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Original Article

Body Dysmorphic Disorder and psychological features in an Italian community sample in need of medical aesthetic treatments

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Abstract. *Body Dysmorphic Disorder (BDD)* is a psychiatric condition characterized by the concern for one or more perceived defects in physical appearance not identifiable by others. The prevalence of BDD across the adult population is estimated to be 1-2%, increasing to 5-15% in patients who require medical-aesthetic procedures. The scientific community is still discussing the status of BDD that could be contraindicated for cosmetic surgery. The aim of the study was to perform an assessment of BDD using validated questionnaires. A group of 205 patients has been evaluated with a test, including one general information form and two questionnaires: *Questionario sul Dismorfismo Corporeo (QDC)*, in order to assess BDD phenomenology and related clinical features; *Body Dysmorphic Disorder Questionnaire (BDDQ)*, regarding concerns about body appearance. The group was composed of women (97%), married (43.4%), with a high level of education (31.7% university degree) and a full-time job (76.1%). In the sample group, 12.2% showed a test outcome with QDC>130 and, consequently, BDD symptoms. Significant correlations have been found between QDC and psychological disorders and between QDC and concerns for physical appearance assessed by BDDQ. The QDC represents a reliable questionnaire for the early recognition of BDD. This study has showed that patients with BDD required more often medical-aesthetic procedures than the rest of the patients tested. The BDD was often associated with further psychological disorders and these patients have shown extreme concern for their physical appearance, that impacts their social interactions.

Key words: assessment, body dysmorphic disorder, psychological features, psychopathological features, questionario sul dismorfismo corporeo, body dysmorphic disorder questionnaire

Introduction

Body Dysmorphic Disorder (BDD) is a psychiatric condition characterized by preoccupation for one or more perceived defects in physical appearance not identifiable by others[1,2,3,4].

Usually, in patients with BDD, the concern for just one part of the body is rare; most of them focus their apprehension on three or four body areas during the course of the disease[5,6] especially with their skin, hair or nose[7,8,9,10].

Patients spend most of the day - in a range between 3 to 8 hours - thinking about perceived defects,

often connected with obsessive ideas and compulsive behaviors, such as to compromise their own daily life[11].

BDD generally begins in adolescence and is most common in the female gender[12,13]; the prevalence of BDD across the adult population is estimated to be 1-2%, increasing to 5-15% in patients who require medical-aesthetic procedures[14-16].

Approximately 76% of patients with BDD doesn't require psychiatric treatment but is continuously looking for aesthetic medicine and plastic surgery procedures[17].

The scientific community is still discussing the status of BDD that could be contraindicated for cosmetic and plastic surgery, being a disorder linked to misperception of the body image that would not reach any improvement following aesthetic treatments[18], keeping patient's dissatisfaction unchanged or, in the worst case, increased[19-24].

Therefore, considering the high risk of not properly treating these individuals[25], the early identification of this psychopathology through a fast and objective evaluation of the patients is essential to facilitate the aesthetic doctor's choice whether to provide an aesthetic procedure and eventually submit a preliminary psychological assessment to the patient[26,27].

The diagnosis of BDD is difficult in many cases, because patients affected by this pathology very often have a poor awareness[25]. This disorder is frequently accompanied by emotions such as shame or embarrassment that make it difficult to communicate symptoms to doctors.

Currently there is few information about the prevalence and phenomenology of BDD in Italy due to the lack of data relating to this disorder, despite the fact that the *Diagnostic and Statistical Manual of Mental Disorders* (5th Italian edition) widely defines and describes the criteria for assessment.

Several questionnaires have been developed internationally that investigate BDD, the most commonly used are the *Body Dysmorphic Disorder Questionnaire (BDDQ)*, the *Body Image Disturbance Questionnaire (BIDQ)* and the *Dysmorphic Concern Questionnaire (DCQ)*.

However, due to some limitations of these questionnaires, Cerea and collegues in 2017 developed, in Italy, a new test named *Questionario sul Dismorfismo Corporeo (QDC)* able to identify and evaluate the characteristics and clinical manifestations of BDD; this questionnaire proved to be extremely reliable, with excellent test-retest replicability in one month[28].

This test also shows an important association with all the other self-assessment questionnaires used, highlighting how the characteristics of BDD are related to low self-esteem, high levels of social anxiety, general discomfort, obsessive-compulsive symptoms and eating disorders[29-31].

The aim of this study was to perform a screening of BDD in an Italian sample of patients requiring aesthetic medicine treatments, using validated questionnaires.

Materials and methods

The experimental study consisted in administering to a heterogeneous sample (female, male, wide age range, across the nation) of patients, belonging to the Outpatient Service of Aesthetic Medicine, Isola Tiberina – Gemelli Isola Hospital, in Rome, an evaluation test including a general information form and 2 questionnaires, the BDDQ and the QDC.

The general information form is divided into 3 sections. The first part aims to gather the personal data such as the marital status, education level, type of occupation, the presence of a psychological problem and, eventually, the presence of psychopathology in a family member, neurological diseases or physical illnesses, and drugs used.

A second one allowed to collect information about the aesthetic medicine field: the reason why the patient requests an aesthetic examination; which imperfection she/he would like to fix; the need of a preventive or corrective treatment; the assessments performed during the aesthetic medicine visit; the treatments that have already been done (specifying the type, number of times, date of the first one, motivation and grade of satisfaction) and those already scheduled (specifying the expected date of the treatment, type, motivation and grade of need).

The last part focuses on the collection of information relating to the field of plastic surgery: any interventions previously performed (specifying the type, number of times, date of the first one, motivation and grade of satisfaction) and possible plastic surgery interventions to be defined (specifying the expected date of the treatment, type, motivation and grade of need).

The BDDQ represents a reliable screening test to investigate appearance concerns, with a sensitivity of 100% and a specificity of 89%[32-34].

During the interview, the patient could reveal discomforts due to defects or imperfections of his body. In case of a positive answer, the screening proceeds with specific questions: how these defects appear to the others (mild or unobservable); list and sort – in descending order – the importance given to each defect, assigning them a score from 0 to 10 (0 for minimum importance, 10 for maximum importance).

Furthermore, it is evaluated if the concern relating to the presence of defects and/or imperfections in the physical appearance that could drive the subject to begin a series of repetitive behaviors (i.e. looking in the mirror frequently, excessive self-care, looking for reassurances from others, continuously comparing his own body with the others).

If the patient answers "No" to both questions regarding the concern for physical defects and about obsessive attitudes, the questionnaire is over. Otherwise, it would be necessary to continue further with other questions. The first one analyzes if the main concern is about not being thin enough or the fear of getting too fat in the near future. The effect of concerning about the presence of defects and/or imperfections in physical appearance in life is examined as follows: whether the defect causes stress and/or discomfort; whether the defect interacts with the individual's social life and, in case of, clarifying the impact on work, school or other significant activities and highlighting any avoidance of specific activities due to the defect/imperfection. The last question regards how much time the patient spends thinking about the defect/imperfection; the patient can choose among three options: "less than 1 hour", "1-3 hours each day", "more than 3 hours each day".

Within the QDC questionnaire, 40 questions investigate the presence of aesthetic defects/imperfections in the physical appearance. Each item has a score ranging between 1 ("strongly disagree") and 7 ("strongly agree"), with the other scores in the middle considering a value of 4 as neutral ("neither agree nor disagree").

The patient must also agree to fill and sign the privacy statement and the General Data Protection Regulation (EU) 2016/679 (GDPR) form.

Results

The study population consisted of 205 patients, 97% of which women, married (43.4%), with a high level of education (64.4% university degree) and with a full-time job (76.1%) (Table 1).

Table 1. Demographic features [N number of patients interviewed].

		N=205
		n (%)
Gender	F	199 (97%)
Marital status	Cohabitant	29 (14.1%)
	Divorced	19 (9.3%)
	Engaged not cohabitant	11 (5.4%)
	Separeted	11 (5.4%)
	Single	41 (20%)
	Married	89 (43.4%)
	Widower	5 (2.4%)
School education	Primary school	1 (0.5%)
	Secondary school	7 (3.4%)
	High school diploma	65 (31.7%)
	University degree	132 (64.4%)
Employment	Housewife	4 (2%)
	Unemployed	3 (1,4%)
	Precarious work	4 (2%)
	Full time job	156 (76.1%)
	Part-time	11 (5.4%)
	Pensioner	24 (11.7%)
	Student	3 (1.4%)

As regards psychological and neurological problems, 48 patients (23%) were affected by a psychopathology, no patients presented any neuropathology; 156 patients (75.1%) were not taking drugs; the rest of the sample analyzed was taking drugs because of several diseases (Table 2). This data is important in order to evaluate the association between patients with a history of psychopathology and a predisposition to dysmorphism, as BDD is frequently associated with further psychic sphere disorders.

The reasons why patients decided to apply for an aesthetic consultation was the desire to feel better about themselves for 141 (68.8%) of them, followed by physical well-being in 55 patients (26.8%), rejuvenation for 52 patients (25.4%), professional image enhancement for 15 patients (7.3%), slimming for 11

Table 2. Clinical features [N number of patients interviewed].

		N=205
		n (%)
Psychopathology	Yes	48 (23%)
Neuropathology	No	205 (100%)
Drugs taken	No	156 (75.1%)
	Alendronic acid	1 (0.5%)
	Antiarrhythmic drugs	1 (0.5%)
	Anticoagulant drugs	1 (0.5%)
	Antidepressant drugs	1 (0.5%)
	Antipertensive drugs	9 (4.4%)
	Estrogen/progestogen combinations	3 (1.5%)
	Anticancer drugs	1 (0.5%)
	Biological drugs	1 (0.5%)
	Gastroprotective drugs	2 (1%)
	Insulin	1 (0.5%)
	Levothyroxine	20 (9.8%)
	Mesalazine	1 (0.5%)
	Metformin	2 (1%)
	PPI	1 (0.5%)
	Propylthiouracil	1 (0.5%)
	Mood stabilizing drugs	1 (0.5%)
	Statins	1 (0.5%)

patients (5.4%), curiosity for 6 patients (2.9%), post-pregnancy blemishes for 5 patients (2.4%) and post-menopausal blemishes for 2 patients (1%) (Table 3).

As it was a multiple-choice questionnaire, the patients may have given multiple reasons.

Looking at the overall sample, 60% of the patients asked for a corrective treatment whereas 40% were interested in a preventive one.

The main imperfection that needed to be fixed was considered by the majority of the patients (53.2%) to be facial wrinkles, followed by cellulitis (47.3%), skin laxity (26.8%), sun spots (21.5%), venous insufficiency (20.5%), facial blemishes (19.5%), overweight/obesity (11.2%), hypertrichosis (1.5%) and baldness (1%).

Also in this case, the patients may have given multiple reasons for giving feedback to a multiple-choice questionnaire.

The first aesthetic medicine treatment, performed by 184 patients, was botulinum toxin injection in 41.5% of cases, biostimulation in 28.8%, fillers in 7.3%, peeling and carboxytherapy in 3.4%, laser epilation in 1.5%, suspension threads, radiofrequency and cryolipolysis in 1%, laser therapy and mesotherapy in 0.5% of cases.

Only 148 subjects decided to apply for a second aesthetic medicine treatment: 47 patients (22.9%)

Table 3. Reasons for medical aesthetic advice [N number of patients interviewed].

Reasons for medical aesthetic advice	*N=205*
	n (%)
Feeling better about yourself	141 (68.8%)
Physical well-being	55 (26.8%)
Skin rejuvenation	52 (25.4%)
Professional image enhancement	15 (7.3%)
Slimming	11 (5.4%)
Curiosity	6 (2.9%)
Post pregnancy blemishes	5 (2.4%)
Post menopause blemishes	2 (1%)

preferred skin biostimulation, 44 patients (21.5%) filler, 30 patients (14.6%) peeling, 5 patients (2.4%) laser therapy, carboxytherapy, radiofrequency and mesotherapy, 2 patients (1%) laser epilation, intense pulsed light and cryolipolysis and just one patient (0.5%) implant of threads.

No more than 100 patients chose to resort to a third aesthetic medicine treatment: 33 patients (16.1%) required fillers, 18 patients (8.8%) peeling, 10 patients (4.9%) laser epilation, 10 patients (4.9%) radiofrequency, 9 patients (4.4 %) mesotherapy, 6 patients (2.9%) suspension threads, 6 patients (2.9%) carboxytherapy, 5 patients (2.4%) intense pulsed light, 2 patients (1%) cryolipolysis, 1 patient (0.5%) laser treatment.

An even smaller number of patients (48) applied for a fourth aesthetic medicine treatment. In detail: 11 patients (5.4%) preferred peeling, 7 patients (3.4%) intense pulsed light, 6 patients (2.9%) radiofrequency, 6 patients (2.9%) suspension threads, 5 patients (2.4%) laser therapy, 5 patients (2.4%) carboxytherapy, 5 patients (2.4%) mesotherapy, 2 patients (1%) laser epilation and 1 patient (0.5%) filler implants.

Only 20 patients resorted to a fifth aesthetic medicine treatment: 5 (2.4%) patients were treated with radiofrequency, 4 patients (2%) with peeling, 4 patients (2%) with mesotherapy, 3 patients (1.5%) with carboxytherapy, 2 patients (1%) with intense pulsed light, 1 patient (0.5%) with cryolipolysis and 1 patient (0.5%) with laser therapy (Table 4).

The QDC represents a valid tool for evaluating BDD in the Italian context, with a cut-off threshold >130[28].

Table 4. Treatments required for I, II, III, IV and V treatment [N number of patients treated].

	First treatment *N=184*	*Second treatment* *N=148*	*Third treatment* *N=100*	*Fourth treatment* *N=48*	*Fifth treatment* *N=20*
Type of treatment	n (%)	n (%)	n (%)	n (%)	n (%)
Botulinum toxin	85 (41.5%)				
Skin biostimulation	59 (28.8%)	47 (22.9%)			
Hyaluronic acid filler	15 (7.3%)	44 (21.5%)	33 (16.1%)	1 (0.5%)	
Suspension threads	2 (1%)	1 (0.5%)	6 (2.9%)	6 (2.9%)	
Peeling	7 (3.4%)	30 (14.6%)	18 (8.8%)	11 (5.4%)	4 (2%)
Laser therapy	1 (0.5%)	5 (2.4%)	1 (0.5%)	5 (2.4%)	1 (0.5%)
Laser epilation	3 (1.5%)	2 (1%)	10 (4.9%)	2 (1%)	
Carboxytherapy	7 (3.4%)	5 (2.4%)	6 (2.9%)	5 (2.4%)	3 (1.5%)
Radiofrequency	2 (1%)	5 (2.4%)	10 (4.9%)	6 (2.9%)	5 (2.4%)
Intense pulsed light		2 (1%)	5 (2.4%)	7 (3.4%)	2 (1%)
Cryolipolysis	2 (1%)	2 (1%)	2 (1%)		1 (0.5%)
Mesotherapy	1 (0.5%)	5 (2.4%)	9 (4.4%)	5 (2.4%)	4 (2%)

Indeed, the QDC showed high specificity and sensitivity with a cut-off point of 130, indicating that individuals who score above 130 should be referred for further assessment because they might be characterized by BDD symptoms or may be at high-risk of developing BDD[28].

Looking at the complete analysis, it appears that 25 (12.2%) out of 205 patients obtained a QDC score >130 points, such as to determine a tendency towards the diagnosis of body dysmorphism. About the remaining 180 patients, 50% showed a cut-off of 73 points, 25% achieved a score below 63 points, and 75% achieved a score minor o equal to 93 points (Figure 1).

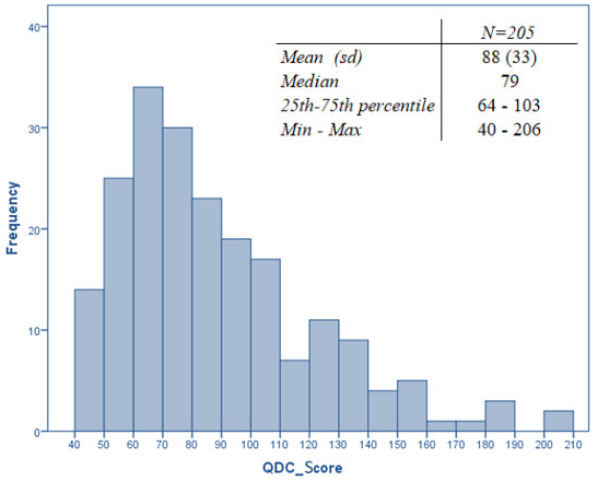

Figure 1. Questionario sul Dismorfismo Corporeo QDC analysis.

The 25 patients with BDD symptoms (QDC score >130 vs others: T-test p<0.0001) were female, mainly single, with a mean age of 42 years (sd=11.7), lower than the rest of the sample.

By dividing the results obtained into 4 score ranges, 40-49, 50-99, 100-130 and >130, it was shown that most patients (63.9%) had a QDC value ranging between 50-99 (Table 5).

As regards the correlation between QDC and psychopathology, a statistically significant association (Fisher exact test p=0.003) emerged between QDC classes and the presence of psychological disorders, with a direct proportionality relationship: the more the questionnaire score increased, the higher the percentage of patients with some psychopathology (Figure 2).

Table 5. Classes of Questionario sul Dismorfismo Corporeo QDC [N number of patients interviewed].

QDC classes	***N=205***
	n (%)
40-49	14 (6.8%)
50-99	131 (63.9%)
100-130	35 (17.1%)
>130	25 (12.2%)

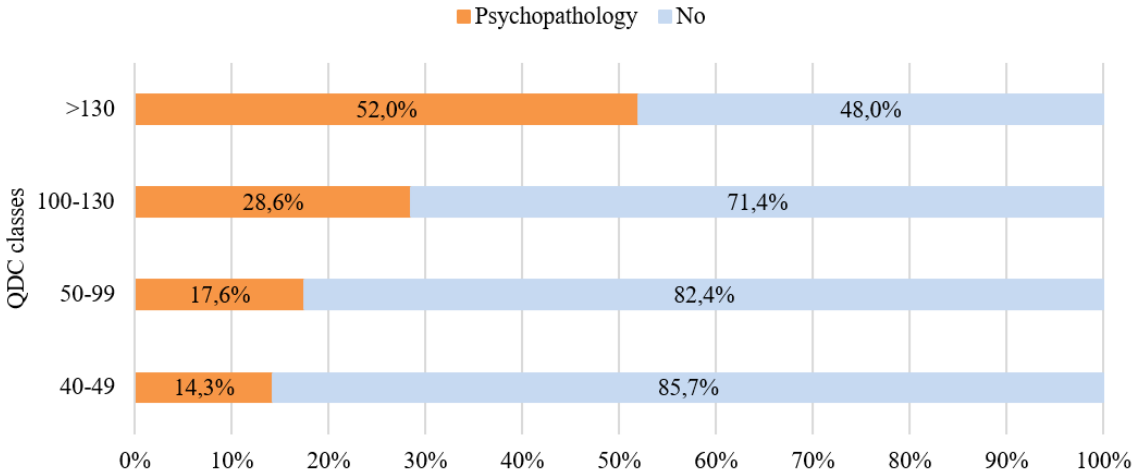

Figure 2. Questionario sul Dismorfismo Corporeo QDC and presence of psychopathologies.

Fifty-two percent of patients - those with QDC>130 – were affected by psychic problems, mainly anxiety disorder and eating disorder.

Patients with psychopathology were younger than the subjects without disorders affecting the psychologic sphere.

A statistically significant direct proportionality relationship was found between the QDC classes and the concern for physical defects assessed by BDDQ (Chi-squared test p<0.001): while only 29% in the QDC 40-49 class were concerned by their physical defects, the proportion rose up to 85% for patients with QDC>130 (Figure 3).

A similar significant association was highlighted between the presence of repetitive behaviors due to physical appearance and QDC class (Fisher exact test p<0.001).

QDC classes also related to questions about the concern for thinness/obesity, the stress or discomfort caused by perceived defects, their interferences with social life and meaningful activities.

The rate of patients who answered positively increased with a QDC class rise; for instance, 40% of patients in the class 40-49 revealed that the defects could cause stress/discomfort, a proportion that increase to 42% in the class 50-99, to 59% in the class

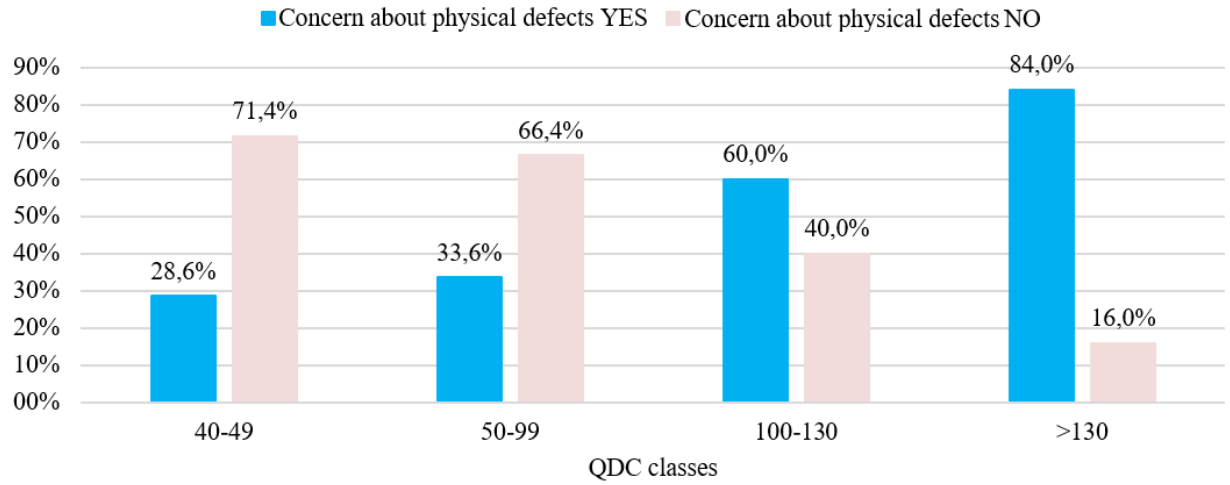

Figure 3. Questionario sul Dismorfismo Corporeo QDC and concern for physical defects.

100-130 and up to 86% of patients in the last class with QDC>130.

Relatively to the outcome relating to the number of hours spent in front of the mirror, in all 4 classes most subjects declared that they spent less than 1 hour; in the class QDC>130, 28.6% reported a time frame between 1 and 3 hours and 14.3% more than 3 hours (Table 6).

Information about perceived defects available for 72 subjects (skin, hair, mouth, nose, jaw, lips, eyes,

Table 6. Questionario sul Dismorfismo Corporeo QDC classes and Body Dysmorphic Disorder Questionnaire BDDQ questions [N number of patients evaluated with Body Dysmorphic Disorder Questionnaire BDDQ].

		QDC classes				
		40-49 *N=5*	**50-99** *N=48*	**100-130** *N=22*	**>130** *N=21*	***p***
Concern about obesity and thinness	*Yes*	3 (60%)	10 (20.8%)	11 (50%)	14 (66.7%)	0.001
Defects cause stress or discomfort	*Yes*	2 (40%)	20 (41.7%)	13 (59.1%)	18 (85.7%)	0.004
Defects interfere with social life	*Yes*	0 (0%)	3 (6.3%)	2 (9.1%)	8 (38.1%)	0.006
Defects interfere with meaningful activities	*Yes*	0 (0%)	1 (2.1%)	2 (9.1%)	6 (28.6%)	0.008
Avoiding social activities	*Yes*	0 (0%)	5 (10.6%)	1 (4.5%)	8 (38.1%)	0.014
Time spent in front of the mirror	*Less than 1 hour a day*	5 (100%)	46 (95.8%)	19 (86.4%)	12 (57.1%)	0.003
	1-3 hours a day	0 (0%)	2 (4.2%)	2 (9.1%)	6 (28.6%)	
	More than 3 hours a day	0 (0%)	0 (0%)	1 (4.5%)	3 (14.3%)	

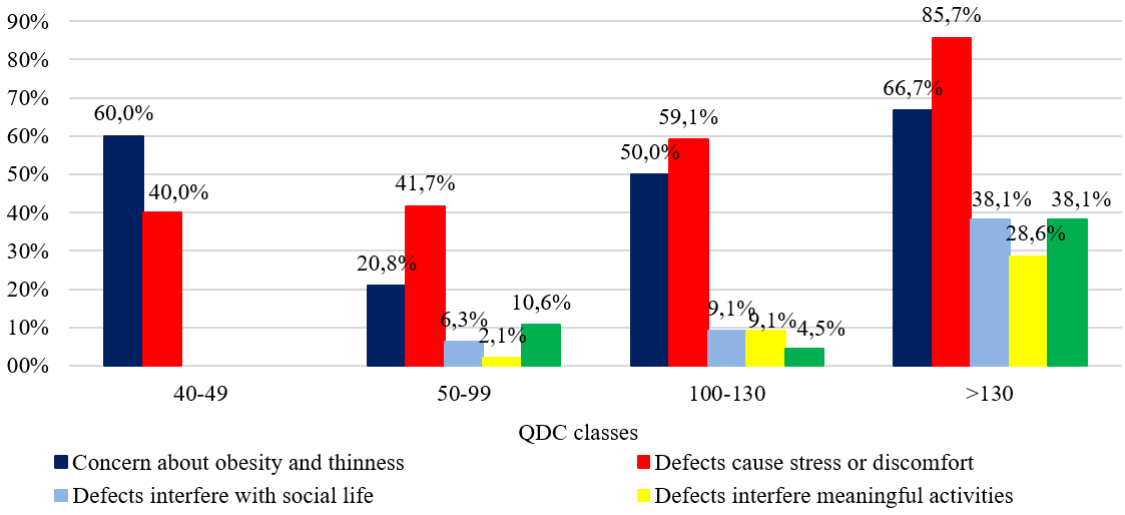

Figure 4. Analysis of the association between Questionario sul Dismorfismo Corporeo QDC classes and Body Dysmorphic Disorder Questionnaire BDDQ questions.

chest, hips, buttocks, legs, genitals, breasts, slender/strong build, arms, abdomen, feet) showed that the most common defect regarded the skin (63%), followed by the nose (22%), the other defects are reported in a lower percentage.

There was no significant association between QDC classes and type of perceived defect, excluding the abdomen (p value 0.01). Patients with QDC>130 perceived the abdomen as a defect in a higher percentage than the other groups (Table 7).

Regarding the post-treatment satisfaction rate, no statistically significant difference has been observed through the various QDC classes.

Discussion

Overall, this study confirms that body dissatisfaction is associated with a high interest in aesthetic medicine and surgery procedures and that patients with BDD tend to require such treatments more frequently than the healthy population[13,35].

Considering the analyzed sample, the most common treatment was biostimulation (54%), but first approach with aesthetic medicine was botulinum toxin injections (41,5%).

Recognizing the BDD in the early stages of the disease could improve treatment outcomes: in fact, early diagnosis, as well as early psychological therapy, represent the most important positive prognostic factors for BDD[36].

What is just mentioned assumes extreme importance considering that patients affected by BDD, in many cases, are unaware of their pathology, continuously looking for medical-aesthetic and plastic surgeon treatments, owing to chronic dissatisfaction with the results obtained by the various treatments done.

Focusing on QDC analysis in the study population, it is interesting to underline that 25 out of 205 (12.2%) patients had a score >130, therefore at risk of BDD. That confirms what is reported in the Literature: the prevalence of BDD across the adult population is estimated to be 1-2%, increasing to 5-15% in patients who decide to apply for a medical-aesthetic treatment.

Table 7. Association between Questionario sul Dismorfismo Corporeo QDC classes and perceived defects [N number of patients with perceived defects].

	QDC classes				
Perceived defects	**40-49** *N=4*	**50-99** *N=38*	**100-130** *N=14*	**>130** *N=16*	***p***
Jaw	0 (0%)	1 (2.6%)	0 (0%)	0 (0%)	0.999
Hair	0 (0%)	1 (2.6%)	1 (7.1%)	3 (18.8%)	0.187
Feet	0 (0%)	2 (5.3%)	1 (7.1%)	0 (0%)	0.811
Abdomen	1 (25%)	1 (2.6%)	1 (7.1%)	5 (31.3%)	0.01
Arms	0 (0%)	0 (0%)	2 (14.3%)	0 (0%)	0.085
Body size	0 (0%)	6 (15.8%)	2 (14.3%)	4 (25%)	0.747
Breast	0 (0%)	4 (10.5%)	3 (21.4%)	4 (25%)	0.414
Legs	0 (0%)	3 (7.9%)	5 (35.7%)	2 (12.5%)	0.08
Glutes	0 (0%)	6 (15.8%)	3 (21.4%)	1 (6.3%)	0.666
Hips	0 (0%)	2 (5.3%)	1 (7.1%)	5 (31.3%)	0.055
Eyes	0 (0%)	3 (7.9%)	0 (0%)	0 (0%)	0.504
Lips	0 (0%)	1 (2.6%)	0 (0%)	1 (6.3%)	0.725
Nose	1 (25%)	8 (21.1%)	2 (14.3%)	5 (31.3%)	0.667
Skin	3 (75%)	21 (55.3%)	10 (71.4%)	11 (68.8%)	0.673
Mouth	1 (25%)	6 (15.8%)	1 (7.1%)	1 (6.3%)	0.526

We observed a statistically significant correlation between QDC classes and the presence of a psychopathology, thus confirming the association of BBD with mental disorders demonstrated in previous studies.

A statistically significant correlation was observed as well between QDC scores and BDDQ results, an observation that corroborates the close relationship between the concern for physical defects and the tendency towards dysmorphophobia. Similarly, the clinical manifestations assessed by BDDQ increased considerably in patients with higher QDCs.

A particularly significant finding was the link between a QDC score >130 and the perception of a dysmorphic abdomen in a higher percentage compared to the other QDC classes.

Actually, there is no real contraindication in submitting patients with BDD to aesthetic medicine treatments, but it is necessary to carry out a detailed analysis of each case because these patients could easily complain of low satisfaction with the treatment received due to unrealistic expectations and to the illusion that one's physical defects can disappear completely. Sometimes it may be necessary to suggest starting a psychological course before having any aesthetic treatment.

Strengths and limitations

Our study has some strengths and limitations. As regards the strengths, the results were obtained with a robust statistical analysis that permitted to demonstrate the reliability and effectiveness of QDC as a useful tool for the patients' stratification in evaluating a risk of BBD during a visit in an aesthetic medicine practice.

Limitations may be found in a not so wide heterogeneity of the patients included in this study.

Conclusions

The QDC score is an easy-to-use and reliable tool that facilitates an aesthetic doctor to recognize the presence of a BDD in patients seeking help to improve perceived physical defects that negatively impact the quality of their life. As a dysmorphic body perception is associated with a tendency to search for aesthetic procedures, it might sometimes be necessary to refer the patient to a psychiatrist or a psychologist before implementing any aesthetic procedures.

It would be useful to conduct other studies similar to ours increasing the number and heterogeneity of the sample, although current research has involved a large number of participants, in order to obtain a greater quantity of data.

Ethics Committee: This study was approved by the Ethics Committee of the Isola Tiberina - Gemelli Isola Hospital, Rome.

Conflict of Interest: The authors declare no conflict of interest.

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