 % ± 1.0 vs. 7.3 % ± 1.0 vs. 7.4 % ± 1.1, $p = 0.02$), diastolic blood pressure (74 ± 10 vs. 76 ± 9 vs. 77 ± 1 mmHg, $p<0.01$), triglycerides (115 ± 68 vs. 130 ± 65 vs. 148 ± 81 mg/dl, $p<0.01$) and showed a significantly lower prevalence of DR (21.1 % vs. 32.0 % vs. 31.9 % $p = 0.01$). No differences between the three groups were observed regarding the other micro- and macrovascular diabetes-related complications (Table 1).

In order to exclude the influence of other vascular complications on the association between DR and abdominal adiposity, we calculated, among individuals with DR, the percentage of nWC, AF and Ob individuals having one (32.2 % vs. 30.9 % vs. 33.3 %, respectively, $p = 0.66$) or more than one (19.2 % vs. 21.5 % vs. 22.4 %, respectively, $p = 0.45$) concomitant micro/macrovascular complications. No significant differences emerged from these analyses.

The multivariate logistic regression analysis, accounting for possible confounders (HbA1c, diabetes duration, triglycerides, smoking habit, systolic and diastolic blood pressure), demonstrated a significantly lower prevalence of DR in nWC group compared to both AF (OR 0.58, 95 CI 0.34–0.96; $p = 0.03$) and Ob (OR 0.57, 95 CI 0.33–0.98; $p = 0.04$) individuals.

We also analyzed the percentage of use of the different diabetes therapies among the three subgroups (Table 1). In OB and AF, compared to nWC subjects, we observed a significantly higher prevalence of insulin use (51.1 % vs. 48.1 % vs. 40.5 %, respectively, $p<0.01$). At multivariate analysis, the occurrence of DR within the three subgroups was influenced by diabetes duration (OR 1.07, 95 CI 1.05–1.10, $p<0.01$) and insulin therapy (OR 1.68, 95 CI 1.14–2.50, $p<0.01$). Furthermore, in Ob individuals, compared to AF and nWC, we detected a higher percentage of use of glucagon like peptide-1 (GLP-1) receptor agonists (25.8 %, $p<0.001$) and a lower prevalence of dipeptidyl peptidase-4 (DPP-4) inhibitors (6.8 %, $p<0.001$) (Table 1). Nevertheless, the multivariate model did not show any relation between DR and the use of either GLP-1 receptor agonists (OR 0.87, 95 CI 0.54–1.40; $p = 0.55$) or DPP-4 inhibitors (OR 0.90, 95 CI 0.53–1.50; $p = 0.68$) (Table 2).

Further gender-specific analyses showed that a significantly higher prevalence of AF (41,7 % vs. 26,9 %, $p<0.01$) and obesity (46.3 % vs. 31.1 %, $p<0.01$) was observed among females compared to males (Fig. 1).

Besides, the multivariate logistic regression indicated an association between DR and a higher WC (OR 1.27, 95 CI 1.07–1.50, $p = 0.03$) and W/H (OR 1.23, 95 CI 1.11–1.36, $p = 0.02$). This phenomenon was particularly pronounced among females (Fig. 2). To investigate whether there was an interaction effect of the patient's gender with the association between abdominal adiposity and the occurrence of DR, we introduced an interaction term in the logistic regression model (gender x WC), finding a significant interaction effect ($p = 0.023$).

We also analyzed the prevalence of the different stage of DR within the considered study groups based on BMI and WC. The prevalence of NPDR was significantly lower ($p = 0.02$) in the nWC group (12.6 %) compared to both AF (21.2 %) and Ob subjects (17.6 %). Instead, the rate of the most advanced stages of DR, namely PDR, were significantly higher ($p = 0.03$) among the Ob (13.2 %), compared to both AF (8.8 %) and nWC individuals (8.1 %) (Fig. 3).

4. Discussion

The detection of modifiable risk factors for micro- and macrovascular damage is crucial for the proper and individualized clinical management of diabetic patients in the precision medicine era.

Our study investigated the association between generalized and abdominal adiposity and the presence of chronic vascular complications in Caucasian T2D outpatients. We found that non-obese T2D individuals without visceral fat distribution have a lower prevalence of DR compared to both obese patients and, notably, also to

Table 1 Clinical and biochemical characteristics of the studied population.

Patients characteristics	OVERALL (n = 769)	nWC (n = 220)	AF (n = 260)	Ob (n = 289)	P
Clinical characteristics					
Age (years)	67.2 ± 10.0	66.4 ± 11.3	69.3 ± 8.6[a]	65.8 ± 9.8	**<0.01**
Gender: Male (n, %)	443 (57.6)	182 (82.7)[b]	121 (46.5)	140 (48.4)	**<0.01**
Smoke (n, %)	325 (42.6)	106 (48.2)	109 (41.9)	110 (38.1)	0.07
BMI (Kg/m^2)	28.9 ± 5.2	24.0 ± 2.5[b]	26.9 ± 2.1	34.3 ± 3.8	**<0.01**
WC (cm)	104.5 ± 12.1	92.5 ± 6.4[b]	102.9 ± 7.1	114.8 ± 9.8	**<0.01**
W/H	0.98 ± 0.7	0.95 ± 0.5[b]	0.99 ± 0.6	1.00 ± 0.9	**<0.01**
Diabetes duration (years)	15.0 ± 9.7	14.6 ± 9.8	16.1 ± 9.1	14.4 ± 9.9	0.12
HbA1c (%)	7.3 ± 1.1	7.1 ± 1.0[b]	7.3 ± 1.0	7.4 ± 1.1	**0.02**
Systolic blood pressure (mmHg)	132 ± 16	130 ± 17	132 ± 16	134 ± 15	0.11
Diastolic blood pressure (mmHg)	76 ± 10	74 ± 10[b]	76 ± 9	77 ± 1	**<0.01**
Total cholesterol (mg/dl)	161 ± 38	158 ± 36	162 ± 36	161 ± 38	0.29
LDL-C (mg/dl)	87 ± 33	87 ± 32	88 ± 32	87 ± 34	0.93
HDL-C (mg/dl)	46 ± 13	46 ± 14	48 ± 12	45 ± 14	0.20
Triglycerides (mg/dl)	133 ± 73	115 ± 68[b]	130 ± 65	148 ± 81	**<0.01**
Diabetes therapy					
Metformin (n, %)	621 (80.4)	164 (76.3)	212 (80.9)	245 (83.1)	0.16
GLP-1 receptor agonists (n, %)	135 (17.5)	20 (9.3)	39 (14.9)	76 (25.8)[c]	**<0.01**
SGLT-2 inhibitors (n, %)	127 (16.5)	35 (16.3)	42 (16.0)	50 (16.9)	0.96
DPP-4 inhibitors (n, %)	123 (15.9)	52 (24.2)[b]	51 (19.5)	20 (6.8)	**<0.01**
Pioglitazone (n, %)	23 (3.0)	11 (5.1)	5 (1.9)	7 (2.4)	0.09
Acarbose (n, %)	50 (6.5)	17 (7.9)	18 (6.9)	15 (5.1)	0.42
Sulfonylureas or Repaglinide (n, %)	67 (8.7)	21 (9.8)	25 (9.5)	21 (7.1)	0.48
Insulin (n, %)	366 (47.4)	87 (40.5)[b]	126 (48.1)	153 (51.9)	**0.04**
Diabetes complications					
Macrovascular					
MI (n, %)	138 (18.1)	35 (16.2)	53 (20.5)	50 (17.5)	0.43
Stroke (n, %)	67 (8.8)	17 (7.8)	23 (8.9)	27 (9.4)	0.80
Carotid artery atherosclerosis (n, %)	463 (61.3)	144 (66.7)	163 (64.4)	172 (60.1)	0.45
Lower limb atherosclerosis (n, %)	259 (34.8)	72 (33.6)	97 (38.5)	90 (32.5)	0.28
Microvascular					
Retinopathy (n, %)	216 (28.9)	45 (21.1)[b]	81 (32.0)	90 (31.9)	**0.01**
Albuminuria (n, %)	279 (41.6)	86 (44.8)	94 (41.6)	99 (39.3)	0.58
eGFR<60 ml/min (n, %)	178 (24.4)	42 (20.8)	67 (26.8)	69 (25.0 %)	0.13
Peripheral neuropathy (n, %)	185 (25.7)	46 (22.3)	67 (27.2)	72 (26.9)	0.39

Data are presented as means ± standard deviation (SD) or numbers and percentages (%).
Abbreviations: nWC, non-obese with normal WC; AF, non-obese with excess of abdominal fat; Ob, obese; BMI, body mass index; WC, waist circumpherence; W/H, waist to hip ratio; HbA1c, glycated hemoglobin; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; GLP-1, glucagon like peptide-1; SGLT-2, sodium-glucose cotransporter-2; DPP-4, Dipeptidyl Peptidase 4; MI, myocardial infarction; eGFR, estimated glomerular filtration rate.
[a] Indicates statistical significance vs. nWC and Ob.
[b] Indicates statistical significance vs. AF and Ob.
[c] Indicates statistical significance vs. nWC and AF.

Table 2 Multivariate logistic regression model exploring the association between clinical and biochemical parameters and the occurrence of diabetes retinopathy in the studied population.

	B	SE	Wald	OR (95 % CI)	P
Groups based on BMI and WC (nWC, AF, and OB)	0.25	0.12	4.31	1.28 (1.01–1.61)	**0.04**
Gender	−0.35	0.20	3.25	0.70 (0.48–1.03)	0.07
Smoke	−0.07	0.19	0.13	0.94 (0.65–1.35)	0.72
Diabetes duration	0.07	0.01	44.60	1.07 (1.05–1.10)	**<0.01**
HbA1c	0.04	0.09	0.24	1.05 (0.88–1.24)	0.63
LDL-C	−0.001	0.003	0.06	1.00 (0.99–1.01)	0.81
Triglycerides	−0.0003	0.001	0.05	1.00 (0.00–1.00)	0.82
Systolic blood pressure	0.01	0.007	4.03	1.01 (1.0003–1.03)	**0.045**
Diastolic blood pressure	−0.007	0.01	0.40	0.99 (0.97–1.01)	0.53
Insulin	0.52	0.20	6.80	1.68 (1.14–2.50)	**<0.01**
GLP-1 receptor agonists	−0.14	0.24	0.35	0.87 (0.54–1.40)	0.55
DPP-4 inhibitors	−0.11	0.26	0.18	0.90 (0.53–1.50)	0.68
Constant	*−3.78*	*1.08*	*12.28*	*0.02*	*<0.001*

Abbreviations: B, regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval; BMI, body mass index; nWC, non-obese with normal waist circumference; AF, non-obese with excess of abdominal fat; OB, obese; HbA1c, glycated hemoglobin; LDL-C, low density lipoprotein cholesterol; GLP-1, glucagon like peptide-1; SGLT-2, sodium-glucose cotransporter-2.

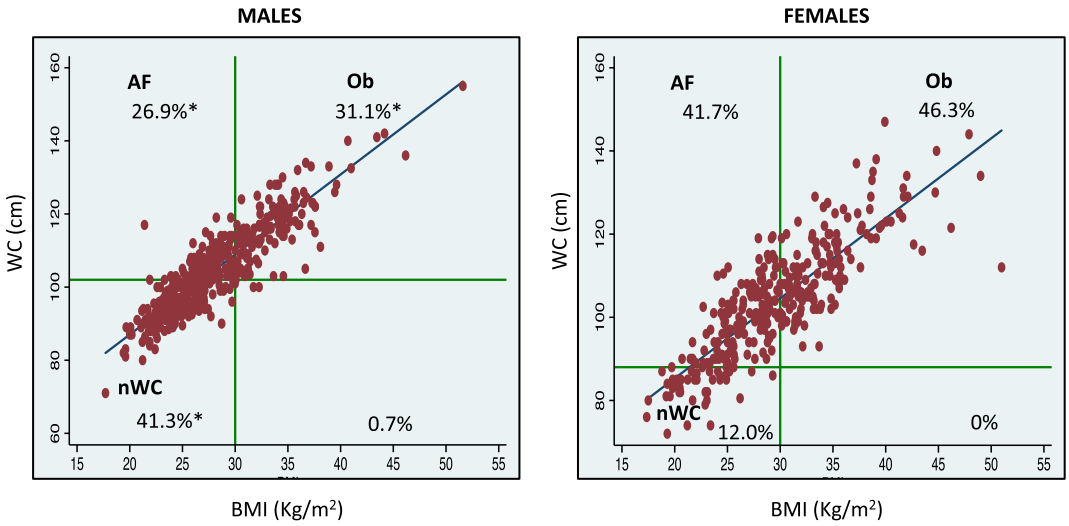

Figure 1 Correlation between BMI and WC in males and females. Abbreviations: BMI, body mass index, WC, waist circumpherence, nWC, non-obese with normal WC; AF, non-obese with excess of abdominal fat; Ob, obese. $*P<0.01$ at Pearson χ^2 test in males vs. females.

the patients with visceral fat distribution but classified as non-obese based on the BMI. While exploring the association between adiposity and the degree of DR, we found that the excess of visceral fat contributes to the development of NPDR in non-obese individuals similarly to those affected by obesity. Instead, the prevalence of the advanced stages of DR was mainly burdened by the presence of obesity.

Similarly to our data, a recent meta-analysis by Fu and colleagues, including 24 studies for a total of 5596 DR subjects and 17907 non-DR subjects, found that abdominal obesity was associated with an increased risk of DR, mainly in Caucasian population, but no correlation between abdominal adiposity and the different degrees of DR was detected [26]. These findings, support the meaning that BMI should not be considered as an accurate measure of fat mass excess (as it also includes both muscle and bone mass), and further measurements, such as WC and, or W/H ratio, should be evaluated to assess fat distribution and its associated metabolic and vascular risk.

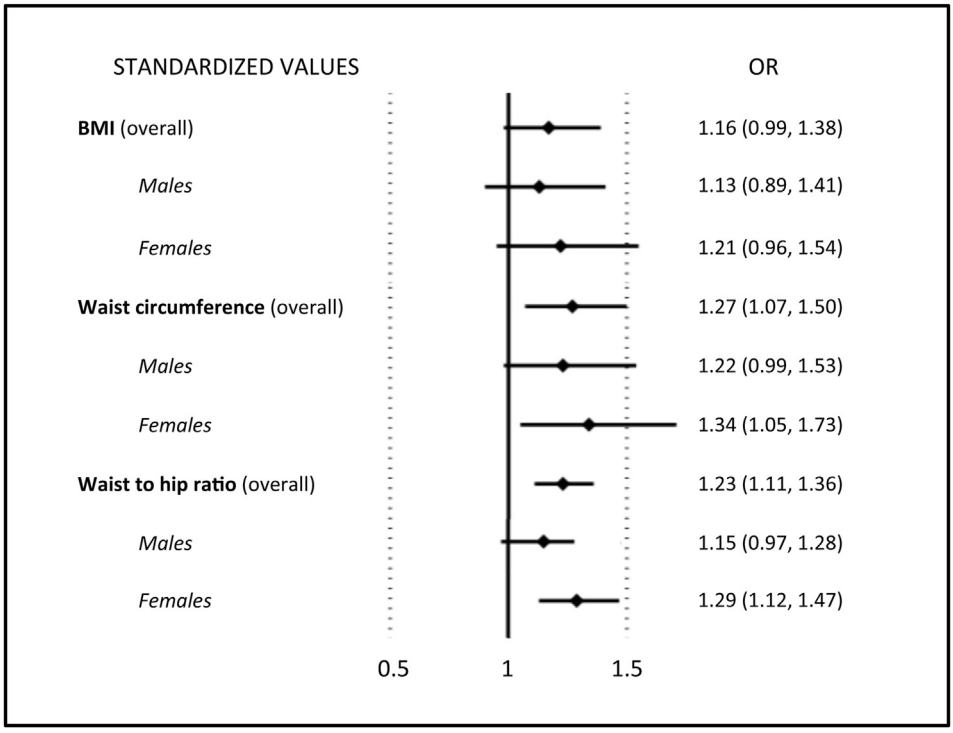

Figure 2 Relation between diabetic retinopathy and standardized indices of total and centripetal fat distribution. Data were adjusted for HbA1c, diabetes duration, triglycerides, smoking habit, systolic and diastolic blood pressure, and insulin therapy.

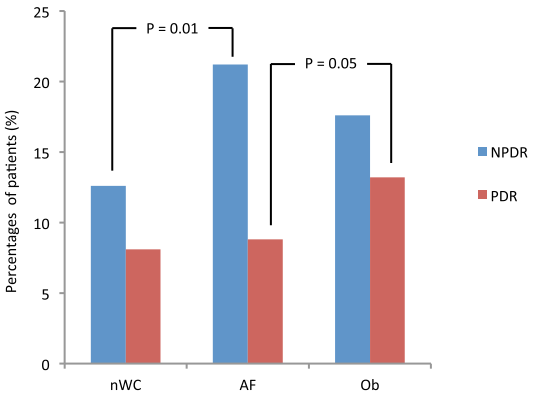

Figure 3 Prevalence of the different stage of diabetic retinopathy within the considered study groups based on BMI and WC. Abbreviations: nWC, non-obese with normal WC; AF, non-obese with excess of abdominal fat; Ob, obese; NPDR, non-proliferative DR; PDR, proliferative DR.

While the positive association between the macrovascular diabetes complications and generalized/visceral obesity has been strongly demonstrated [27,28], the evidence regarding the ocular microvascular consequences of chronic fat mass excess are not conclusive and, conflicting. Diabetes retinopathy is the worldwide most common visual complication of diabetes mellitus representing the leading cause of vision loss and blindness in the working-age population [29]. Modifiable (i.e., hyperglycaemia, hypertension, hyperlipidemia, dietary intake, physical activity, obesity, and cigarette smoke) and non-modifiable factors (i.e., duration of diabetes, puberty, pregnancy and genetic/epigenetic susceptibility) are involved in its development [30,31].

Most of the evidence on the influence of fat mass excess in the course of DR arises from Asian studies, and reported either the lack [32] or even an inverse association between adiposity and DR [33,34]. Conversely, western studies, such as the Hoorn Study, demonstrated a significant positive association between higher BMI and the risk of DR [35].

These conflicting data could be explained by the inappropriate use, in Asian subjects, of BMI classifications validated among white populations [36]. Nevertheless, further analyses, based on Asian endorsed BMI categorizations, confirmed this divergence on the role of adiposity in the risk for DR [34]. However, these studies did not consider the mutually confounding effect of generalized and abdominal obesity, thus reducing the strength of their evidence. Hence, the need to carry out studies focused on the differential impact of generalized and visceral fat distribution on the risk for DR. Further insights on this relationship arise, once again, from an Asian cross-sectional study examining the differential association between generalized/abdominal adiposity and the prevalence of DR. The authors found that, while a higher BMI was inversely associated with retinopathy, a higher W/H ratio was associated with the presence and severity of this complication, specifically among women [22]. Our study confirmed the direct W/H-DR association, but in our investigation, also BMI was directly associated to DR.

The pathophysiological mechanisms underlying the detrimental impact of a higher BMI and W/H ratio on DR are, so far, unclear. However, it is known that abdominal obesity contributes to insulin resistance, inflammation, and oxidative stress, which are believed to contribute to the pathogenesis of DR [13,37].

Weight loss could improve both glucose control and several risk factors for DR (e.g., blood pressure, lipid profile, oxidative and inflammatory stress). Due to the cross sectional design of our study, we cannot evaluate neither the longitudinal weight change of the observed subjects, nor its influence in the occurrence or progression of DR. Current evidence on this matter, although not conclusive, suggest that weight reduction in overweight/obese subjects could reduce the risk of DR. In “The Finnish Diabetes Prevention Study” [38], a lifestyle intervention (diet and physical activity) was related to a decreased occurrence of retinal microaneurysms compared to placebo group. Similarly, in a large Korean nationwide prospective study [39], evaluating 181.872 subjects with new-onset diabetes, weight loss was associated to a lower risk for DR (HR, 0.52; 95 % CI, 0.33 to 0.83), while weight gain with a three-fold increased risk of this complication (HR, 3.20; 95 % CI, 2.51 to 4.08). Recently, a Danish nationwide cohort study [40] did not observe any significant association between weight loss after bariatric surgery and the risk for DR. Thus, in our opinion, further studies are needed to better clarify the role of weight loss on the course of DR.

Interestingly, our research highlights on some gender-specific findings: both generalized and visceral adiposity are much more frequent among females (OR 5.58, 95 CI 3.74−8.31; $p<0.01$), where are associated with the presence of DR. Previous studies found that women are at higher risk not only for cardiovascular disorders [41], but also for diabetes-related eye microvascular damage [22]. Therefore, it is conceivable that this postulated gender-specific susceptibility might play a role in the direct association between adiposity and DR, despite further studies are necessary to better explain the mechanisms underlying this association.

The first limitation of our study is the cross-sectional design, which does not allow determining either the causality or the temporal sequence of the reported associations. Secondarily, the fact that the studied population is composed only by Caucasian subjects affects the generalizability of our results. Finally, our study was based on the evaluation of indirect parameters of abdominal obesity in a population of individuals consecutively referred to our Center. Therefore, a more precise direct Dual-energy X-ray absorptiometry (DXA)- or computed tomography (CT)-derived measure of adiposity would have significantly increased the impact of our findings.

The current knowledge on risk factors and etiopathogenesis of DR did not provide a comprehensive view of this disease. Indeed, several diabetes subjects without the already known risk factors favouring the retinal damage could also develop DR.

Our data contribute to clarify the role of adiposity in the development of DR, both identifying which anthropometric phenotypes, among T2D population, might be related to the development of microvascular eye damage in its different stages and to get insight the gender-related distribution of this phenomenon. Nevertheless, further longitudinal studies with larger population are needed to better specify the role of chronic excess of adiposity in DR.

Preventive and therapeutic strategies intended to reduce body weight and adipose tissue, focused on lifestyle behaviour and pharmacological interventions, are mandatory to tackle the increased burden of DR and to mitigate the fearful advanced stages of retinal injury and the vision-related worsening of quality of life.

Declaration of competing interest

The authors have nothing to disclose.

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