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Original Article

Metabolic diseases and mental disorders in female subfertility: first results on assessment and correction by cognitive behavioral therapy

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Abstract

Women with subfertility and metabolic diseases (MD) are more prone to depression and anxiety, worsening quality of life on their way to pregnancy. We investigate the mental disorders prevalence in women with subfertility and MD for their correction using cognitive behavioral therapy (CBT). The study involved 609 women with MD, 314 of whom were primary or secondary subfertile. We have developed, proposed, and implemented the 5-step assessment and correction algorithm in the CBT context, using women's subfertility and MD peculiarities. The results of the first 2 steps of the assessment and correction algorithm were presented. Obese subfertile women had an increased level of anxiety and depressive disorders and a lower cognitive level compared to patients with dyslipidemia ($p \leq 0.05$). Subfertility and metabolic syndrome were accompanied by reduced cognitive function ($p \leq 0.05$). The automatic thoughts index in subfertile women with MD was >2.5. The highest score in the subfertile women for "Preparation" means "patient is ready for changes shortly", which seems very promising. Based on the determined patterns, CBT seems to be effective in correcting mental disorders in women with subfertility and chronic MD, as it helps to change destructive beliefs and develop healthy behaviors.

Keywords: metabolic syndrome, obesity, mental disorders, subfertility, type 2 diabetes, cognitive behavioral therapy

Introduction

Mental disorders (MDs) are a serious challenge for modern medicine, significantly affecting the quality of life. According to the National Institute of Mental Health, one in eight people in the world has a mental disorder [1]. They include mood disorders, anxiety, psychotic disorders, and substance abuse [1, 2]. MDs are associated with poorer control of comorbidities [3], sexual health, and increased risk of suicide [4].

MDs often complicate the course of chronic diseases such as diabetes, obesity, and cardiovascular disease (CVD) [5, 6]. Patients with chronic illnesses are more prone to depression and anxiety [1]. Treatment of such

diseases causes psychological stress, which exacerbates mental disorders. In addition, unhealthy behavior (low physical activity, unbalanced diet, poor adherence to treatment) contributes to the exacerbation of both physical and mental conditions [7].

The prevalence of diabetes mellitus (DM) is steadily increasing: in 1980, there were 108 million patients, and in 2014, there were already 422 million [8]. This is due to population aging and lifestyle changes [8]. DM is associated with premature mortality, disability, and significant economic costs [9, 10]. Studies have shown a complex relationship between T2DM and depression: among patients with T2DM, depression occurs in 18–25% of cases, which is significantly higher than in the general population [11]. The biological mechanisms of this relationship include dysfunction of the hypothalamic-pituitary-adrenal axis, insulin resistance, inflammation, and circadian disorders [12].

Obesity, which used to be considered a sign of wealth, is now associated with an increased risk of depression, anxiety disorders, and social stress [13]. People with high BMI often face stigma, which worsens their psycho-emotional state [14, 15]. Metabolic syndrome (MS) includes increased waist circumference, dyslipidemia, hypertension, and hyperglycemia, which increases the risk of diabetes and CVD [1, 2]. Patients with depression due to physical inactivity have a higher risk of developing MS [7]. Studies on the relationship between MS and depression have yielded contradictory results [16–21], so this issue requires further analysis.

Given the prevalence of T2DM, obesity, and MS and their association with MD, it is important to develop personalized therapeutic approaches. One of the most effective methods is cognitive behavioral therapy (CBT). This psychotherapeutic method helps patients identify and change destructive thought patterns that affect behavior and emotions [22].

Subfertility is difficulty getting pregnant. Couples who have regular sex without any protection and have not become pregnant are considered subfertile. Couples who have sex every two to three days have an 84% chance of conceiving in a year. Even those who have been trying unsuccessfully for three years have a 1 in 4 chance of getting pregnant naturally in the next year [23].

Decreased fertility is common and affects one in six couples, half of whom cannot explain their delay in becoming pregnant. Both MD and metabolic diseases are directly and indirectly linked with fertility problems. Assisted reproduction can overcome barriers to fertility caused by fallopian tube disease and low sperm counts, but little progress has been made in reducing the impact of increasing age on ovarian function [24].

The effectiveness of CBT has been proven in the treatment of depression, generalized anxiety disorder, panic disorder, post-traumatic stress disorder, eating disorders, and addictions [25–28]. The main mechanism of CBT is cognitive restructuring – correcting negative beliefs, which helps to form adaptive thinking patterns. It also uses the method of fear avoidance to help patients overcome anxiety [29].

Our research aimed to study the prevalence of mental disorders in women with subfertility and metabolic diseases and to determine the feasibility of these disorders' correction using cognitive behavioral therapy.

Material and methods

Study design and patients

The study involved 609 women diagnosed with type 2 diabetes mellitus, obesity, dyslipidemia, and metabolic syndrome. Of these, 314 had primary or secondary subfertility, and this was our sample group. By design, our study included women aged 25 to 44 years. The inclusion criteria for the study were: consent to participate in the study; female gender; age 25–44; diagnosis of type 2 diabetes mellitus, obesity, dyslipidemia, metabolic syndrome, subfertility.

A couple was considered subfertile if they had not had regular pregnancy after 2 years of unprotected sex. This definition requires some explanation:

- To become pregnant means to have vaginal intercourse with the intention of becoming pregnant (so no use of condoms or contraception);
- Becoming pregnant is anything other than having a live baby: miscarriages, stillbirths etc. are also counted as pregnancies;
- Regular intercourse means at least once or twice around ovulation each month (11–14 days of the cycle in a regular cycle).

We have developed and proposed an algorithm of actions in the context of mental disorders and CBT, taking into account the peculiarities of the above-mentioned metabolic disorders. It should be noted that our research team has far-reaching plans. This article presents the results of the first two stages of implementation of our model, but the research is ongoing, and we offer you a complete model of the approach to the treatment of mental disorders in patients with metabolic disorders.

Laboratory, anthropometric and clinical data collection

STAGE 1. Psychological assessment and setting of therapeutic goals: the mental state was assessed using standardized questionnaires: PHQ-9, GAD-7, MoCA, and MMSE. Assessment of self-esteem and motivation (Prochaska & DiClemente questionnaire).

We would like to remind you that the PHQ-9 depression scale is a module or cluster related to the detection of depressive symptoms of the Patient Health Questionnaire (PHQ), which is currently used in diagnosis separately from the main questionnaire.

Anxiety Test (GAD-7) – a questionnaire designed to test anxiety in adults. The Montreal Cognitive Assessment (MoCA) is a widely used screening tool for cognitive impairment. The scale assesses several cognitive functions, including short-term, spatial, and visual abilities, multiple aspects of executive functions, attention, concentration, and working memory, language functions, abstract thinking, and time and space orientation.

The Mini-Mental State Examination (MMSE) is a short 30-item questionnaire that is widely used for initial assessment of cognitive function and screening for cognitive impairment, including dementia.

The Prochaska & DiClemente questionnaire is based on the Stages of Change Model, which explains how people change their behavior, including in the areas of health and health habits.

The main stages of change

1. Precontemplation – a person is not aware of the problem and does not plan to change their behavior;
2. Contemplation – a person recognizes the problem but is not yet ready to act;
3. Preparation – a decision has been made to change behavior shortly;
4. Action – active changes in behavior;
5. Maintenance – maintaining new habits;
6. Relapse (not always highlighted) – a return to the old behavior, after which the cycle of change may be repeated.

Interpretation was based on the fact that the questionnaire helps to determine at what stage a person is concerning a particular behavior (*e.g.*, smoking cessation or weight loss). If the majority of responses indicate pre-contemplation, the person is not ready to change the behavior.

Contemplation indicates internal doubts - the person is thinking but not yet acting. If the predominant responses are in the Preparation or Action stage, then changes are already underway or are planned shortly.

The maintenance stage indicates that the person has already changed their behavior and is working to maintain it. Formulation of individual goals

This was followed by the stage of setting SMART goals: specific, measurable, achievable, realistic, and time-bound (*e.g.*, "reduce episodes of emotional eating from 5 to 2 times a week in a month").

STAGE 2. Working with cognitive distortions: identifying automatic thoughts

Automatic thoughts are quick, involuntary judgments that occur in response to certain situations. They are often negative and distort reality. People may have these thoughts when they are obese:

Black and white thinking: "*If I don't lose 5 kg this month, I'm a complete failure*";

Catastrophising: "*If I can't control my weight, no one will love me*";

Negative filtering: "*Even if I lose a little weight, it doesn't matter because I still look bad*";

Personalization: "*People are laughing – it's definitely because of my weight*";

Must/obligation thinking: "*I have to follow my diet perfectly, otherwise it's all for nothing*".

STAGE 3. Formation of healthy behavioral strategies: work on habits, exposure therapy for eating behavior, and formation of healthy physical habits.

According to the design, the third stage will be implemented through the introduction of self-monitoring techniques (food diary, reminders about meals), finding alternatives to overeating (replacing food with other methods of coping with stress), introducing a system of rewards for achieving goals, teaching hunger tolerance, food as pleasure, guilt after breakdowns, using the "food challenge" technique (deliberate consumption of "forbidden" foods in controlled conditions), and developing healthy physical habits.

At the same time, in the third stage, patients will be offered a small-step approach, for example: 10 minutes of exercise every day is better than nothing etc. Identification of possible barriers to activity and their overcoming etc.

STAGE 4. Dealing with stress and emotional regulation: stress management techniques, emotional regulation.

Relaxation techniques: diaphragmatic breathing, mindfulness, progressive muscle relaxation. Work with overeating triggers (stress, loneliness, boredom). Development of emotional awareness skills. Using the Stop Impulse technique before overeating

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STAGE 5. Support and relapse prevention: creating an action plan for relapse, analyzing the factors that caused the relapse, and developing an avoidance strategy, group support, psychotherapy groups, long-term follow-up, regular sessions (initially weekly, then once a month), and support through telemedicine (online consultations).

Statistical analysis

Descriptive statistical methods were employed to process the obtained data. For the analysis of categorical variables, particularly in assessing the prevalence of chronic diseases and the frequency of automatic thoughts, frequency analysis was conducted with results presented as percentages (%). Mean values and standard deviations (Mean±SD) were calculated for quantitative variables, assuming a normal or near-normal distribution, which was preliminarily verified using the Shapiro–Wilk normality test.

A qualitative analysis of automatic thoughts was conducted to identify the characteristics of cognitive patterns associated with disordered eating behavior. Initially, the patient's responses were coded, during which distinct meaningful units – automatic thoughts – were identified. Each respondent's statement was coded based on its essential content without imposing any pre-existing categories. Subsequently, the codes were grouped into thematic categories according to shared cognitive patterns. The frequency of mentions for each identified theme among all surveyed patients was calculated to represent the findings. Specifically, the percentage of respondents who endorsed the corresponding cognitive pattern as characteristic of themselves was determined for each automatic thought.

All statistical data processing was performed on the 90th day of therapy, using Microsoft Excel (Microsoft Corporation, 2018) licensed software and standard SPSS Statistica 21.0 programs (IBM Corp., Armonk, NY, USA). Estimation of the probability of the difference of average values was taken into account qualitative and quantitative variables performed using the Student's paired t-test. The significance level was set at $p<0.05$.

Results

At the time of publication, 314 women with subfertility participated in the study. The average age of the patients was 42±1.42 years. As indicated by the study design, patients had chronic metabolic disease (Table 1).

We have listed the questionnaires we used in the Material and Methods section. The results are shown in Figures 1–4.

It should be noted that in all groups, a significant level of depressive symptoms higher than a clinical cut-off score of 5 points was determined. The highest depression scores, according to the PHQ-9 questionnaire, were observed in patients with obesity and metabolic syndrome. In obese patients, the average score was 8.1±0.51, which corresponds to mild depression, and in patients with metabolic syndrome, the average score was 12.3±1.03, which was considered moderate depression.

Figure 2 shows that patients tended to have a similar pattern to the PHQ-9 in relation to the GAD-7. Patients with obesity, diabetes mellitus, and metabolic diabetes had more severe symptoms of anxiety disorder. Obese patients had the highest score, namely 13.2± 0.54 points.

Although patients with metabolic syndrome had a higher average in PHQ-9 compared to other groups, this difference remained within the transition from mild to moderate depression, which does not indicate sharply different clinical conditions. Similarly, the increased GAD-7 values among obesity patients tended to moderate anxiety but did not show significant exacerbation of symptoms compared to other nosological groups. However, there is a clear tendency for patients with obesity and MS to be the risk group for the development of concomitant psychopathological changes.

Regarding cognitive functioning, the difference in the MMSE scale between groups also remained within the variability of mild cognitive disorders, without clear signs of significant deterioration of cognitive status in any of the subgroups (Figure 3).

Most patients had mild cognitive disorders, while in patients with dyslipidemia, the average corresponded to the norm, namely 28.1±0.89 points. The MoCA results, which are more sensitive to mild cognitive disorders within a wide range, confirmed the highlighted trends. A noteworthy finding is the reduction of the absolute score among groups of people with dyslipidemia and obesity (Figure 4).

Patients with dyslipidemia showed the highest mean MoCA score (24.3±1.21 points) compared to other metabolic subgroups. While a score of 26 and above is generally considered normal according to standard MoCA interpretation guidelines, scores between 18 and 25 are indicative of mild cognitive impairment (MCI). Thus, although the group with dyslipidemia exhibited relatively better cognitive performance compared to

Table 1: Subfertile patients' distribution according to comorbidity

Diseases	Type 2 diabetes	Obesity	Dyslipidemia	Metabolic syndrome
No. of patients (%)	153 (48.73%)	232 (72.86%)	185 (58.92)	163 (51.91%)

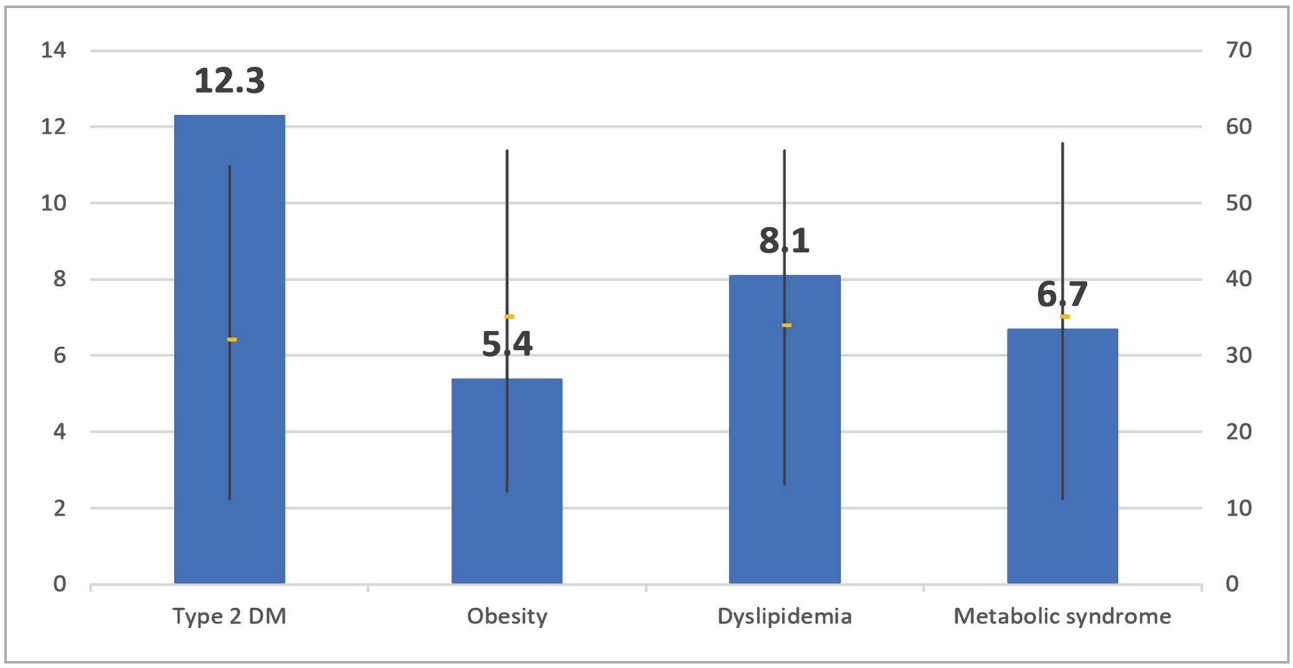

Figure 1: PHQ-9 questionnaire results in subfertile patients according to comorbidity.

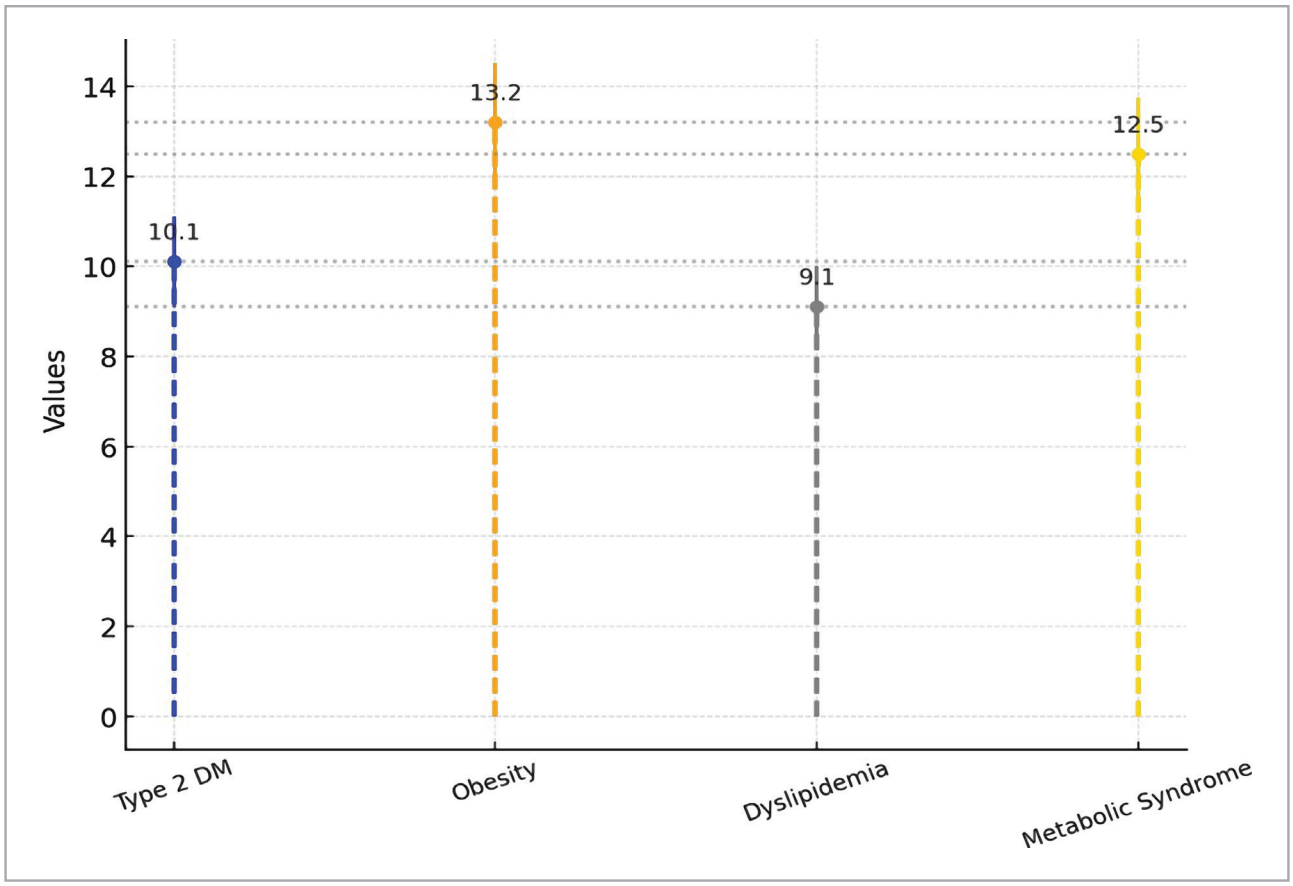

Figure 2: GAD-7 results in subfertile patients according to comorbidity.

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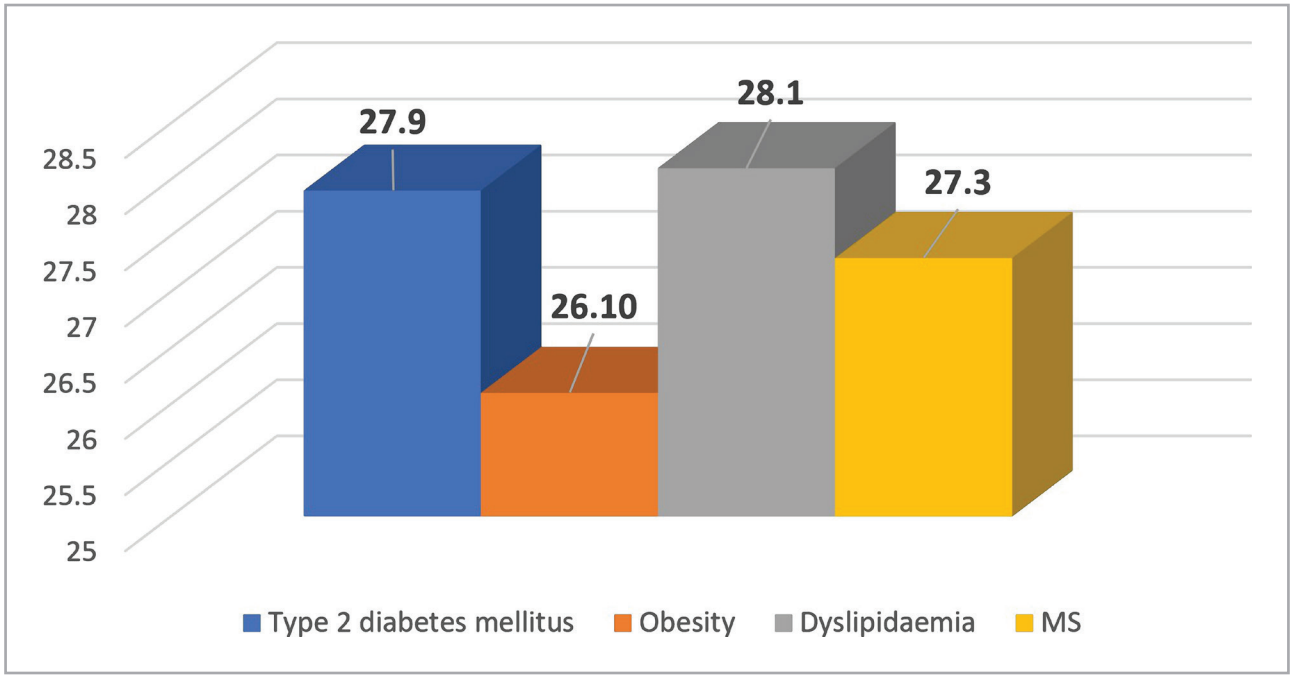

Figure 3: MMSE questionnaire results in subfertile patients according to comorbidity.

patients with obesity, diabetes, or metabolic syndrome, their mean scores still suggested the presence of mild cognitive difficulties.

Dyslipidemia alone, in the absence of more severe metabolic or vascular comorbidities, may have a less pronounced impact on cognitive function in early disease stages. Alternatively, the relatively better cognitive performance may reflect less cumulative systemic inflammation or fewer comorbid risk factors compared to groups with obesity and metabolic syndrome, where cognitive compromise is often more evident due to multisystemic dysregulation.

The data presented in Table 2 demonstrates a clear high level of readiness for changes in patients, which can be seen as a positive prognostic factor for interventions aimed at behavioral change. Most of the respondents had the highest score at the "Preparation" point, which means that the patient is ready for change in the near future. However, relatively lower results at the "Support" stage indicate the potential risks of difficulty in fixing the changes made.

The design of the study in the second stage was working with cognitive distortions: detection of automatic thoughts.

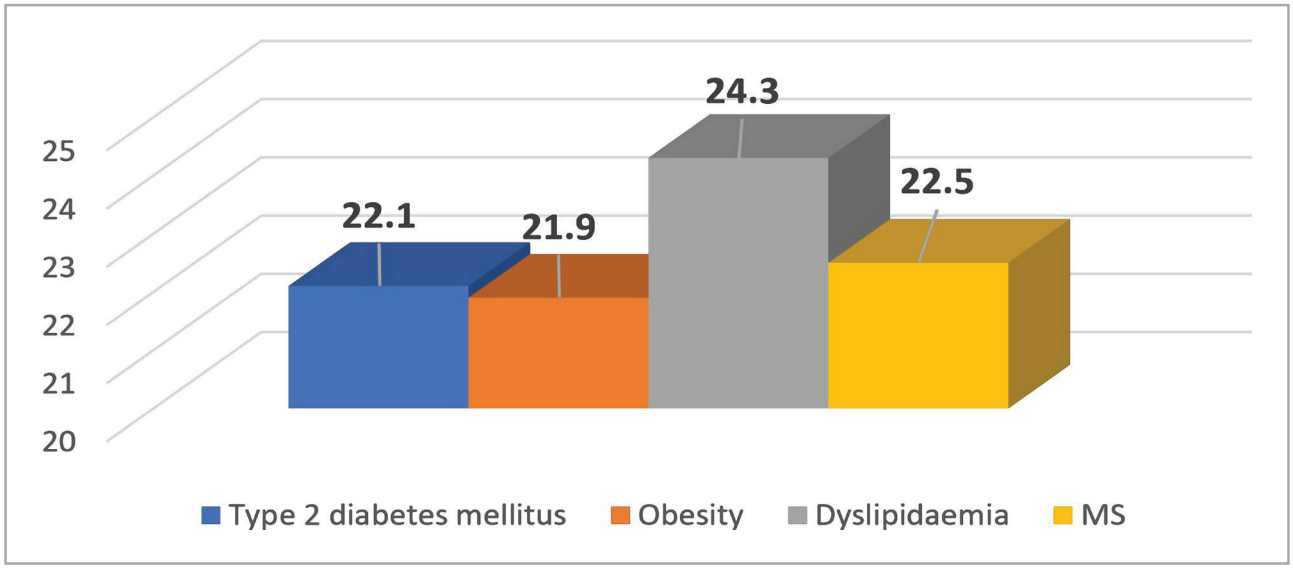

Figure 4: MoCA questionnaire results in subfertile patients according to comorbidity.

Table 2: Prochaska & DiClemente questionnaire results in subfertile patients with metabolic diseases.

Stage	Points (1–5)	Conclusions
Pre-contextualization	2.1±0.05	Low motivation, lack of intention to change behavior
Contemplation	3.8±0.21	People think about changes, but they don't act on them yet
Preparation	4.2±0.54	Readiness for changes in the near future
Action	3.5±0.33	Changes have been initiated but not consolidated
Support	2.9±0.15	You need to work on stabilizing the new behavior

Based on quantitative analysis of qualitative data, several categories of automatic thoughts were identified. The primary themes that emerged reflected a sense of helplessness in controlling eating behavior, catastrophizing the consequences of dietary lapses, negative self-evaluation of body image, and fear of social rejection due to body weight (Table 3).

Qualitative analysis of automatic thoughts found that the most common cognitive distortions among patients were the installation for the irreversibility of weight changes and the low self-esteem caused by it. In particular, the statements "*I will always be thick*" and "*Diet does not work, I still gain weight*" respectively in 63.41% and 60.32% of cases. Such patterns of thinking are an important psychological barrier to a successful modification of lifestyle and require purposeful psychological intervention.

Discussion

Symptoms of depression, including major depressive disorder (MDD), are much more common among patients with diabetes mellitus than among the healthy population. For example, depression is twice as likely to be diagnosed in patients with type 2 diabetes (T2D) [30]. The reasons for this phenomenon remain controversial: some studies indicate that diabetes precedes depression due to the psychological stress associated with the diagnosis [31], while others point to the possibility of an inverse relationship, with depression acting as a risk factor for the development of T2D [30]. According to the WHO, people with a combination of T2D and depression are more likely to rate their health as poor compared to patients with only one of these diseases [31].

Our research confirms that subfertile women with type 2 diabetes have anxiety-depressive disorders according to the PHQ-9 and GAD-7 questionnaires, namely 6.7 and 10.1 points, respectively ($p \leq 0.05$).

Obese patients who present to mental health professionals are not typical patients, and understanding the relationship between obesity and MD requires more systematic work based on the general population. The results of this approach have not been entirely clear, as while some studies have shown that obesity is associated with depression and anxiety [32], others have argued that people living with obesity have markedly better mental health, coining the unfortunate term "happy fats" [33].

Table 3: Common automatic thought distribution in subfertile patients with metabolic diseases.

Automatic thoughts	% of patients who had them
"I am weak, so I cannot control what, when and how I eat"	34.21±0.03
"Dieting doesn't work, I'll gain weight anyway"	60.32±1.23
"I will always be fat"	63.41±2.36
"If I break my diet once, it's a disaster"	43.57±1.47
"No one will love me because of my weight"	54.31±1.03

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People with obesity are subject to stigma and discrimination in relation to their body weight. This can be defined as a negative social perception of obesity. People who are overweight are often devalued and undermined, characterized as lazy, undisciplined and weak [34, 35]. Discrimination is evident in many situations, from employment and education to healthcare, with evidence that people with higher body weight are less likely to be promoted, are considered less capable of learning and therefore ignored in educational settings, and are less worthy of treatment for other health conditions [36]. Stigmatization in educational settings is particularly harmful because it can lead to school avoidance and poor academic performance, resulting in lower socioeconomic trajectories and lost advancement opportunities [37]. This occurs through peer bullying as well as teacher neglect, and in recent years, online bullying has become a growing problem [38]. These trends are reinforced in images in the media, including television, shops, newspapers and magazines, social media, and even children's books, where characters living with overweight and obesity are portrayed as unpleasant, silly, or funny figures [39–41].

For example, we found that obese subfertile women had higher levels of anxiety and depression and lower cognitive levels than patients with dyslipidemia ($p \leq 0.05$).

One of the consequences of stigma can be overeating, consumption of high-calorie comfort foods, and further weight gain [42]. Another is increased psychological stress. A meta-analysis of 105 cross-sectional studies with multiple mental health outcomes found an association between perceived weight stigma and greater depression, anxiety, psychological distress, and poor quality of life [43]. Research on weight stigma and psychological distress has focused on the perceptions of victims rather than on objective evidence of discrimination. This is not surprising, as the fact that an observer perceives certain situations as discriminatory does not mean that the individual evaluates these situations in the same way, and many overweight people learn to cope effectively [44–47]. It is difficult to assess how important weight stigma is to weight maintenance and weight gain; notably, research on weight stigma has almost always controlled for BMI, but research on mechanisms associated with weight gain rarely controls for weight stigma.

Working with cognitive distortions helps to change attitudes towards oneself and weight, which is important for long-term lifestyle changes. Under our supervision, patients experienced positive subjective changes in their attitudes toward automatic thoughts. However, due to the short follow-up period, we are unable to provide statistical data on these approaches and their effects on patient weight and fertility progress. However, we will provide data on this in our next publications.

In addition to the above, we have found that patients with MS have reduced cognitive function according to the standardized MoCA and MMSE questionnaires ($p \leq 0.05$).

The results indicated that although metabolic diseases are associated with a certain tendency to deteriorate psycho-emotional state and cognitive functions, they do not reach the level of clinically significant effects in the study. This suggests that cognitive functions can remain relatively intact in the early stages of metabolic disorders, and pronounced cognitive deficits develop later or in the presence of multifactorial complications (such as vascular disorders). However, this may indicate a compensatory multiplicity and the need for a long period to detect progression.

The small amount of differences may indicate that the main factor in the formation of psycho-emotional and cognitive changes is not the metabolic disease at the studied stages, but rather a concomitant health-related distress and illness perception among discussed population groups.

However, there are gaps in our publication, namely, the mechanisms of the relationship between metabolic and mental disorders have not been sufficiently investigated – most studies focus on individual factors, but a comprehensive approach requires further study. The role of stigma in the development of depression and anxiety in obese patients is not fully understood – more research is needed on social influence and self-stigma.

There is limited data on the effectiveness of CBT in patients with comorbidity of metabolic and mental illnesses – most studies focus on either mental or somatic disorders. The long-term results of CBT in patients with metabolic disorders are not defined – an analysis of the effectiveness of therapy 6–12 months after the intervention is needed. The effect of CBT on changing behavioral strategies and correcting metabolic parameters (weight, glycemia, lipid profile) remains insufficiently studied.

As mentioned above, this study is the beginning of a large project on the correction of mental disorders in women with subfertility and metabolic diseases. This publication opens new perspectives and horizons for researchers around the world to conduct more rigorous studies in the future and extend our results.

Conclusions

Mental disorders are common among subfertile women with metabolic diseases – especially depression and anxiety, which are most common in obese women with metabolic syndrome.

Subfertile women with obesity have increased rates of anxiety and depressive disorders and lower cognitive levels compared to patients with dyslipidemia ($p<0.05$), which may affect reproductive function.

Subfertile women with metabolic syndrome have reduced cognitive function according to the standardized MoCA and MMSE questionnaires ($p<0.05$).

Cognitive behavioral therapy (CBT) seems to be effective in correcting mental disorders in women with subfertility and chronic metabolic disorders, as it helps to change destructive beliefs and develop healthy behaviors.

The CBT model of stepwise intervention for women with subfertility and metabolic and mental disorders includes psychological assessment, correction of cognitive distortions, development of healthy habits, stress management, and relapse prevention.

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Conflict of interest

The authors declare no conflict of interest.

Ethics approval

The approval for this study was obtained from the Ethics Commission in Conducting Experimental and Clinical Research Communal Non-profit Enterprise "Maternity Hospital No. 5" Odesa City Council, protocol No. 1 on June 6th 2024. All methods were performed according to the Declaration of Helsinki.

Consent to participate

Written informed consent was obtained from all the participants.

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