

Efficacy of a fasting-mimicking diet in functional therapy for depression: A randomised controlled pilot trial

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Abstract

Objective: This randomized controlled trial examined the efficacy of adding a fasting-mimicking diet to a structured psychotherapy protocol for treating depression.

Design: Of 20 patients with depression, 10 were randomly assigned to psychotherapy and dieting (i.e., experimental group) and the other 10 to psychotherapy only (i.e., control group). Patients in both groups received 20 individual sessions of functional therapy along with nutrition consultation. Patients in the control group were instructed to maintain their usual daily diets.

Results: Both treatments were effective in reducing depression as well as increasing self-esteem and quality of life. The experimental group showed improved self-esteem and psychological quality of life as well as a reduction in their mean body mass index, in comparison to the control group.

Conclusions: The study revealed initial evidence of the efficacy of combining psychotherapy with a fasting-mimicking diet to treat depression and its correlates.

KEY WORDS

depression, fasting-mimicking diet, functional therapy, psychotherapy outcome, self-esteem

1 INTRODUCTION

Depression, which affects 4.4% of the world's population (World Health Organization, 2017), is a systemic disorder recognized as a leading cause of illness and disability worldwide. Depression raises the risk of several disorders (Sotelo & Nemeroff, 2017), partly due to its association with inflammation (Halaris, 2019) and potential to be influenced by changes in microbiota (Winter, Hart, Charlesworth, & Sharpley, 2018). Current research suggests that depression is caused by a combination of genetic (Dunn et al., 2015), environmental (Gotlib, Goodman, & Humphreys, 2020), and psychological factors (Hammen, 2018), including child abuse (Infurna et al., 2016), stressful life events (Berg, Rostila, & Hjern, 2016), and low self-esteem (Shah et al., 2020). Indeed, recent findings showing that individuals with high self-esteem reported a lower risk for developing depression support the vulnerability model of low self-esteem and depression (Orth, Robins, Meier, & Conger, 2016).

To date, psychotherapy programs shown to be effective in treating depression include cognitive-behavioral therapy (Grosse Holtforth et al., 2019), psychodynamic (de Roten et al., 2017), and mind-body approaches (e.g., Chan et al., 2016). Empirical evidence also suggests that functional therapy, by directly intervening in the mind-body system, can induce changes in an individual's cognitive, emotional, and psychological systems (Maniaci et al., 2018; Perciavalle et al., 2017). For depression, the purpose of functional therapy is to increase mood and self-esteem via several bodily, cognitive, and emotional techniques geared toward helping patients to improve the basic

experiences of the self that are altered by the disorder (for an explanation of functional theory, see Dipasquale, Magnano, Blandini, Gueli, & Fecarotta, 2019; Rispoli, 2016).

A considerable body of literature highlights the role of a healthy diet in reducing the risk of depression (Lassale et al., 2019). By contrast, eating according to Western dietary patterns has been associated with depressed mood (Masana et al., 2018). Indeed, the typology of diet modulates several key biological processes, including inflammation, involved in mood disorders (Halaris, 2019). A specific typology of diet that includes fasting has been shown to affect several health-related parameters, including stress resistance, self-renewal, and lineage-balanced regeneration (De Braud et al., 2018), as well as to reduce immunosuppression and mortality caused by chemotherapy in mice (Cheng et al., 2014). It also promoted hippocampal neurogenesis and improved cognitive performance and motor coordination (Brandhorst et al., 2015). Currently, several ongoing clinical trials are evaluating the effects of fasting-mimicking diets in cancer patients (De Braud et al., 2018; Vernieri et al., 2019) and in the treatment of Type 2 diabetes (e.g., ClinicalTrials.gov NCT03811587). However, though the association between diet and depression is fairly certain, to our knowledge no studies have investigated the effects of a fasting-mimicking diet protocol on depression.

Given those premises, our clinical trial had two aims: (a) to verify the efficacy of a structured functional therapy program delivered in individual sessions for patients with depression and (b) to determine whether the integration of a fasting-mimicking diet protocol into the structured functional therapy program can significantly improve clinical outcomes. In our study, the primary treatment outcome was a significant reduction of depressive symptoms in all patients, although we hypothesized to observe a significantly greater reduction among

patients who received the integrated treatment than in the ones who received psychotherapy alone. The secondary outcome was a significant improvement in all patients' self-esteem and quality of life, but again, greater improvements were hypothesized among patients who received functional therapy integrated with a fasting-mimicking diet than in ones who received functional therapy only.

2 | METHODS

2.1 | Study design and procedure

Our randomized controlled trial (RCT) to compare the effects of functional therapy versus functional therapy along with a fasting-mimicking diet among patients with depression was conducted in the outpatient clinic of the Psychiatry Section of the Department of Biomedicine, Neuroscience, and Advanced Diagnostics at the University of Palermo. Patients could volunteer to enroll in the study during a 9-month period from September 2018 to May 2019 by responding to an advertisement posted in the outpatient clinic, on flyers distributed to pharmacies and medical offices, and on social media. All volunteers were subjected to structured telephone screening to determine their eligibility in terms of the following inclusion and exclusion criteria: aged from 18 to 60 years old, seeking treatment for mood problems, not receiving any concurrent treatment, not receiving any psychopharmacological treatment for depression in the previous 12 months, and not practicing yoga or meditation. Patients with past or current drug abuse or addiction (excluding nicotine), chronic inflammation disease, severe

hepatic failure, serious infection (e.g., hepatitis B), cancer in the previous 6 months or regular use of anti-inflammatory drugs for >15 days per month were also excluded.

To further examine other eligibility criteria and depression, consultations with a clinical psychologist and psychiatrist were organized together with the administration of the psychological tests. To qualify to participate in the RCT, patients had to score >13 points on the Beck Depression Inventory-II (BDI-II) and report a body mass index (BMI) between 18.5 and 30.0 at the initial assessment. The exclusion criteria were an intelligence quotient (IQ) <65, active suicidal ideation with a plan, and a current or lifetime diagnosis of any psychotic disorder, eating disorder, bipolar disorder, primary anxiety disorder, or a borderline, schizotypal, or antisocial personality disorder. All participants provided their written informed consent, and all measures were administered with respect for their privacy. To assign participants into the study's groups, a randomization sequence was created using an online randomization service (www.randomization.com). Participants were randomized into either an experimental group or a control group via block randomization, with five blocks of Size 4, such that participants in the groups were evenly distributed among the therapists. Afterward, all subjects received a nutrition consultation, who prescribed the fasting-mimicking diet to the experimental group, whereas those in the control group were asked to maintain their usual diets and to not make any dietary changes, which they monitored by reporting all food and beverages consumed in a food diary. Last, all participants received the functional therapy protocol. All measures were administered at baseline, at the end of treatment (i.e., 3 months after baseline), and at follow-up (i.e., 6 months after baseline).

The study was approved by the ethical review board of the Policlinico "P. Giaccone" in Palermo, Italy (07/2017),

and was registered with clinicaltrials.gov (NCT04050475). All procedures performed involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments.

2.2 | Measures

2.2.1 | Screening measures

To verify the absence of exclusion criteria, an ad hoc sociodemographic questionnaire, a shortened version of the Wechsler Adult Intelligence Scale—Revised (Velthorst et al., 2013), and the Italian version of the Millon Clinical Multiaxial Inventory-III ($\alpha = .65-.80$; $r = .76-.93$; Zennaro, Ferracuti, Lang, & Sanavio, 2008) were used to assess sociodemographic variables (e.g., age, sex, marital status, and occupation), IQ, and personality disorders and primary psychiatric disorders, respectively.

2.2.2 | Outcome measures

The primary outcome measure was the Italian version of the BDI-II, used to assess the severity of depressive symptoms (Ghisi, Flebus, Montano, Sanavio, & Sica, 2006). The test has shown good psychometric properties ($\alpha = .80-.87$; $r = .76$; Sica & Ghisi, 2007).

The secondary outcome measures were the Basic Self-Esteem Scale (Forsman, Johnson, Ugolini, Bruzzi, & Raboni, 2003), used to assess self-esteem, and the brief Italian version of the World Health Organization Quality of Life (WHOQOL-BREF) instrument (De Girolamo et al., 2000), used to assess subjective perception of quality of life. The Italian Basic Self-Esteem Scale has shown good psychometric properties ($\alpha = .85$; $r = .81-.83$; Forsman et al., 2003), as well as the WHOQOL-BREF ($\alpha = .65-.80$; $r = .76-.93$; De Girolamo et al., 2000). At the end of the psychological assessment, anthropometric parameters (i.e., weight, height, and waist circumference) were measured, after which patients received a consultation with a nutritionist.

2.3 | Intervention

Five clinical psychologists with 4 years postgraduate training in functional therapy implemented the intervention after receiving refresher training in the application of the structured functional therapy protocol for depression. From a senior clinical psychologist with specialist training in functional therapy, they also received weekly clinical supervision focused on maintaining fidelity to the programmed intervention. Each therapist treated four patients. A nutritionist prescribed the fasting-mimicking diet protocol following consultation with each patient. After the assessment, each eligible patient was randomized to receive either functional therapy with the fasting-mimicking diet or functional therapy only and assigned to the next available therapist on the intervention schedule. Although 42 consecutive treatment-seeking patients were screened, four were excluded due to

psychotic symptoms and another 18 due to meeting other exclusion criteria. The resulting sample comprised 20 participants with depression, four of whom dropped out after attending an average of 4.6 (standard deviation = 1.86) treatment sessions. Figure 1 depicts the CONSORT flow chart.

2.4 | Treatments

2.4.1 | Experimental group

During a 3-month period, participants randomized into the experimental group were administered the functional therapy protocol over the course of 20 individual sessions, scheduled to occur twice weekly for the first 2 months and once weekly for the last month. The treatment program was customized to treat depression by increasing mood, self-esteem, and quality of life (Rispoli, 2008). More precisely, the program was geared toward reducing or eliminating mood imbalances through several bodily, cognitive, and emotional techniques (e.g., deep breathing and specific guided imagery), as well as techniques to improve assertiveness and social abilities (please contact the corresponding author if you are interested in learning more about the focus of each session). Participants in the experimental group also followed a fasting-mimicking diet protocol developed by Wei et al. (2017) consisting of three 5-day cycles per month. On Day 1, the fasting-mimicking diet prescribed 1,090 kcal (i.e., 10% protein, 56% fat, and 34% carbohydrates); on Days 2–5, that formulation was proportionally reduced to 725 kcal (i.e., 9–10% protein,

2.4.2 | Control group

Participants randomized into the control group completed the same functional therapy program administered in the experimental group but did not follow the fasting-mimicking diet protocol. As a control condition, at the end of their nutrition consultation, the nutritionist advised them to keep a food diary, and they were instructed to continue their usual daily diets. If they had any doubts or questions, then they were free to send an email to the nutritionist.

2.5 | Statistical analysis

Group-based differences in demographic features and pretreatment measures were analyzed with the Mann–Whitney test or Fisher's exact tests. We used the Friedman test to evaluate any statistically significant difference on depression, self-esteem, and quality of life, within the groups at baseline, after treatment, and follow-up. In case of a significant value, the Wilcoxon signed-rank test was performed to evaluate which time points were significantly different from one another. Last, the Mann–Whitney test was performed to analyze differences between groups before and at each time point during the study. Effect size was also calculated ($r = z/\text{square root of } N$), and Cohen's guidelines were used to judge the size of the effect (Field, 2013). All statistical analyses were performed in the Statistical Package for the Social Sciences for Windows 22.0 and assumed an alpha risk of 5%.

3 | RESULTS

3.1 | Baseline data

No significant differences between groups emerged in the sociodemographic characteristics of age ($U=48.500$; $z=-0.114$; $p=.912$); gender, $p=.650$; marital status, $p=1.000$; or level of education ($U=30.500$; $z=-1.575$; $p=.163$). At baseline, both groups were also homogeneous in terms of the primary and secondary outcome measures of depressive symptoms ($U=45.500$; $z=-0.341$; $p=.739$); self-esteem level ($U=29.500$; $z=-1.661$; $p=.123$); and quality of life, in terms of physical health ($U=33.000$; $z=-1.298$; $p=.218$); psychological health ($U=46.000$; $z=-0.307$, $p=.796$); social relationships ($U=46.000$, $z=-0.308$, $p=.796$); and environmental health ($U=48.000$; $z=-.152$; $p=.912$). Baseline BMI between the groups did not significantly differ, either ($U=28.000$; $z=-1.663$; $p=.105$).

3.2 | Outcomes and estimation

3.2.1 | Within-group differences

Experimental group

A Friedman test showed a significant difference after treatment on depression levels $\chi^2(2) = 14.800, p = .00005$; levels of self-esteem $\chi^2(2) = 16.800, p = .000$; and all dimensions of quality of life, such as physical $\chi^2(2) = 10.889, p = .003$; psychological $\chi^2(2) = 14.727, p = .000$; social relationships $\chi^2(2) = 11.879, p = .001$, and environmental $\chi^2(2) = 13.556, p = .0003$. Furthermore, a statistically significant difference on BMI was found $\chi^2(2) = 13.556, p = .0003$. The results of the Wilcoxon test indicated a significant main effect of time after treatment for depression levels ($z = -2.668; p = .008$), levels of self-esteem ($z = -2.716; p = .007$), all dimensions of quality of life, such as physical ($z = -2.547; p = .011$), psychological ($z = -2.668; p = .008$), social relationships ($z = -2.521; p = .012$), and environmental ($z = -2.666; p = .008$); and BMI ($z = -2.666; p = .008$). At follow-up, the Wilcoxon test indicated that there was no significant difference 3 months after the experimental group received the treatment.

Control group

A Friedman test showed a significant difference on depression levels $\chi^2(2) = 12.452, p = .001$; levels of self-esteem $\chi^2(2) = 6.333, p = .049$; physical quality of life $\chi^2(2) = 7.770, p = .015$; and social relationships quality of life $\chi^2(2) = 8.087, p = .010$. Post hoc tests using a the Wilcoxon signed-rank test revealed a significant main effect of time after treatment, meaning that functional therapy led to significantly reduced levels of depression ($z = -2.527; p = .012$), together with increased levels of self-esteem ($z = -2.121; p = .034$); physical ($z = -2.527; p = .012$) and social relationships quality of life ($z = -2.401; p = .016$). As well as in the experimental group, the Wilcoxon test indicated

that there was no significant difference 3 months after the control group received the treatment.

3.2.2 | Between-group differences

A Mann–Whitney test indicated that the increase of self-esteem at the end of the treatment was significantly greater for the experimental group ($Mdn = 75.000$) than for the control group ($Mdn = 25.000$), $U = 6.500$, $z = -2.949$, $p = .002$; $r = -.715$. A significant increase of psychological quality of life was highlighted in the experimental group ($Mdn = 27.085$) compared to the control group ($Mdn = 12.500$), $U = 11.000$, $z = -2.210$, $p = .027$; $r = -.375$. Furthermore, significant differences between groups were highlighted regarding the decrease of BMI ($U = 10.000$, $z = -2.276$, $p = .02$; $r = -.569$), with greater change in the experimental group ($Mdn = -1.8$) than in the control group ($Mdn = -0.05$). No significant differences from T1 to T2 were found. Moreover, a Mann–Whitney test indicated that there were no significant differences between groups (pretreatment and posttreatment) in depression levels ($U = 27.000$; $z = -0.868$; $p = .204$), and physical ($U = 25.000$; $z = -1.060$; $p = .309$), social relationships ($U = 33.500$; $z = -0.245$; $p = .840$) and environmental ($U = 33.000$; $z = -0.290$, $p = .796$) quality of life.

4 | DISCUSSION

Our RCT was designed to evaluate the efficacy of a fasting-mimicking diet protocol

integrated into a structured functional therapy program for patients with depression in terms of its effects on their depressive symptoms, self-esteem, and quality of life. Among our results, depressive symptoms significantly decreased in both groups. Although the average expected change was greater for patients in the experimental group than in the control group, this difference was not substantial, which may have been due to the small sample size. Furthermore, from posttreatment to the 3-month follow-up, no significant worsening surfaced in any outcome measures in both groups, which implies that improvements had been maintained. Beyond that, a reduction in mean BMI in the experimental group only suggests good compliance with the fasting-mimicking diet prescribed and general health benefits, because no patients showed a BMI below the normal level.

As several researchers have shown, unhealthy diets can be associated with depression, whereas healthy ones can positively affect mood (Masana et al., 2018). In particular, a Mediterranean-style diet has been found to be effective in improving depressed mood (Parletta et al., 2019), preventing the recurrence of depression, and improving the quality of life of patients with previous episodes of depression (Sánchez-Villegas et al., 2019). Although a fasting-mimicking diet has also demonstrated positive effects in decreasing risk factors for age-related diseases in humans (Brandhorst et al., 2015), to the best of our knowledge the efficacy of such a diet in treating depression has not been investigated in clinical trials. The fasting-mimicking diet combined with functional therapy significantly improved the self-esteem in patients with depression. Because following the fasting-mimicking diet protocol can be challenging for patients, it is possible that managing to complete it could have partly enhanced their self-esteem and, consequently, the effects of functional therapy. Our findings are consistent

with those of a recent study that found an association between adherence to a Mediterranean diet and high levels of self-esteem (Knox & Muros, 2017). Ketogenic diets have also been used in a clinical treatment to control brain seizures (Simeone, Simeone, & Rho, 2017), which suggests that ketone bodies and possibly other factors raised or lowered during fasting could promote changes in the nervous system that contribute to effects on depression.

Among other findings, functional therapy combined with the fasting-mimicking diet was significantly more effective than functional therapy alone in improving psychological quality of life. Our result is consistent with previous findings that showed that healthy dietary changes improved mental health and quality of life of people with depression (Parletta et al., 2019). It is possible that practicing a healthy diet can improve patients' quality of life, because they can gain a sense of their full strength as well as their capacity to manage and enjoy their everyday lives. Moreover, patients randomized to complete the functional therapy-fasting-mimicking diet program demonstrated good compliance and rarely dropped out, which aligns with reported dropout rates of approximately 20% in recent similar studies (Cooper & Conklin, 2015; Zilcha-Mano et al., 2016).

Such findings suggest the usefulness of working through depression by following an integrated approach that involves food as a medicine for improving the outcomes of psychotherapy. In fact, because of the connections between the central nervous system and the immune system via the hypothalamic-pituitary-adrenal axis, a disruption of one can disrupt the other and cause low-grade systemic inflammation

(Halaris, 2019).

Although it may be difficult for patients with depression to adopt radical and chronic dietary changes, a periodic fasting-mimicking diet undertaken for only 5 days per month could prove to be more feasible and effective than a strict daily diet followed for 3 months. Not only would that arrangement allow patients with depression to continue observing a diet that they enjoy for the remaining 25 days each month, but it would also slowly improve their everyday diets based on the effects of a periodic fasting-mimicking diet.

4.1 | Strengths and limitations

The chief limitation of our study was its small sample. As a pilot study, its results are promising and consistent with our hypotheses, at least concerning self-esteem and quality of life; however, further research is needed to verify those findings. Another limitation was the use of a fasting-mimicking diet based on the prescription of real food versus a standardized box including the same foods for everyone. Indeed, the different origins of foods and ways of preparing them could have partially influenced the outcomes. Another possible limitation was bias related to compliance with following the fasting-mimicking diet protocol. As in other research protocols, we cannot be sure that all patients in the experimental group strictly followed the prescribed diet; however, the reduction in BMI only in the experimental group suggests good compliance with the fasting-mimicking diet protocol. Furthermore, we did not evaluate whether the participants practiced any physical activity, which would represent a confounding variable

if they did. Despite those limitations, our pilot study suggests that treatment combining functional therapy and a fasting-mimicking diet may be effective in treating depression and its psychological correlates.

For researchers, the next step could be conducting another RCT with a larger sample, also including a detailed evaluation and monitoring of the food patterns (e.g., via the prescription of a standardized box) and physical activity of participants. Another possible direction would be to investigate how such an integrated treatment can alter inflammatory parameters related to depression and how such changes relate to improving mood.

5 | CONCLUSIONS

With presumably good compliance and few dropouts, our study revealed positive outcomes in patients with depression treated with a structured functional therapy program combined with a fasting-mimicking diet protocol. Outcomes regarding self-esteem and psychological quality of life were especially promising, for improvements along those lines were maintained at 3-month follow-up. In conclusion, our study has confirmed the relevance and efficacy of psychotherapy for treating depression, as well as suggested the potential applicability of lifestyle modification such as the introduction of a periodic fasting-mimicking diet protocol.

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CONFLICT OF INTERESTS

Manfredi Rizzo is currently Director, Clinical Medical & Regulatory Affairs, Novo Nordisk Europe East and South. Valter Longo has equity interest in the company L-nutra which produces medical food. All other authors declare that they have no conflict of interests.

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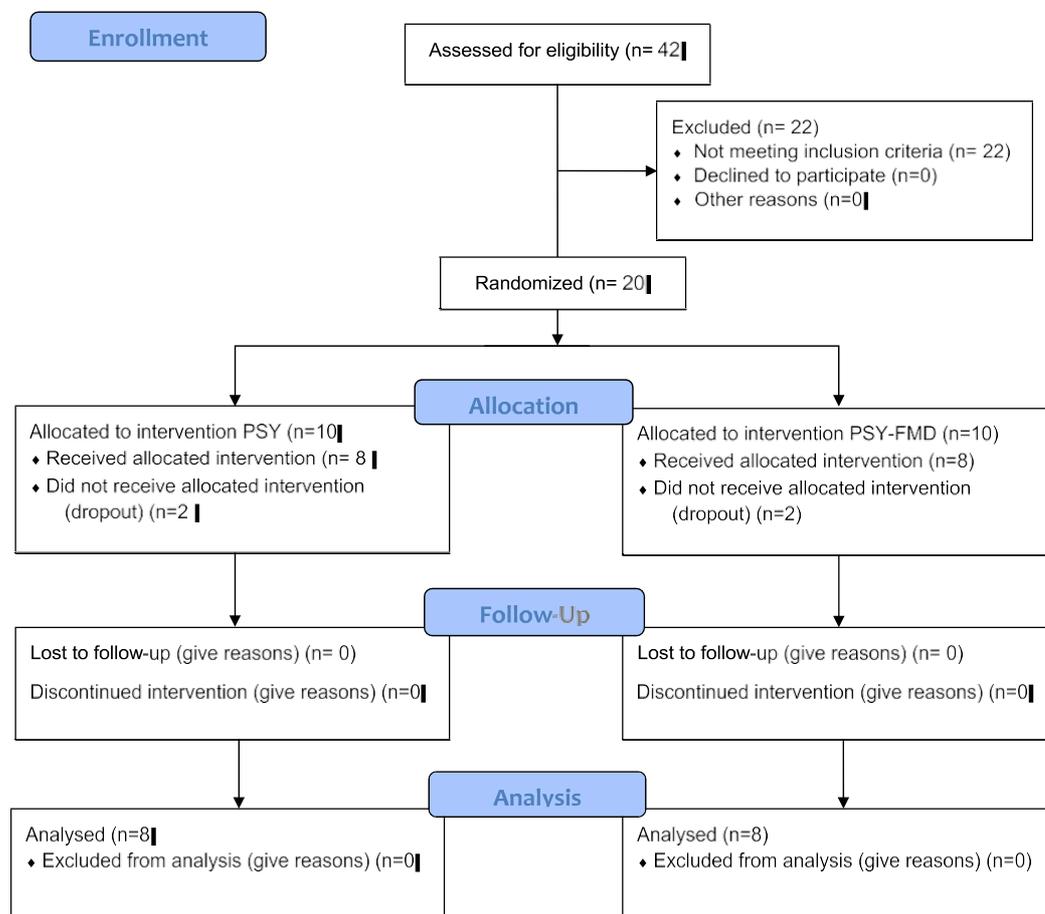


FIGURE 1 CONSORT 2010 flow diagram

44–56% fat, and 34–47% carbohydrates). Between the cycles, participants were not subject to any study-imposed dietary restrictions. Once treatment ended, all participants again completed the assessment administered prior to treatment to analyze their achievement of the expected outcomes. They completed the same assessment one more time 3 months after treatment had ended.

