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The Burden of Obesity in Type 1 Diabetic Subjects: A Sex-specific Analysis From the AMD Annals Initiative

Annalisa Giandalia,[1,*] Giuseppina Tiziana Russo,[1,*] Patrizia Ruggeri,[2] Annalisa Giancaterini,[3] Elisabetta Brun,[4] Mariarosaria Cristofaro,[5] Anna Bogazzi,[6] Maria Chiara Rossi,[7] Giuseppe Lucisano,[7] Alberto Rocca,[8] Valeria Manicardi,[9] Paolo Di Bartolo,[10] Graziano Di Cianni,[11] Chiara Giuliani,[12,*] and Angela Napoli[13,14,15,*] On behalf of the AMD Annals Study Group and of the Gender Medicine Study Group of AMD

[1]Department of Clinical and Experimental Medicine, University of Messina, 98100 Messina, Italy
[2]UOD Diabetes Center, ASST Cremona, 26100 Cremona, Italy
[3]UOSD Endocrine, Metabolic and Nutrition Diseases, ASST Brianza, Desio Hospital, 20832 Desio, Italy
[4]UOC Endocrine, Metabolic and Nutrition Diseases, Ospedale Civile di Vicenza, 36100 Vicenza, Italy
[5]S.C. Diabetes and Endocrine Diseases, Cardarelli Hospital, 86100 Campobasso, Italy
[6]SSVD Diabetes and Endocrine Diseases, ASL TO 3, 10024 Torino, Italy
[7]Center for Outcomes Research and Clinical Epidemiology, CORESEARCH, 75100 Pescara, Italy
[8]SS Diabetes and Metabolic disease, Bassini Hospital, Cinisello Balsamo, 20019 Milano, Italy
[9]Fondazione AMD, 42121 Reggio Emilia, Italy
[10]AUSL Diabetes Unit Romagna, 48121 Ravenna, Italy
[11]Diabetes and Metabolic Diseases Unit, Health Local Unit North-West Tuscany, 57100 Livorno, Italy
[12]Department of Experimental Medicine, Sapienza University of Rome, 00044 Rome, Italy
[13]Israelitico Hospital, 00044 Rome, Italy
[14]Cdc Santa Famiglia, 00044 Rome, Italy
[15]Human Nutrition Sciences, International Medical University Unicamillus, 00044 Rome, Italy
Correspondence: Annalisa Giandalia, MD, Department of Clinical and Experimental Medicine, University of Messina, Via C. Valeria, 98100 Messina, Italy. Email: agiandalia@yahoo.it.
*These authors equally contributed to the manuscript.

Abstract

Objective: Obesity is a growing emergency in type 1 diabetes (T1D). Sex differences in obesity prevalence and its clinical consequences in adult T1D subjects have been poorly investigated. The aim of this study was to investigate the prevalence of obesity and severe obesity, clinical correlates, and potential sex differences in a large cohort of T1D subjects participating to the AMD (Associazione Medici Diabetologi) Annals Initiative in Italy.

Research Design and Methods: The prevalence of obesity [body mass index(BMI) ≥ 30 kg/m^2] and severe obesity (BMI ≥ 35 kg/m^2) according to sex and age, as well as obesity-associated clinical variables, long-term diabetes complications, pharmacological treatment, process indicators and outcomes, and overall quality of care (Q-score) were evaluated in 37 436 T1D subjects (45.3% women) attending 282 Italian diabetes clinics during 2019.

Results: Overall, the prevalence of obesity was similar in the 2 sexes (13.0% in men and 13.9% in women; mean age 50 years), and it increased with age, affecting 1 out of 6 subjects ages >65 years. Only severe obesity (BMI >35 kg/m^2) was more prevalent among women, who showed a 45% higher risk of severe obesity, compared with men at multivariate analysis. Cardiovascular disease risk factors (lipid profile, glucose, and blood pressure control), and the overall quality of diabetes care were worse in obese subjects, with no major sex-related differences. Also, micro- and macrovascular complications were more frequent among obese than nonobese T1D men and women.

Conclusions: Obesity is a frequent finding in T1D adult subjects, and it is associated with a higher burden of cardiovascular disease risk factors, micro- and macrovascular complications, and a lower quality of care, with no major sex differences. T1D women are at higher risk of severe obesity.

Key Words: obesity, type 1 diabetes, sex, age, AMD Annals Initiative

Abbreviations: AMD, Associazione Medici Diabetologi (Italian Association of Clinical Diabetologists); BMI, body mass index; BP, blood pressure; CSII, continuous subcutaneous insulin infusion; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; MAU, micro/macroalbuminuria; SBP, systolic blood pressure; SGLT2i, sodium/glucose cotransporter-2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes.

The prevalence of type 1 diabetes (T1D) is growing worldwide, with an estimate of an incidence increase of 2.7% to 3.4% per year in recent decades [1, 2]. In Italy, the prevalence of T1D is 0.5% [3, 4].

Obesity in T1D has progressively increased in recent years. In the DCCT/EDIC study, 30% of youth with T1D had overweight/obesity [5], and a European study reported a prevalence of 15% of obesity in adults with T1D [6].The estimated prevalence of obesity in people with T1D, however, ranges between 2.8% and 37.1%, varying by the definition of obesity, age of the examined patients, and country [7].

Notably, in overweight/obese children, T1D is diagnosed at younger ages, and obesity has been suggested to be an *accelerator* in the pathogenesis of T1D [8, 9]. Obesity is also associated with insulin resistance and other cardiovascular (CV) risk factors in T1D patients [5]. In this regard, the FinnDiane study showed that more than 40% of T1D subjects had the diagnostic criteria for the metabolic syndrome [10]. Furthermore, the impact of some risk factors, such as hypertension and hyperglyceridemia, seems to increase with the degree of obesity in subjects with T1D [11].

The prevalence of severe obesity, ie, the presence of body mass index (BMI) value ≥ 35 kg/m^2, has been reported to be higher in women than in men with type 2 diabetes (T2D) [12], with a higher risk for cardiovascular disease (CVD) mortality [13]. Furthermore, obesity phenotypes may differently impact on CVD risk in men and women with acute coronary syndrome, including T2D subjects [14].

Data from the DPV database (Diabetespatienten Verlaufsdokumentation) on 53.108 young T1D patients ages <20 years showed that T1D girls were at higher risk of obesity [15]. Conversely, in adult T1D subjects, sex differences in obesity and its correlates are still largely unexplored.

Sex differences in the quality of care relative to the year 2011 were reported in the 28 802 T1D participants to the AMD Annals Initiative, an ongoing study started in 2006 and involving approximately one-third of diabetes clinics in Italy with the aim of exploring quality of care in both T2D and T1D subjects [16]. In this report, T1D women showed a 33% higher likelihood of having out-of-target glycated hemoglobin A1C (HbA1c) values, 29% lower risk of high blood pressure values, and 27% lower risk of micro/macroalbuminuria (MAU) than T1D men, while low-density lipoprotein LDL-cholesterol (LDL-c) levels, estimated glomerular filtration rate (eGFR), and a validated indicator of overall quality of care (Q-score) did not significantly differ [17, 18]. However, an age- and BMI-stratified analysis was not reported in that study; furthermore, specific correlates of the obese phenotypes have not been investigated separately for T1D men and women.

The aim of the current study was to analyze potential age and sex differences in the prevalence of obesity and its association with major clinical variables, including metabolic characteristics, CVD risk factors, and chronic diabetes complications, as well as with several indicators of the quality of diabetes care, including a validated score (Q-score), separately in T1D men and women participating in the AMD Annals Initiative.

Research Design and Methods

The AMD Annals Initiative

Since 2006, the Italian Association of Clinical Diabetologists [Associazione Medici Diabetologi-(AMD)] promoted a continuous quality improvement initiative called AMD Annals.

In this context, AMD identified a set of process and intermediate outcome indicators to be used for benchmarking activities [19, 20]. Furthermore, the use of glucose-lowering, antihypertensive, and lipid-lowering drugs is evaluated.

Centers share the same software for data extraction from electronic medical records. Data are collected in a standardized format (AMD Data File). The database is anonymous by design. Information is extracted by the medical records system without any data allowing the identification of patients and centers. Both are identified by numeric codes, and analysis is centralized and based on aggregated data [19, 20]. Given the nature of the study, the Italian regulations require an ethics approval but not the signature of the informed consent. The entire project is conducted without allocation of extra resources or financial incentives but simply through a physician-led effort, made possible by the commitment of the specialists involved.

Sample Selection

All patients with diagnosis of T1D were included. Clinical data collected during the year 2019 were extracted from electronic medical records. In case of multiple records collected during the year for the same patient, the last available value was included in the quality-of-care profiling [19-23].

Obesity was defined according to BMI values: BMI < 30 kg/m^2 for nonobese and BMI $\geq$30 kg/m^2 for obese subjects. The severity of obesity was categorized according to BMI values: 30-34.9 kg/m^2 class I; 35-39.9 kg/m^2 class II; $\geq$40 kg/m^2 class III. Class II and III obesity were combined and defined as severe obesity (BMI $\geq$ 35 kg/m^2).

Quality-of-Care Indicators

Process measures are expressed as the proportion of patients with at least 1 evaluation of the following clinical parameters during the previous year: HbA1c, blood pressure (BP), lipid profile [LDL-c or total and high-density lipoprotein cholesterol (HLD-c) and triglycerides], renal function, and eye examination [19-23].

Intermediate outcome measures include the proportion of patients with at-target values for major risk factors. Outcomes are considered satisfactory if HbA1c levels are $\leq$7.0% ($\leq$53 mmol/mol), BP values are $\leq$130/80 mmHg, and LDL-c levels are <2.59 mmol/L (100 mg/dL).

Indicators of treatment intensity/appropriateness are also measured, taking into consideration the use of pharmacologic treatments in relation to the achievement of the targets: no lipid-lowering agents despite LDL-c $\geq$ 3.37 mmol/L (130 mg/dL), no antihypertensive treatments despite BP $\geq$ 140/90 mmHg, no angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers despite MAU, not treated with antiplatelets in spite of history of CVD events (indicating patients not adequately treated) and LDL-c $\geq$ 3.37 mmol/L (130 mg/dL) in spite of lipid-lowering treatment, and BP $\geq$140/90 mmHg in spite of antihypertensive treatment (indicating patients not reaching targets in spite of treatment) [19-23].

The quality-of-care summary score (*Q-score*) was derived from the combination of process and outcome indicators based on levels and treatment of HbA1c, blood pressure, LDL-c, and MAU [23]. The score ranges between 0 and 40; the higher the score, the better the quality of care. Two validation studies [17, 18] documented that the risk to develop a

new CV event was 80% higher in patients with a score <15% and 20% higher in those with a score between 15 and 25, as compared to those with a score >25.

If not recorded in electronic medical records, LDL-c was estimated by the Friedwald equation. MAU was defined as albumin excretion rate ≥20 mcg/min, albumin/creatinine ratio >2.5 (men) or >3.5 (women) mg/mmol, or urine albumin >30 mg/L. The glomerular filtration rate was calculated with the Chronic Kidney Disease Epidemiology Collaboration formula (24).

Statistical Analyses

Patients' characteristics and quality indicators according to sex are described as mean and standard deviation or frequencies, as appropriate. The denominators for the different quality indicators vary according to the availability of the information in the index year. No missing imputation was performed. Patient characteristics and quality indicators by BMI classes or sex (overall and by age classes) were compared using the Mann-Whitney U-test for continuous variables and the χ^2 test for categorical ones.

Multivariate analyses were also performed to identify correlates of obesity (BMI ≥30) and severe obesity (≥35 kg/m^2) in the total study population and in the 2 sexes separately. Covariates tested in the model were sex, age, diabetes duration, smoking habit, HbA1c levels, lipid profile, BP values, eGFR, MAU, diabetes treatments, treatment with antiplatelets, antihypertensive or lipid-lowering agents, and history of micro- and macrovascular complications. Backward variable selection was adopted. Results are expressed as odds ratios with their 95% confidence intervals. P-values <.05 were considered statistically significant. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

Results

BMI Classes Distribution in T1D Subjects According to Sex

Data from 37 436 T1D subjects, 20 474 men (54.7%) and 16 971 women (45.3%), mean age 49.6 years, mean BMI 28.6 kg/m^2, seen in 282 Italian diabetes outpatient clinics during the year 2019 were included in the present analysis. Distribution of BMI classes according to sex is shown in Fig. 1.

Overall, 49.6% of T1D men and 59.0% of T1D women had normal BMI values (<25 kg/m^2), while overweight (BMI 25-29.9 kg/m^2) was observed in 37.4% of men and 27.1% of women. The prevalence of obesity (BMI >30 kg/m^2) was similar in the 2 sexes (13.9% vs 13.0% in women and men, respectively). The distribution of obesity classes is shown in the legend of the same figure (Fig. 1): the prevalence of severe obesity (classes II and III obesity, BMI ≥35 kg/m^2) was nearly double among T1D women compared to men (4.0% in women vs 2.3% in men) (P < .0001) (Fig. 1).

Obesity in T1D Subjects by Age and Sex

Distribution of BMI classes by age and sex is shown in Supplementary Table S1 (25). Overall, mean BMI values increased with age in both sexes, ranging from 21.4 ± 4.0 kg/m^2 in men and 22.3 ± 4.5 kg/m^2 in women ages ≤18 years to

26.1 ± 4.0 kg/m^2 in men and 25.6 ± 5.1 kg/m^2 in women ages >65 years (P < .0001 for both sexes).

As shown in Fig. 2, the prevalence of obesity progressively increased with age in both sexes. Obesity prevalence ranged from 1.7% before the age of 18 years to 16.3% after 65 years in men and from 6.2% (<18 years) up to 17.2% (>65 years) in women. Consistently, severe obesity also increased with age, ranging from 0.7% to 2.2% in T1D men and from 1.7% to 5.0% in women (Fig. 3).

Clinical Characteristics and Pharmacological Treatments in T1D Men and Women According to the Presence of Obesity

The distribution of clinical characteristics, major CV risk factors, and diabetes long-term complications in obese and nonobese subjects in T1D men and women separately is shown in Table 1. Overall, obese subjects were older; had a longer diabetes duration; had higher HbA1c, triglycerides, systolic blood pressure (SBP), and diastolic blood pressure (DBP) and lower HDL-c levels; and were less frequently smokers, irrespective of sex, whereas LDL-c levels were higher in obese women only.

As for chronic diabetes complications, impaired renal function (eGFR < 60 mL/min) was also overall more frequent among obese than nonobese subjects (9.5% vs 15.7% in nonobese and obese men; 10.9% vs 17.8% in nonobese and obese women, respectively; P < .0001 for both comparisons), especially in women, with only 52% of obese T1D women having an eGFR ≥90 mL/min. The prevalence of MAU was also significantly higher among obese subjects in both sexes, especially in men.

Notably, also retinopathy and CV events were more frequent in obese than in nonobese subjects, both among men (retinopathy: 32.6% vs 47.1%; CV events: 5.6% vs 9.9%) and women (retinopathy: 30.6% vs 43.9%, CV events: 3.3% vs 6.1%) (P < .0001 for all comparisons).

As for treatments, subjects with obesity were more frequently treated with continuous subcutaneous insulin infusion (CSII) than nonobese ones, irrespective of sex. Similarly, also treatment with metformin, SGLT2 inhibitors (SGLT2i), lipid-lowering agents, and antihypertensive and antiplatelets drugs was more frequent among men and women with obesity as compared to nonobese subjects (Table 1).

Diabetes Care Process and Outcome Indicators in T1D Men and Women According to the Presence of Obesity

Diabetes care, process, and outcome indicators in obese and nonobese T1D men and women are shown in Table 2. Process indicators, ie, the proportion of patients who were yearly monitored for major clinical parameters, were also analyzed according to sex and obesity status (Table 2). Obesity did not influence these parameters, with the exceptions of creatinine measurement, which was more frequent among obese than nonobese subjects in both sexes, and BP, which was slightly less monitored in obese T1D men.

Table 2 also shows that the achievement of HbA1c, LDL-c, and BP recommended targets was less frequent among obese subjects both in T1D men and women. Moreover, indicators of appropriateness of treatment showed that obese T1D subjects were less appropriately treated than nonobese ones in
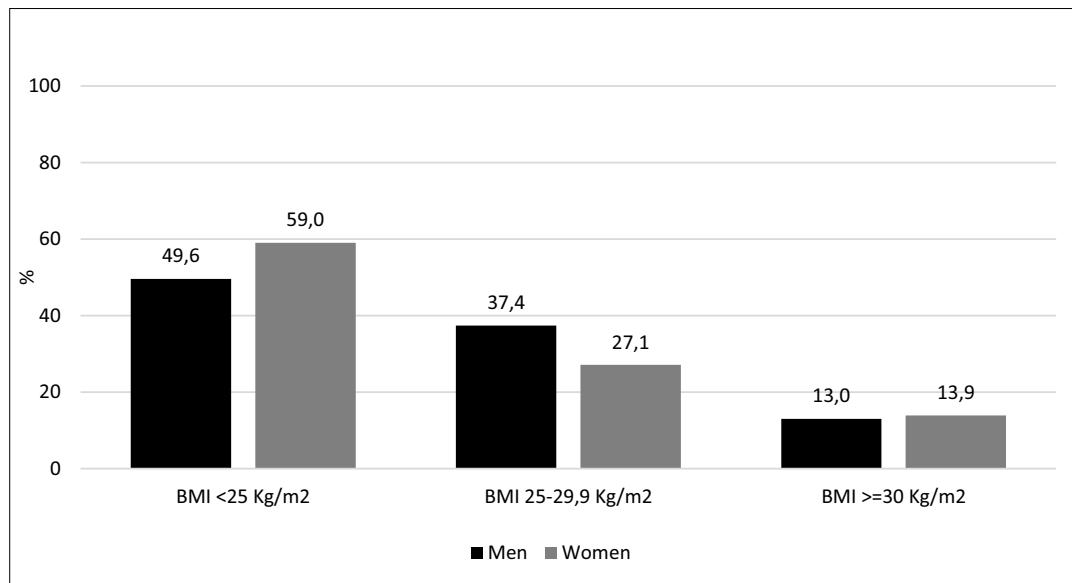
Data are expressed as % of subjects within each BMI-class.

Mean BMI values in study subjects according to gender and BMI-classes

BMI class (kg/m²)	Gender	N	%	BMI (kg/m²)					P-Value*
				Mean	Standard Deviation	Standard Error	Minimum	Maximum	
BMI ≤ 25	Female	9789	59.0	21,7	2,1	0,0	12,3	25,0	**< 0,0001**
	Male	9922	49.6	22,4	1,9	0,0	12,0	25,0	
BMI 25.1-29.9	Female	4480	27.1	27,1	1,4	0,0	25,0	30,0	0,108
	Male	7451	37.4	27,1	1,4	0,0	25,0	30,0	
BMI ≥ 30.0	Female	2313	13.9	33,8	3,7	0,1	30,0	58,8	**< 0,0001**
	Male	2608	13.0	32,9	3,1	0,1	30,0	59,9	
BMI 30.0-34.9	Female	1655	9.9	32,0	1,4	0,0	30,0	35,0	**< 0,0001**
	Male	2137	10.7	31,8	1,3	0,0	30,0	35,0	
BMI ≥ 35	Female	658	4.0	38,5	3,7	0,1	35,0	58,8	**0,0368**
	Male	471	2.3	38,0	3,5	0,2	35,0	59,9	

Data are expressed as mean BMI with standard deviation, standard error and minimum and maximum within each BMI-class
*Unpaired t-Test. Statistically significant p-value (<0.05) are in bold

Figure 1. Body mass index classes distribution in men and women with type 1 diabetes from the AMD Annals Initiative according to sex.

both sexes, with the exception of subjects with previous CV events and those being treated with antiplatelets at the same rate irrespective of obesity status; as for subjects with out-of-target values in spite of treatment, a marker of therapeutic inertia, and/or lack of adherence, no differences were noted for LDL-c, whereas for BP, the lack of target values in spite of treatment was higher among obese subjects, both in men and women. Furthermore, Q-score values, an indicator of the overall quality of diabetes care, were significantly lower in T1D obese that in nonobese patients in both sexes (Table 2).

Factors Associated With Obesity and Severe Obesity in T1D Men and Women

Table 3 shows factors associated with obesity and severe obesity in T1D patients at multivariate analyses. Notably, the

impact of sex was larger in severe obesity, as being female conferred a small (10%) increase in obesity risk but a 45% higher risk of severe obesity compared to men.

Furthermore, increasing age, duration of diabetes, LDL-c, and BP levels were associated with a higher likelihood of obesity and severe obesity. Obesity and severe obesity were also associated with a higher likelihood of being treated with CSII, metformin, SGLT2i, and antihypertensive and lipid-lowering drugs. As for diabetes complications, obesity and severe obesity were associated with a higher likelihood of retinopathy and a lower likelihood of eGFR <60 mL/min/1.73m². Severe obesity was also associated with a higher likelihood of MAU.

Similar associations, although with some differences in the strength of these associations, were noted when multivariate models were applied in T1D men and women separately (Supplementary Tables S4 and S5) (25).
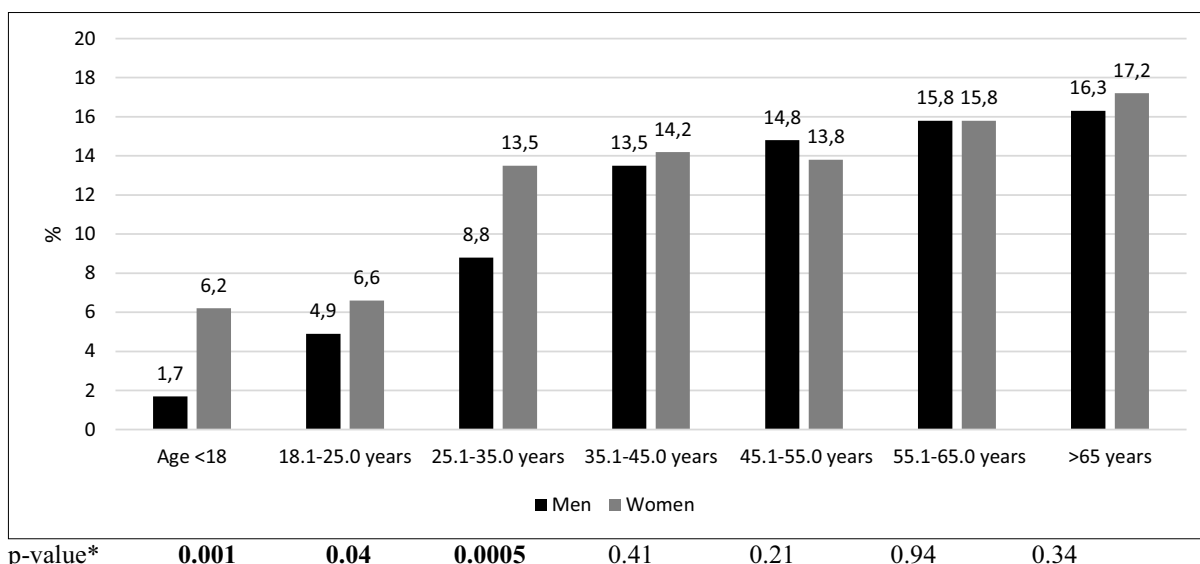
*chi-square test. Statistically significant p-value (<0.05) are in bold

Data are expressed as mean BMI (standard deviation) within each age-group.
*Unpaired t-Test. Statistically significant p-value (<0.05) are in bold

Mean BMI values in men and women with obesity (BMI ≥30 Kg/m2) according to age-classes

Age class (years)	Gender	N	%	BMI (kg/m2)					
				Mean	Standard Deviation	Standard Error	Minimum	Maximum	P-Value*
<18.0	Female	22	6,2	33,0	3,1	0,7	31,1	40,9	0,3529
	Male	7	1,7	34,5	2,2	0,8	32,3	37,5	
18.1-25.0	Female	85	6,6	33,9	3,1	0,3	30,1	42,4	0,0402
	Male	79	4.9	33,0	2.9	0,3	30.0	44,1	
25.1-35.0	Female	274	13.5	33,8	3.8	0,2	30.0	56,5	0,0039
	Male	257	8.8	33,0	3.1	0,2	30.0	50,3	
35.1-45.0	Female	397	14.2	33,9	3.8	0,2	30.0	51,3	0,0003
	Male	511	13.5	33,0	3.3	0,1	30.0	59,9	
45.1-55.0	Female	502	13.8	34,0	4.0	0,2	30.0	58,8	0,0005
	Male	705	14.8	33,2	3.3	0,1	30.0	55,4	
55.1-65.0	Female	480	15.8	33,7	2.4	0,2	30.0	52,9	<,0001
	Male	575	15.8	32,8	2.9	0,1	30.0	48,5	
>65.0	Female	543	17.2	33,9	3.8	0,2	30.0	56,4	<,0001
	Male	467	16.3	32,5	2.5	0,1	30.0	49,6	

Figure 2. Prevalence of obesity in type 1 diabetes subjects participating in the study, according to sex and age classes (years).

Sex Differences in Clinical Characteristics, Long-term Diabetes Complications, and Process Indicators and Outcomes in the Obese and Nonobese Subgroups

Potential sex differences in the clinical characteristics within the obese and nonobese groups were also analyzed (Supplementary Table S2) (25). In both obese and normal weight groups, when comparing men vs women, women were older than men, despite a similar diabetes duration.

Women also showed higher values of HbA1c, total cholesterol, and HDL-c; lower values of SBP, DBP, and triglycerides; and a lower percentage of smokers when compared to T1D men, both in the group of subjects with obesity and in the group of nonobese subjects.

Mean LDL-c levels were higher in women than in men in the obese group, whereas no differences were observed in the normal-weight group. Cardiovascular events were overall more frequent in T1D men than in women, in both the obese and nonobese groups; conversely, retinopathy was equally frequent in both sexes in the obese group, while it was more frequent among men than in women in the group of nonobese subjects.
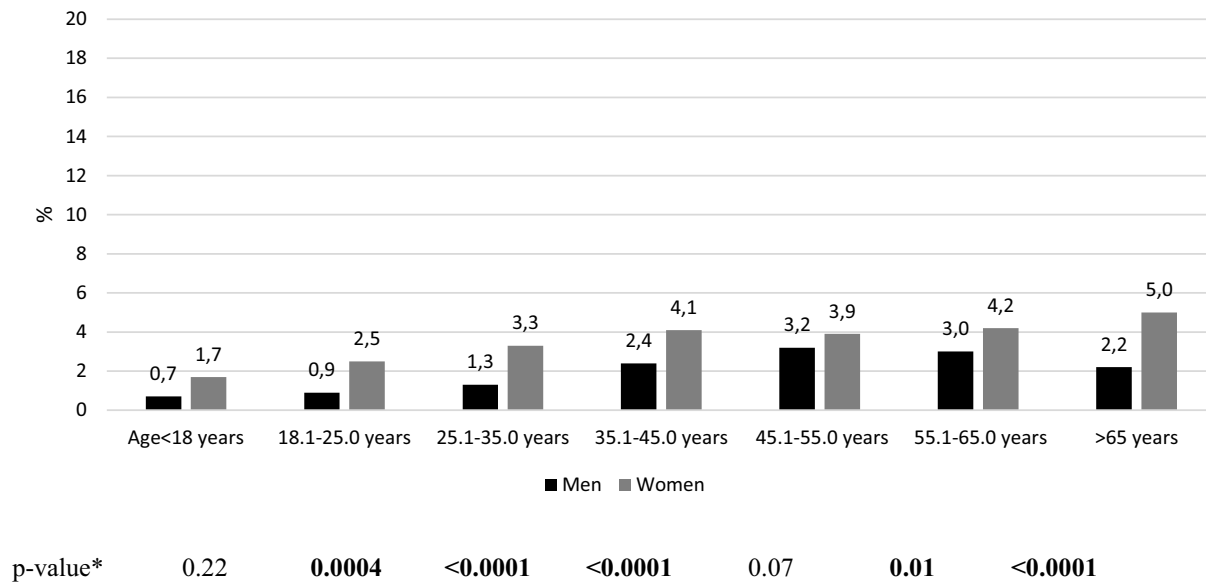
| p-value* | 0.22 | **0.0004** | **<0.0001** | **<0.0001** | 0.07 | **0.01** | **<0.0001** |

chi-square test. Statistically significant p-value (<0.05) are in bold

Mean BMI values in men and women with severe obesity (BMI ≥35 Kg/m2) according to age-classes

Age class (years)	Gender	N	%	BMI (kg/m2)					
				Mean	**Standard Deviation**	**Standard Error**	**Minimum**	**Maximum**	**P-Value***
<18.0	Female	6	1.7	37,5	2,2	0,9	35,6	40,9	0,6002
	Male	3	0.7	36,7	1,0	0,6	35,6	37,5	
18.1-25.0	Female	32	2.5	37,3	1,7	0,3	35,0	42,4	0,1441
	Male	14	0.9	38,2	2,2	0,6	35,6	44,1	
25.1-35.0	Female	76	3.3	38,5	3,8	0,4	35,0	56,5	0,9516
	Male	40	1.3	38,5	3,8	0,6	35,0	50,3	
35.1-45.0	Female	116	4.1	38,7	3,4	0,3	35,0	51,3	0,614
	Male	90	2.4	38,5	4,2	0,4	35,0	59,9	
45.1-55.0	Female	143	3.9	38,9	4,4	0,4	35,0	58,8	0,1411
	Male	152	3.2	38,2	3,7	0,3	35,0	55,4	
55.1-65.0	Female	126	4.2	38,2	3,4	0,3	35,0	52,9	0,1899
	Male	109	3.0	37,7	2,6	0,3	35,0	48,5	
>65.0	Female	159	5.0	38,4	3,9	0,3	35,0	56,4	0,0567
	Male	63	2.2	37,4	3,0	0,4	35,0	49,6	

Data are expressed as mean BMI with standard deviation, standard error and minimum and maximum within each BMI-class
*Unpaired t-Test.

Figure 3. Prevalence of severe obesity in type 1 diabetes subjects participating in the study, according to sex and age classes (years).

The percentage of subjects with impaired eGFR values (eGFR <60 mL/min) was higher in T1D women than in men, whereas MAU was more frequent in men than in women both in the obese and nonobese subgroups.

Sex differences in the pharmacological treatment, process, and outcome indicators in the obese and nonobese subgroups were also evaluated (Supplementary Table S3) (25).

Discussion

The obesity trend is progressively increasing, and, according to the World Health Organization, more than 650 million people (13% of the world population) are affected by obesity (26).

T1D subjects have long been considered to be protected from obesity, but recent data pointed to an increase of this burdensome clinical condition also in T1D, with prevalence estimates ranging from 2.8% to 37.1% (27-29), depending on definition of obesity, age of the examined population, and country. However, most of the evidence comes from pediatric studies (15, 29, 30), while data on adult T1D subjects are sparse.

In our large cohort of T1D subjects, including >37 000 adults followed up in one-third of diabetes centers in Italy, we found a high prevalence of obesity, affecting ~13% of our population, which is in line with current data in T1D worldwide (7) and 3 recent European studies on adult T1D

Table 1. Clinical characteristics and pharmacological treatments in T1D men and women participating to the AMD Annals Initiative, according to the presence of obesity (BMI ≥30 kg/m^2)

	Men			Women		
	Nonobese	Obese	*P^a*	Nonobese	Obese	*P^a*
n (%)	17 373 (87.0)	2608 (13.0)		14 269 (86.1)	2313 (13.9)	
BMI (kg/m^2)	24.4 ± 2.9	32.9 ± 3.1	<.0001	23.4 ± 3.2	33.8 ± 3.7	<.0001
Age (yrs) median (IQR)	47.2 (34.2-58.0)	51.5 (41.7-61.2)	<.0001	48.8 (35.0-60.8)	53.0 (40.6-64.4)	<.0001
Diabetes duration (years)	18.0 (9.0-29.0)	22.0 (11.0-33.0)	<.0001	18.0 (9.0-30.0)	22.0 (12.0-33.0)	<.0001
Clinical characteristics						
HbA1c (%)	7.7 ± 1.3	7.9 ± 1.2	<.0001	7.8 ± 1.3	8.1 ± 1.2	<.0001
(mmol/mol)	61 ± 6.3	63 ± 5.3		62 ± 6.3	65 ± 5.3	
HbA1c < 7% (≤53 mmol/mol)	29.1%	21.4%	<.0001	23.6%	16.2%	<.0001
HbA1c 7-9% (53-75 mmol/mol)	59.1%	64.1%		63.1%	65.7%	
HbA1c > 9% (≤75 mmol/mol)	11.8%	14.5%		13.3%	18.1%	
Smokers (%)	30.6%	26.4%	.0003	22.4%	15.4%	<.0001
Total cholesterol (mmol/L)	4.5 ± 0.9	4.5 ± 1.0	.0514	4.7 ± 0.9	4.6 ± 0.9	.06
HDL cholesterol (mmol/L)	1.45 ± 0.36	1.27 ± 0.32	<.0001	1.73 ± 0.39	1.52 ± 0.38	<.0001
LDL cholesterol (mmol/L)	2.56 ± 0.76	2.55 ± 0.85	.0832	2.57 ± 0.71	2.64 ± 0.97	.001
LDL cholesterol >1.8 mmol/L	85.0%	80.1%	<.0001	87.2%	85.8%	.11
Triglycerides (mmol/L)	1.04 ± 0.7	1.44 ± 1.02	<.0001	0.9 ± 0.53	1.21 ± 0.78	<.0001
SBP (mmHg)	127.4 ± 17.3	136.0 ± 17.9	<.0001	123.3 ± 18.8	131.9 ± 18.8	<.0001
SBP ≥140 mmHg	27.3%	46.6%	<.0001	21.9%	37.7%	<.0001
DBP (mmHg)	75.2 ± 9.4	78.8 ± 10.1	<.0001	72.9 ± 9.5	76.3 ± 9.8	<.0001
DBP >90 mmHg	3.6%	8.8%	<.0001	2.4%	4.7%	<.0001
eGFR (mL/min)	94.0 ± 28.5	86.8 ± 28.3	<.0001	90.7 ± 28.7	85.0 ± 30.3	<.0001
T1D long-term complications						
DKD^b	22.3%	31.4%	<.0001	20.7%	29.1%	<.0001
GFR ≤60 mL/min	9.5%	15.7%	<.0001	11%	17.8%	<.0001
MAU	20.4%	27.8%	<.0001	16.3%	21.8%	<.0001
Retinopathy	32.6%	47.1%	<.0001	30.6%	43.9%	<.0001
CV events^c	5.6%	9.9%	<.0001	3.3%	6.1%	<.0001
Pharmacological treatments						
CSII	14.6%	17.1%		20.7%	25.4%	
MDI	83.%1	80.5%		77.3%	72.7%	
Metformin	9.1%	28.3%	<.0001	9%	28%	<.0001
SGLT2i	1.9%	7.9%	<.0001	1.9%	7.8%	<.0001
Lipid-lowering agents	35.2%	55.4%	<.0001	32.3%	47.4%	<.0001
Antihypertensive treatment	28.2%	51.2%	<.0001	27%	48.1%	<.0001
Antiplatelets	16.4%	27%	<.0001	15%	25.6%	<.0001

Data are N, proportion or mean ± SD; median and IQR where specified.

Abbreviations: BMI, body mass index; CSII, continuous subcutaneous insulin infusion; CV, cardiovascular ; DBP, diastolic blood pressure; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; MAU, micro/macroalbuminuria; MDI, multiple daily injection; SBP, systolic blood pressure; SGLT2i, sodium/glucose cotransporter-2 inhibitor; T1D, type 1 diabetes.

^{a}Chi-square test or Mann-Whitney U-test, as appropriate.

^{b}DKD, MAU, and/or eGFR ≤60 mL/min.

^{c}Cardiovascular (myocardial infarction, revascularization/reperfusion procedures), cerebrovascular (stroke), peripheral vascular disease (revascularization/reperfusion procedures).

Table 2. Diabetes quality of care, process, and outcome indicators in T1D men and women participating to the AMD Annals Initiative, according to the presence of obesity (BMI ≥30 kg/m²)

	Men			Women		
	Nonobese	Obese	P^a	Non obese	Obese	P^a
Process indicators (proportion of patients with at least 1 yearly monitoring of						
HbA1c (%)	97.3	97.3	.93	97.5	97.8	.35
Lipid profile (%)	78.8	79.9	.21	78.8	79.6	.36
BP (%)	90.6	89.3	.05	90.2	89.6	.35
Albuminuria (%)	72.9	71.3	.07	72	72.7	.53
Creatinine (%)	85.0	86.9	**.01**	84.7	87.2	**.002**
Eye examination (%)	44.7	44.9	.86	44.4	45.5	.30
Intermediate favorable outcome indicators (proportion of patients reaching risk factors targets)						
HbA1c ≤7.0% (≤53 mmol/mol) (%)	32.7	24.4	**<.0001**	26.7	18.8	**<.0001**
LDL-c <2.6 mmol/L (%)	54.2	55.4	.33	54.2	50.2	**.001**
BP ≤130/80 mmHg (%)	61.4	40.5	**<.0001**	69.0	50.2	**<.0001**
Indicators of treatment intensity/appropriateness (proportions of patients not adequately treated)						
Not treated with lipid-lowering agents despite LDL-C ≥ 3.36 mmol/L (%)	62.9	50.9	**<.0001**	64.1	55.6	**.005**
Not treated with antihypertensive treatments despite BP ≥140/90 mmHg	53.6	40.8	**<.0001**	50.3	37.9	**<.0001**
Not treated with ACE-I and/or ARBs despite MAU (%)	59	36.5	**<.0001**	65.7	50.4	**<.0001**
Not treated with antiplatelets in spite of the presence of history of CV events (%)[b]	22.2	17.0	.07	24.8	21.8	.46
Indicators of treatment intensity/appropriateness (proportions of patients not reaching targets in spite of treatment):						
With LDL-c ≥ 3.36 mmol/L in spite of lipid-lowering treatment (%)	13.4	13.9	.63	13.4	15.6	.07
With BP ≥140/90 mmHg in spite of antihypertensive treatment (%)	47.7	57.0	**<.0001**	42.6	52.0	**<.0001**
Overall quality of care						
Q-score (mean ± SD)	29.0 ± 8.4	26.2 ± 8.9	**<.0001**	29.1 ± 8.3	26.1 ± 8.6	**<.0001**
Q-score <15 (%)	3.8	8.0	**<.0001**	3.4	7.2	**<.0001**

Statistically significant comparisons ($P < .05$) are in bold. Data are proportion or mean ± SD.
Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CV, cardiovascular; HbA1c, glycated hemoglobin A1c; LDL-c, low-density lipoprotein cholesterol; MAU, micro/macroalbuminuria; T1D, type 1 diabetes.
[a]Chi-square test or Mann-Whitney U-test, as appropriate.
[b]Cardiovascular (myocardial infarction, revascularization/reperfusion procedures), cerebrovascular (stroke), peripheral vascular disease (revascularization/reperfusion procedures).

subjects, in which the prevalence of obesity was 18%, 17%, and 15.3%, respectively (6, 11, 31).

Moreover, severe obesity was detected in a nonnegligible percentage of our study subjects (2.3% men and 4.0% women), comparable with data from a recent study conducted in Catalonia, where 4.3% of subjects with T1D had a BMI value >35 kg/m² (11).

These figures reflect our country-specific prevalence of obesity in the general population, which has been estimated to be 11% in Italy in 2019 (32), a very different figure when compared with data from the United States (33). Conversely, other authors have found a higher prevalence of obesity in young T1D subjects than in the age-matched non-diabetic population (29).

The progressive ageing of T1D subjects in our cohort has influenced these results. Thus, in our data set, age had an impact on obesity prevalence, which progressively increased with aging in both sexes, reaching 17% of the T1D population ages >65 years old, ie, 1 out 6 T1D subjects. The same increasing trend with aging was reported in Catalonia, with the prevalence of obesity reaching 21% in T1D subjects ages >40 years old (11).

This finding has important clinical implications since the plethora of aging T1D subjects is increasing thanks to a better management of the disease; this fact, coupled with the observed age-related increase in the prevalence of obesity, requires health systems to face a large group of T1D subjects with a long diabetes duration and a high burden of obesity in the next few years.

Also, sex may impact the epidemiology of obesity, and sex differences have been reported both in the general population and in subjects with T2D. Thus, in the general population in Italy, the prevalence of obesity is overall higher in men (11.7% men vs 10.3% women) (32), whereas in T2D subjects, severe obesity is more prevalent among women (12, 21), in whom it is associated with an higher mortality risk than in men (12, 13, 16).

When evaluating the sex-specific distribution of BMI classes in our study, we found a similar prevalence of obesity in the two sexes (13% men vs 13.9% women). T1D women had a higher prevalence of severe obesity only, and this difference was evident in all age groups (Fig. 3). Multivariate analysis also confirmed the effect of sex on severe obesity, as women had a 45% higher risk than men.

Table 3. Factors associated with obesity (BMI > 30 kg/m^2) and severe obesity (BMI > 35 kg/m^2) in T1D patients participating in the AMD Annals Initiative at the multivariate analysis

	BMI ≥30 kg/m^2		BMI ≥35 kg/m^2	
	OR	ORCI	OR	ORCI
Male sex (vs female)	**0.90**	**0.85-0.96**	**0.55**	**0.48-0.62**
Age (years)				
≤25.0 (RC)	1.00 (RC)	—	1.00 (RC)	—
25.1-35.0	**1.72**	**1.45-2.05**	1.2	0.86-1.67
35.1-45.0	**1.79**	**1.51-2.12**	1.15	0.84-1.57
45.1-55.0	**1.34**	**1.13-1.59**	0.88	0.64-1.21
>55.0	1.04	0.87-1.23	**0.54**	**0.39-0.75**
Duration (years)				
≤2.0	1.00 (RC)	—	1.00 (RC)	—
2.1-5.0	1.19	0.98-1.43	0.94	0.67-1.31
5.1-10.0	**1.39**	**1.18-1.64**	0.78	0.57-1.06
>10.0	**1.66**	**1.44-1.91**	1.14	0.89-1.45
HbA1c				
<53 mmol/mol (7.0%)	1.00 (RC)	—	1.00 (RC)	—
53-64 mmol/mol (7.0-8.0%)	**1.22**	**1.12-1.34**	**1.23**	**1.03-1.47**
65-75 mmol/mol (8.1-9.0%)	**1.53**	**1.39-1.68**	**1.54**	**1.28-1.87**
>75 mmol/mol (9.0%)	**1.58**	**1.41-1.76**	**1.64**	**1.33-2.03**
Smoking (Yes vs No)	**0.74**	**0.67-0.81**	**0.7**	**0.58-0.84**
LDL-cholesterol (mmol/L)				
<1.8	1.00 (RC)	—	1.00 (RC)	—
1.8-2.6	0.94	0.84-1.04	0.89	0.72-1.09
2.61-3.36	1.06	0.95-1.19	1.15	0.93-1.42
3.36-4.13	**1.37**	**1.19-1.57**	1.17	0.90-1.53
≥4.13	**1.61**	**1.32-1.97**	1.39	0.95-2.03
DBP ≥90 mmHg (Yes vs No)	**1.62**	**1.39-1.88**	**1.9**	**1.48-2.43**
SBP ≥140 mmHg (Yes vs No)	**1.64**	**1.52-1.77**	**1.64**	**1.42-1.90**
Insulin schemes:				
CSII	1.00 (RC)	—	1.00 (RC)	—
Basal-bolus vs CSII	**0.76**	**0.69-0.83**	**0.72**	**0.60-0.87**
Premix vs CSII	**0.73**	**0.56-0.95**	**0.49**	**0.26-0.94**
Metformin (Yes vs No)	**2.09**	**1.75-2.49**	**1.83**	**1.37-2.44**
SGLT2i (Yes vs No)	**1.67**	**1.42-1.97**	**1.61**	**1.26-2.04**
Antihypertensive treatment (Yes vs No)	**1.85**	**1.71-2.01**	**2.11**	**1.81-2.47**
Lipid-lowering agents (Yes vs No)	**1.35**	**1.25-1.46**	**1.44**	**1.24-1.67**
eGFR (>60 vs ≤60 mL/min)	**0.70**	**0.63-0.77**	**0.54**	**0.46-0.64**
Retinopathy (Yes vs No)	**1.30**	**1.18-1.43**	**1.27**	**1.04-1.54**
MAU (Yes vs No)	—	—	**1.35**	**1.14-1.59**
Antiplatelets (Yes vs No)	**1.10**	**1.00-1.20**	—	—

The following variables were included in the model: sex; age; diabetes duration; smoking habit; HbA1c levels; lipid profile; BP values; eGFR; MAU; diabetes treatment; treatment with antiplatelets, antihypertensive, and lipid-lowering agents; history of micro- and macrovascular complications. Significant *P* values are in bold.

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; BMI, body mass index; CSII, continuous subcutaneous insulin infusion; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; MAU, micro/macroalbuminuria; OR, odds ratio; RC, reference class; SBP, systolic blood pressure; SGLT2i, sodium/glucose cotransporter-2 inhibitor; T1D, type 1 diabetes.

Notably, the unfavorable health outcomes associated with obesity have been shown to further increase in case of severe obesity (34, 35), and more severe obesity classes have been shown to predict mortality (36).

Data on sex differences in obesity in T1D are sparse and conflicting (37), and a recent study on a large cohort of T1D subjects did not find any sex difference in the prevalence of obesity (11).

The higher prevalence of severe obesity among T1D women cannot be easily explained. The first hypothesis may be related to insulin treatment in adult patients with long-lasting T1D. Overall, women participating in our study were older, but

the duration of diabetes was similar in the 2 sexes. Moreover, women were more frequently treated with CSII than men. Although this data may reflect an indication bias, ie, diabetologists may try a more intensive insulin treatment for the documented difficulties in achieving glucose targets among T1D women, than among T1D men (16, 38, 39), the use of CSII may potentially impact body weight, because of the improvements in blood glucose control, as well as of changes in insulin doses and eating behaviors (40).

However, this explanation is not supported by a recent Australian study in adolescents with T1D, which did not find any increase of BMI-SDS with the implementation of insulin therapy with more intensive schemes (multiple daily injection/CSII) (41). Similarly, a recent Italian study showed comparable body weight gain over a 10-year follow-up in T1D patients on CSII or multiple daily injection, despite improved glycemic control and decreased insulin doses with CSII (42). The higher rate of severe obesity in women than in men is not even related to disparities in the use of adjunctive glucose-lowering therapies, such as metformin and SGLT2i, which was similar in both sexes, potentially reflecting the attempt to reduce weight and/or reach glucose targets in obese T1D subjects.

Conversely, it is likely that the differences in the prevalence of severe obesity observed in both T1D and T2D may involve complex interactions between biological (sex)- and non-biological (gender)-related variables, many of which have not been fully clarified (43, 44).

Thus, sex-related variables such as hormonal fluctuation through the life span, including menopausal status in women but also sex differences in psychological factors, difficulty in adaptation, and acceptance of the disease and/or depression may be more frequent in T1D women than in T1D men, contributing to their body weight variations. Also, the role of eating disorders and parental control in younger population cannot be ruled out (45, 46).

In spite of all these unsolved questions that might not be adequately addressed by an observational study such as the current one, our data showing the high prevalence of obesity in T1D men and women and of severe obesity among adult women with T1D should be taken into great consideration for the clinical management of these high-risk subjects.

Obesity has an overall similar prevalence in T1D men and women and potentially similar detrimental consequences in terms of CV risk. Thus, our data clearly indicate a worse metabolic and risk factor profile among obese T1D subjects, irrespective of sex. Obese T1D subjects had a worse glucose control and higher values of major CVD risk factors, including SBP, DBP, lipid profile, and micro/macroalbuminuria; moreover, the burden of micro- and macrovascular diabetes complications, including renal disease, retinopathy, and CVD, was also higher among T1D subjects with BMI >30 kg/m^2.

The greater burden of CVD risk factors and diabetes-related micro- and macrovascular complications in obese T1D should be considered in the perspective of their high global CVD risk. Thus, it has been estimated that according to European Society of Cardiology guidelines (47), 64.7% of T1D participants to the AMD Annals Initiative were at very high CVD risk and 28.5% were in the high-risk category (48), with important implications in terms of diabetes management.

In this regard, our data also documented significant differences in the quality of several diabetes care indicators, which were systematically less satisfactory in obese T1D subjects, although they did not differ between men and women. Despite a similar rate of annual monitoring of major risk factors and despite similar or even superior treatment of major risk factors in individuals with or without obesity, process and quality-of-care indicators in our data set showed that subjects with obesity more frequently have off-target values of HbA1c, cholesterol, and BP and more frequently do not reach these targets despite therapy, as compared to nonobese subjects. Moreover, the Q-score, a validated score measuring the overall diabetes care, was significantly impaired in obese T1D subjects, in which a larger percentage of subjects showed Q-score values <15, indicating poor diabetes care that has been associated with a higher CVD mortality risk (18). All of these differences between obese and nonobese subjects were evident in both sexes.

We also searched for potential sex differences in study variables between T1D men and women within the obese and nonobese groups, largely confirming those previously reported in this same population irrespective of BMI (16). Overall, our results are in line with the growing body of literature reporting sex and gender differences for diabetes long-term complications, although not consistently (22, 49-53).

Several potential strengths and limitations should be acknowledged when interpreting our results. The large number of subjects included in the current analysis, which is representative of T1D patients in Italy, as well as the collection of data on process indicators and quality of care according to sex and obesity status, should be acknowledged among the strengths of the study. On the other hand, the cross-sectional nature of our analysis prevents exploration of the causality of the detected associations. Moreover, the lack of information on waist circumference, daily insulin dose, dietary habits, and physical activity are among the limitations of the current study.

In conclusion, our data show that obesity is a frequent condition in men and women with T1D, and it is associated with a higher burden of cardiometabolic risk factors and diabetes long-term complications, as well as with an overall poorer quality of care in both sexes. Obesity prevalence increases with age, and T1D women are at higher risk of severe obesity.

The full list of authors in participating the AMD Annals Initiative is provided as supplementary material (25).

Author Contributions

A.G.., G.T.R., A.N., and C.G. developed the study concept and design, interpreted the data, and wrote the paper. M.C.R. and G.L. developed the research methods and performed the statistical analyses. P.G., A.G.., E.B., M.C., A.B., A.R., V.M., P.DB. and G.DC. critically revised the paper. G.T.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

The authors declare no conflict of interest.

Data Availability

The datasets generated during and/or analyzed in the current study are available from the corresponding author upon reasonable request.

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