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ORIGINAL PAPER

Is metabolic dysregulation associated with antidepressant response in depressed women in climacteric treated with individualized homeopathic medicines or fluoxetine? The HOMDEP-MENOP Study

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Background: **Climacteric is associated with both depression and metabolic dysregulation. Scarce evidence suggests that metabolic dysregulation may predict poor response to conventional antidepressants. Response to depression treatment has not been studied in homeopathic medicine. The aim of this study was to investigate the prevalence of metabolic disorders in depressed climacteric women treated with homeopathic medicines, fluoxetine or placebo, and if these alterations have any association with response to depression treatment.**

Methods: **One hundred and thirty-three Mexican women (40–65 years) with depression, enrolled in the HOMDEP-MENOP study, a randomized, placebo-controlled, double-blind, double-dummy, three-arm trial with a 6 week follow-up, underwent a complete medical history and clinical examination. Metabolic parameters were assessed at baseline. Association between baseline metabolic parameters and response to depression treatment was analyzed with bivariate analysis in the three groups. Odds ratios (OR) with their 95% confidence interval (95% CI) were calculated. Metabolic parameters were considered for inclusion in the logistic regression model if they had a statistically significant relationship with response rate on bivariate analysis at $p < 0.05$ or if they were clinically relevant.**

Results: **Overall combined prevalence (obesity and overweight) was 86.5%; 52.3% had hypertriglyceridemia; 44.7% hypercholesterolemia; 46.7% insulin resistance; and 16% subclinical hypothyroidism. There was no statistically significant association between dyslipidemia, overweight, or insulin resistance and non-response in the homeopathy group [OR (95% CI) 1.57 (0.46–5.32), $p = 0.467$; 0.37 (0.003–1.11), $p = 0.059$; 0.67 (0.16–2.7), $p = 0.579$, respectively].**

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Conclusion: **Metabolic dysregulation was not significantly associated with response to depression treatment in depressed climacteric women treated with individualized homeopathic treatment (IHT), fluoxetine or placebo. Due to the high prevalence of metabolic disorders and its relationship with depression in the climacteric, further investigation should be focused on whether individualized prescriptions based on classical homeopathy for depressed climacteric women have an effect on metabolic parameters, and/or if treating the metabolic disorders at the same time could lead to higher response rates.**
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Keywords: Metabolic dysregulation; Dyslipidemia; Depression; Antidepressant response; Perimenopause; Post menopause; Homeopathy; Individualized homeopathic treatment; Fluoxetine

Background

The climacteric stage is a period of decrease of reproductive capacity in women culminating in the menopause. The perimenopausal period refers to the interval when women's menstrual cycles become irregular due to intense hormonal fluctuations. Menopause is defined by at least 12 months of amenorrhea.[1] Hormonal changes affect the metabolic and cardiovascular parameters. The prevalence of metabolic syndrome (MS) increases as women transition from premenopause to postmenopause.[2] The MS refers to a combination of metabolic abnormalities that increase risk for morbidity and mortality from cardiovascular diseases.[3–7]

Recent studies have demonstrated a significant association between menopausal transition and a higher risk for developing depression. The Study of Women's Health Across the Nation has demonstrated that among middle-aged women, depressive symptoms predicted the MS.[8–10] Depression has been associated with increased cardiovascular risk mediated by alterations in metabolic parameters. In addition, menopausal status has been linked with both MS and depression. Studies indicate a bidirectional association between depression and MS, and support early detection and management of depression among patients with MS and vice versa.[10] Recently, Mansur has described a 'metabolic-mood syndrome', a concept that may have important clinical implications. Several novel interventions have been proposed for both obesity and mood disorders.[11]

Antidepressants are commonly prescribed medications during climacteric. In daily routine, physicians face the challenge of the inter- and even intraindividual variability in antidepressant response.[12] Scarce evidence suggests that metabolic dysregulation may predict poor response to depression treatment. Therefore, it is mandatory to focus research in their interrelation, so both aspects should be integrated in managing women at this stage. Some studies have shown metabolic and inflammatory dysregulation (elevated IL-6, low HDL cholesterol, hypertriglyceridemia, and hyperglycemia) can be found in more chronic forms of depression in antidepressant users.[13] Understanding both inflammatory and metabolic dysregulations as highly related processes may contribute to knowing potentially causal associations.[14] Currently, sparse evidence reveals that inflammation might be associated with non-response in antidepressant users. Specifically, Lanquillon *et al.* conducted a small study with 24 depressed patients with higher blood levels of interleukin IL-6, which was associated with non-response during a 6-week treatment with amitriptyline.[15] Cattaneo *et al.* found that expression of genes related to inflammation is associated with non-response to an 8-week treatment with escitalopram.[16] In contrast, Manoharan *et al.* investigated the potential of serotonin (5-HT) and IL-6 to serve as functional biomarkers of fluoxetine response. Serum IL-6 and 5-HT were measured in 73 depressed patients (39 responders and 34 non-responders) at baseline and after 6 weeks of treatment and in 44 normal controls. Pre- and post-treatment levels of both biomarkers did not significantly differ between responders and non-responders.[17] Although cross-sectional studies in this respect have been conducted, a longitudinal prospective study by Vogelzangs suggested that inflammatory and metabolic dysregulation worsens depression course due to reduced response to depression treatment and that alternative intervention treatments may be needed in these patients.[13]

Besides the metabolic and inflammatory dysregulations, other factors may contribute to response to depression treatment in conventional antidepressants. They appear to work via effects on one or more biogenic amine neurotransmitter systems or they may affect one or more site(s) of action. Other factors are biological variability, age, disease, internal environment, and gene expression, self-dependent changes in the internal milieu of a given individual's body due to factors such as diet, substance abuse, and medications.[12]

In homeopathy, a substance that causes the symptoms of a disease in healthy people will cure similar symptoms in sick people. Few studies have been conducted for proving if homeopathic treatment is effective for menopausal disorders and depression. Response to depression treatment has not been studied in homeopathic medicine. Most of the studies have focused on climacteric complaints only.[18,19]

Possible factors that might contribute to the lack of response have not been assessed. Furthermore, metabolic disorders in depressed menopausal women treated with homeopathy have not been fully studied. Nayak conducted a multicenter, prospective, observational study to ascertain the usefulness of homeopathic treatment in distress during climacteric. Serum levels of cholesterol, triglycerides, and very-low-density lipoprotein decreased significantly.[20] While some studies with homeopathic medicines for metabolic abnormalities in rats have been published, there is a lack of well-designed studies in humans.[21,22]

The aim of the present study was to determine the prevalence of metabolic alterations in a cohort of climacteric women with depression treated with individualized homeopathy or fluoxetine or placebo and investigate if these alterations have any association with the response to depression treatment.

Materials/Methods

Sample

All data for analysis in the current study derived from the HOMDEP-MENOP study and methods used have been previously described in detail. Study sample was composed of women enrolled in the HOMDEP-MENOP study.[23] One hundred and thirty-three Mexican climacteric women with depression were evaluated between March 2012 and December 2013, in the outpatient service of homeopathy in the Juarez of Mexico Hospital. Inclusion and exclusion criteria were fully described previously.[23]

Data collection

Clinical data: All participants underwent a baseline complete medical history and clinical examination including weight, height, and blood pressure (measured after participants were seated for 5 min). Height and weight were measured with the participants barefooted and lightly dressed, with a mechanical scale (Esher®EL-200KG) and height rod, allowing height to be measured the same time as weight. Height was taken at head level to the nearest centimeter, with the subject standing barefooted. Body mass index [BMI: weight/height^2 (kg/m^2)] was used as an estimate of overall adiposity and individuals were classified as normal weight (<25), overweight (25−29.9) or obese (>30) according to their BMI values.

The 17-item Hamilton Rating Scale for Depression (HRSD) determined depression severity. Response to depression treatment (response rate) was defined as the decrease of 50% or more from baseline score in HRSD after the 6-weeks treatment. Remission was defined as HRSD score ≤7 after the 6-weeks treatment.[23]

Laboratory data: Metabolic parameters were assessed at baseline (fasting serum triglycerides, total cholesterol, high-density cholesterol [HDL], low-density cholesterol [LDL], fasting serum glucose, glycosylated hemoglobin, insulin and thyroid-stimulating hormone [TSH]). Blood samples were drawn after 10−12 h of overnight fasting and were centrifuged within 30−45 min of collection. All blood lipid and glucose analyses were undertaken at our research laboratory using an automated chemical analyzer (Advia®1200). Glucose was assayed by the glucose-oxidase method. Total cholesterol and triglyceride were measured enzymatically. Insulin and TSH were measured with a chemiluminescence technique (Immulite®2000TSH Third Generation). The homeostasis model assessment (HOMA), an epidemiologic method for assessing insulin resistance [HOMA-IR = insulin (mU/ml) X glucose (mg/dl)/405] was used as surrogate measure of insulin sensitivity.

Interventions

Study medications have been previously described in detail.[23] Patients were randomly assigned to either one of three groups: (1) individualized homeopathic treatment (IHT) plus fluoxetine dummy-loaded; (2) fluoxetine (20 mg/d) plus IHT dummy-loaded; (3) fluoxetine placebo plus IHT placebo.

Statistical analysis

Data were analyzed with SPSS statistical software (version 17.0). Continuous data were represented by means and standard deviation, whereas a frequency table represented categorical data. Response rates were calculated at 6 weeks and compared among the groups using chi-square test.[23] First, association between baseline metabolic parameters and response to depression treatment was analyzed with bivariate analysis in the three groups. Metabolic parameters were considered for inclusion in the logistic regression model if they had a statistically significant relationship with response rate on bivariate analysis at $p < 0.05$ or if they were clinically relevant. Odds ratios (OR) (95% CI) were calculated using MedCalc (the odds of non-response to depression treatment in those having certain metabolic abnormality divided by the odds of non-response to depression treatment in those with normal metabolic parameter). A $p < 0.05$ was considered statistically significant. Appendix A shows complete data for the OR (95% CI) calculations.

Results

The demographic characteristics of study participants, CONSORT flow diagram, changes in HRSD scores and response rates among groups were reported previously.[23] No significant differences among the three groups were observed with respect to baseline mean (SD) scores in HRSD. After six weeks follow-up, there were significant differences among groups in HRSD. Means differed in IHT group *vs* placebo group ($p < 0.001$) and fluoxetine group *vs* placebo group ($p < 0.001$). IHT group was better than placebo by 5.0 points ($p < 0.001$); fluoxetine group was better than placebo by 3.2 points ($p < 0.001$). Means did not differ between the IHT group and the fluoxetine group ($p = 0.082$).[23]

Overall, in the three groups, response rate was 36.1%. In the IHT group, only 54.5% decreased ≥50% in HRSD

score, 41.3% in fluoxetine group and 11.6% in placebo group (chi-square = 18.1, 2 df, $p < 0.001$)[23] (Table 1).

Table 2 shows baseline metabolic parameters in the three groups. Overall, the mean weight (SD) was 71 (13.8) kg (ANOVA, F = 0.818, 2df, p = 0.443), with a BMI of 30 (5.4) kg/m^2 (ANOVA F = 1.473, 2df, p = 0.233), total cholesterol was 201.1 (38.4) mg/dL (ANOVA F = 0.562, 2df, p = 0.571) and HDL was 52 (12) mg/dL (ANOVA F = 0.637, 2df, p = 0.530). The mean (SD) of TG was higher than the normal values in all groups (ANOVA F = 0.148, 2df, p = 0.863). Fluoxetine group had the highest levels of TG [193.3 (136.3) mg/dL]. All groups had glucose levels above 100 mg/dL (ANOVA F = 0.221, 2df, p = 0.802) and glycosylated hemoglobin above 6.7% (ANOVA F = 0.810, 2df, p = 0.447). Placebo group had the highest level of HOMA [3.8 (3.1)] (ANOVA F = 1.432, 2df, p = 0.244). The mean (SD) of uric acid and TSH in all the study participants was 5 (1.2) mg/dL (ANOVA F = 0.025, 2df, p = 0.975) and [3.3 (2.4) uUI/mL] (ANOVA F = 0.312, 2df, p = 0.733) respectively.

Table 3 shows frequency of metabolic abnormalities and the association between baseline metabolic parameters and response to depression treatment among groups. Combined prevalence of overweight and obesity was 86.5%. No statistical differences were observed among the three groups (chi-square = 10.04, 6df, p = 0.128) (Table 3). The lowest frequency of hypercholesterolemia was observed in the homeopathy group (34.1%) (chi-square = 3.188, 2df, p = 0.195). Prevalence of hypertriglyceridemia and insulin resistance were similar among groups [52.3% (chi-square = 0.586, 2df, p = 0.748) and 46.7% (chi-square = 0.565, 2df, p = 0.739) respectively]. Overall, 66.6% of study participants had dyslipidemia and nearly 50% in all groups had hypoalphalipoproteinemia.

There were no statistically significant associations between metabolic parameters and non-response to depression treatment among groups in the bivariate analysis. Table 3 shows the OR values and 95% CI. In the logistic regression, none of the metabolic parameters was significantly associated with response rates after adjusting for significant covariates in the three groups.

Discussion

To our knowledge, this is the first study evaluating the association between metabolic parameters and response to depression treatment in depressed climacteric women treated with individualized homeopathic medicines, fluoxetine or placebo. Our study confirms data from observational studies reporting the increased prevalence of metabolic changes during transition to menopause.[6]

Nevertheless, prevalence of metabolic alterations was higher in our study (86.5%). The CARMELA study[25] is an observational-based study designed to assess and compare the prevalence of cardiovascular risk factors in women according to age and time from menopause in seven Latin American cities including Mexico City. This study reported that in Mexico City the combined prevalence of overweight and obesity was more than 70%.[26] On the contrary, the Collaborative Group for Research of the Climacteric in Latin America (REDLINC) which included 6079 middle-aged Hispanic women (including Mexican women) reported a lower prevalence of obesity (18.5%).[27] It is important to take into account that all women included in the HOMDEP-MENOP study were depressed and it is unknown if the bidirectional association between depression and metabolic dysregulation could contribute to causing an increased prevalence of metabolic disorders.

Mexico has a high prevalence of obese people with metabolic disorders. Mexican guidelines for managing climacteric include, among others, the diagnosis and treatment of metabolic alterations with changes in lifestyle and prescription of conventional medications in some cases. Women seeking homeopathic treatments due to climacteric complaints are taking at the same time many others

Table 1 Response rates among groups according to 17-item Hamilton Rating Scale for Depression

Response rates	*Homeopathy n (%)*	*Fluoxetine n (%)*	*Placebo n (%)*	*Total n (%)*	*p value*
Response (decrease of ≥50% in HRSD)	24/44 (54.5)	19/46 (41.3)	5/43 (11.6)	48/133 (36.1)	<0.001
No response to depression treatment	20/44 (45.5)	27/46 (58.5)	38/43 (88.3)	85/133 (63.9)	

Table 2 Baseline metabolic parameters in the three groups

Outcome	*Homeopathy*	*Fluoxetine*	*Placebo*	*Total*	*p value*
Age (years) (SD)	49.0 (6.4)	49.2 (5.3)	48.6 (5.8)	49.0 (5.8)	0.944
Weight (kg) (SD)	71.2 (12.1)	69.1 (12.4)	72.9 (16.6)	71.0 (13.8)	0.443
BMI (kg/m^2) (SD)	30.8 (4.8)	29.1 (4.6)	31.1 (6.7)	30.0 (5.4)	0.233
Total cholesterol (mg/dL) (SD)	196.3 (36.8)	203.8 (33.6)	203.9 (44.9)	201.1 (38.4)	0.571
HDL (mg/dL) (SD)	50.4 (10.2)	53.3 (13.6)	52.3 (12.0)	52.0 (12.0)	0.530
LDL (mg/dL) (SD)	125.5 (26.0)	124.3 (30.4)	130.0 (39.8)	126.6 (32.4)	0.701
Triglycerides (mg/dL) (SD)	182.7 (140.3)	193.3 (136.3)	179.5 (92.5)	185.4 (124.7)	0.863
Glucose (mg/dL) (SD)	106 (33.2)	103.2 (36.7)	101.6 (20.1)	103.6 (30.9)	0.802
Glycosylated Hemoglobin (%) (SD)	6.7 (1.2)	6.7 (1.3)	7.0 (1.8)	6.8 (1.4)	0.447
Insulin (mU/ml) (SD)	11.5 (8.2)	11.8 (7.8)	14.8 (10.0)	12.7 (8.8)	0.230
HOMA	2.9 (2.6)	2.8 (2.1)	3.8 (3.1)	3.2 (2.7)	0.244
Uric acid (mg/dL) (SD)	5.0 (1.3)	5.0 (1.2)	5.1 (0.93)	5.0 (1.2)	0.975
TSH (uUI/mL) (SD)	3.0 (2.5)	3.5 (2.5)	3.3 (2.3)	3.3 (2.4)	0.733

Table 3 Frequency of metabolic abnormalities and association between baseline metabolic parameters and response to depression treatment among groups in bivariate analysis

Outcome	*Homeopathy n (%)*			*Fluoxetine n (%)*			*Placebo n (%)*			*Total*[*]	*p Value*
Hypertriglyceridemia (>150 mg/dL)	22/44 (50)			23/46 (50)			24/42 (57.1)			69/132 (52.3)	0.748
Response[†]	Yes n (%) 11/22 (50)	No n (%) 11/22 (50)	OR (95% CI) 1.44 (0.43–4.75) p = 0.545	Yes n (%) 8/23 (34.7)	No n (%) 15/23 (65.2)	OR (95% CI) 1.78 (0.52–5.62) p = 0.370	Yes n (%) 3/24 (12.5)	No n (%) 21/24 (87.5)	OR (95% CI) 0.87 (0.13–5.87) p = 0.890		
Hypercholesterolemia (>200 mg/dL)	15/44 (34.1)			24/46 (52.2)			20/42 (47.6)			59/132 (44.7)	0.195
Response	Yes 8/15 (53.3)	No 7/15 (46.6)	OR (95% CI) 1.07 (0.30–3.76) p = 0.907	Yes 8/24 (33.3)	No 16/24 (66.6)	OR (95% CI) 2.0 (0.60–6.58) p = 0.254	Yes 0/20 (0)	No 20/20 (100)	OR (95% CI) 12.88 (0.66–249.8) p = 0.091		
Dyslipidemia[‡]	26/41 (59.1)			33/46 (71.7)			29/42 (69)			88/132 (66.6)	0.399
Response	Yes 13/26 (50)	No 13/26 (50)	OR (95% CI) 1.57 (0.46–5.32) p = 0.467	Yes 13/33 (39.3)	No 20/33 (60.6)	OR (95% CI) 1.31 (0.36–4.81) p = 0.675	Yes 3/29 (10.3)	No 26/29 (89.6)	OR (95% CI) 1.57 (0.23–10.78) p = 0.643		
Hypoalphalipoproteinemia (HDL < 50 mg/dL)	22/42 (52.4)			23/43 (53.4)			21 (42) (50)			66/127 (52)	0.973
Response	Yes 13/22 (59)	No 9/22 (40.9)	OR (95% CI) 0.69 (0.20–2.34) p = 0.555	Yes 9/23 (39.1)	No 14/23 (60.8)	OR (95% CI) 1.27 (0.37–4.29) p = 0.697	Yes 3/21 (14.2)	No 18/21 (85.7)	OR (95% CI) 0.63 (0.09–4.23) p = 0.635		
Overweight-obese (BMI > 25 kg/m^2)	39/44 (88.6)			38/46 (82.6)			38/43 (88.3)			115/133 (86.4)	0.128
Response	Yes 24/39 (61.5)	No 15/39 (38.4)	OR (95% CI) 0.37 (0.003–1.11) p = 0.059	Yes 16/38 (42.1)	No 22/38 (57.8)	OR (95% CI) 0.82 (0.17–3.96) p = 0.810	Yes 5/38 (13.1)	No 33/38 (86.8)	OR (95% CI) 0.55 (0.02–11.48) p = 0.702		
Insulin resistance HOMA ≥ 2.5	14/33 (42.4)			17/37 (45.9)			18/35 (51.4)			49/105 (46.7)	0.739
Response	Yes 8/14 (57.1)	No 6/14 (42.8)	OR (95% CI) 0.67 (0.16–2.7) p = 0.579	Yes 6/17 (35.2)	No 11/17 (64.7)	OR (95% CI) 1.83 (0.48–6.9) p = 0.368	Yes 2/18 (11.1)	No 16/18 (88.8)	OR (95% CI) 1.71 (0.24–11.78) p = 0.658		
Glucose (>100 mg/dL)	18/44 (40.9)			18/46 (39.1)			16/42 (38)			52/132 (39.3)	0.824
Response	Yes 10/18 (55.5)	No 8/18 (44.4)	OR (95% CI) 0.93 (0.27–3.12) p = 0.910	Yes 8/18 (44.4)	No 10/18 (55.5)	OR (95% CI) 0.80 (0.24–2.68) p = 0.728	Yes 3/16 (18.7)	No 13/16 (81.2)	OR (95% CI) 0.36 (0.05–2.44) p = 0.296		
Subclinical Hypothyroidism[§]	5/42 (11.9)			10/43 (23.3)			5/40 (12.5)			20/125 (16)	0.276
Response	Yes 3/5 (60)	No 2/5 (40)	OR (95% CI) 0.78 (0.11–5.25) p = 0.802	Yes 4/10 (40)	No 6/10 (60)	OR (95% CI) 1.10 (0.26–4.67) p = 0.891	Yes 0/5 (0)	No 5/5 (100)	OR (95% CI) 1.98 (0.09–41.2) p = 0.658		

[*] Some study participants did not provide complete data due to laboratory difficulties to report results so total sample sizes for each outcome variable, per group, are not always the same.
[†] Response (a decrease of ≥50% of HRSD score).
[‡] Dislypidemia (hypercholesterolemia and/or hypertriglyceridemia).
[§] Subclinical hypothyroidism is defined as a state of increased serum thyroid-stimulating hormone (TSH) levels, with circulating thyroxine and tri-iodothyronine concentrations within the population reference range.[24]

medications for dyslipidemia, insulin resistance, diabetes or hypertension.[28,29] Although some studies in rats have shown that homeopathic medicines have effects on metabolic alterations, there is a lack of well-designed studies for women in transition to menopause or post menopause. Sampath *et al.* stated that homeopathic preparations of *Syzygium jambolanum* reported antidiabetic effects in rats.[21] *Helonias dioica* is used for mood disorders in climacteric women and produced antidiabetic effects as well.[30] Furthermore, the relationship between metabolic dysregulation, depression in climacteric and response to depression treatment with homeopathic medicine has not been assessed. Most of the studies conducted for climacteric complaints with homeopathic medicines have studied only its effects on vasomotor and emotional symptoms or quality of life.[18,19]

It has been described that response to depression treatment with conventional medication is relatively low (30−40% non-response) and slow (4−6 weeks).[31] Our study had higher non-response rates after a 6-weeks follow-up (46.5% in IHT and 58.5% in fluoxetine group). Antidepressant non-response has been studied in many conventional medications,[12] but not in homeopathic medicines. A limitation of our study is that some factors that have been shown to predict an unfavorable course with conventional antidepressant medications were not assessed: duration of depression, comorbidity, early onset, metabolism of fatty acids, genetic polymorphism, inflammatory dysregulations, biological variability, age, effect on neurotransmitter systems.[12,32] Moreover, a control group of depressed women without metabolic abnormalities could have helped to compare response to homeopathic treatments for depression in climacteric. Anyway, an important strength of homeopathy for managing biological variability is the individualized prescriptions. Preskorn has suggested, "*personalized medicine is more than just genetics. Claude Bernard over 100 years ago cautioned physicians to recognize that each patient is unique and that this uniqueness can vary over time*".[12]

If all of these factors are better understood, they may be used as novel targets for add-on therapy and/or as early indicators of antidepressant response in both conventional medications and homeopathic medicines. Contrary to some studies, in our study none of the metabolic parameters was significantly associated with response to depression treatment. Some studies indicate a relationship between cholesterol levels, depression presentations and conventional antidepressant response. Both elevated and low cholesterol levels may be associated with serotonergic dysfunction: depressed patients with low levels (<160 mg/dl) appear to be at higher risk of suicide and elevated levels of cholesterol are associated with conventional antidepressant non-response.[33]

The Netherlands Study of Depression and Anxiety (NESDA), a multisite cohort study that investigated the long-term course of depressive and anxiety disorders in 2981 persons aged 18−65 years, concluded that elevated IL-6, low HDL, hypertriglyceridemia, and hyperglycemia were associated with chronicity of depression in antidepressant users. In this study, persons who recently (3 months) started antidepressant medication, having ≥4 dysregulations, were associated with a 6.85 increased odds of depression chronicity (95% CI 1.95−24.06).[13] In this respect, it is unknown if homeopathic treatments could be influenced by these dysregulations causing depression chronicity. Moreover, some limitations of the HOMDEP-MENOP study in comparison are that NESDA study included a larger sample size (2981 vs 133) and a 2-year follow-up. Both studies measured metabolic factors only at baseline. A longitudinal design assessing metabolic parameters at baseline and after depression treatment would help to a better understanding of response to homeopathic treatments for depression.

Further studies in other settings are needed to confirm or refute our results and investigate if there are factors that influence the response in homeopathic treatments. It is important to take into account that the HOMDEP-MENOP study was based on classical homeopathy: only one remedy was selected at each visit and metabolic parameters were measured once at baseline as a part of the routine evaluation climacteric women must have. The homeopathic medicine was selected based on the most characteristic mental symptoms. Metabolic alterations were not taken into account to choose the homeopathic medicine. Therefore, it is not known whether a homeopathic prescription based on mental symptoms has an effect on the metabolic alterations or if treating the metabolic disorders at the same time could lead to higher response rates. In addition, some of the study participants were taking medication for hypertension or diabetes. As previously stated, the effect of homeopathic medicines on metabolic disorders in depressed climacteric women has not been studied.

Conclusion

Homeopathic doctors frequently treat climacteric complaints in daily routine. Metabolic dysregulation is a very common condition among women during transition to menopause and post menopause and is frequently associated with depression. Metabolic dysregulation was not significantly associated with response to depression treatment in climacteric women with depression treated with individualized homeopathic medicines or fluoxetine or placebo. In the presence of these negative results, further investigation should be focused on whether individualized prescriptions based on classical homeopathy for depressed climacteric women have an effect on metabolic parameters and/or if treating the metabolic disorders at the same time could lead to higher response rates.

Conflict of interests

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.homp.2016.11.002.

References

1 Soules MR, Sherman S, Parrott T. Executive summary: stages of reproductive aging workshop (STRAW). *Fertil Steril* 2001; **76**: 874–878.
2 Jansen I, Powell LH, Crawford S, Lasley B, Sutton-Tyrrell K. Menopause and metabolic syndrome. *Arch Intern Med* 2008; **168**(14): 1568–1575.
3 Do KA, Green A, Guthrie JR, Dudley EC, Burger HG, Dennerstein L. Longitudinal study of risk factors for coronary heart disease across the menopausal transition. *Am J Epidemiol* 2000; **151**(6): 584–593.
4 Guthrie JR, Taffe JR, Lehert P, Burger HG, Dennerstein L. Association between hormonal changes at menopause and the risk of a coronary event: a longitudinal study. *Menopause* 2004; **11**(3): 315–322.
5 Lakka HM, Laaksonen DE, Lakka TA, *et al*. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002; **288**: 2709–2716.
6 Carr MC. The emergence of the metabolic syndrome with menopause. *J Clin Endocrinol Metab* 2003; **88**(6): 2404–2411.
7 The National Cholesterol Education Program. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert pannel on detection, evaluation and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA* 2001; **285**: 2486–2497.
8 Avis NE, Brambilla D, McKinlay SM, *et al*. A longitudinal analysis of the association between menopause and depression: results from the Massachusetts Women's Health Study. *Ann Epidemiol* 1994; **4**: 214–220.
9 Goldbacher EM, Bromberger J, Matthews KA. Lifetime history of major depression predicts the development of the metabolic syndrome in middle-aged women. *Psychosom Med* 2009; **7**(3): 266–272.
10 Pan A, Keum N, Okereke OI, *et al*. Bidirectional association between depression and metabolic syndrome. *Diabetes Care* 2012; **35**: 1171–1180.
11 Mansur RB, Brietzke E, McIntyre R. Is there a "metabolic-mood syndrome"? A review of the relationship between obesity and mood disorders. *Neurosci Biobehav Rev* 2015; **52**: 89–104.
12 Preskorn ShH. Prediction of individual response to antidepressants and antipsychotics: an integrated concept. *Dialogues Clin Neurosci* 2014; **16**: 545–554.
13 Vogelzangs N, Beekman ATF, van Reedt Dortland AKB, *et al*. inflammatory and metabolic dysregulation and the 2-year course of depressive disorders in antidepressant users. *Psychopharmacology* 2014; **39**: 1624–1634.
14 Sutherland JP, McKinley B, Eckel RH. The metabolic syndrome and inflammation. *Metab Syndr Relat Disord* 2004; **2**: 82–104.
15 Lanquillon S, Krieg JC, Bening-Abu-Sach U, Vedder H. Cytokine production and treatment response in major depressive disorder. *Neuropsychopharmaology* 2000; **22**: 370–379.
16 Cattaneo A, Gennarelli M, Uher R, *et al*. Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline 'predictors' and longitudinal 'targets'. *Neuropsychopharmacology* 2013; **38**: 377–385.
17 Manoharan A, Rajkumar RP, Shewade DG, Sundaram R, Muthuramalingam A, Paul A. Evaluation of interleukin-6 and serotonin as biomarkers to predict response to fluoxetine. *Hum Psychopharmacol Clin Exp* 2016; **31**: 178–184 http://dx.doi.org/10.1002/hup.2525.
18 Thompson EA. Alternative and complementary therapies for the menopause: a homeopathic approach. *Maturitas* 2010; **66**(4): 350–354.
19 Thompson EA, Reilly D. The homeopathic approach to the treatment of symptoms of oestrogen withdrawal in breast cancer patients. A prospective observational study. *Homeopathy* 2003; **92**(3): 131–134.
20 Nayak C, Singh V, Singh K, *et al*. Management of distress during climacteric years by homeopathic therapy. *J Altern Complement Med* 2011; **17**(11): 1037–1042.
21 Sampath S, Narasimhan A, Chinta R, *et al*. Effect of homeopathic preparations of *Syzygium jambolanum* and *Cephalandra indica* on gastrocnemius muscle of high fat and high fructose-induced type-2 diabetic rats. *Homeopathy* 2013 Jul; **102**(3): 160–171 http://dx.doi.org/10.1016/j.homp.2013.05.002.
22 Chagas VT, França LM, Malik S, Paes AMA. *Syzygium cumini* (L.) skeels: a prominent source of bioactive molecules against cardiometabolic diseases. *Front Pharmacol* 2015; **6**: 259 http://dx.doi.org/10.3389/fphar.2015.00259.
23 Macías-Cortés EdC, Llanes-González L, Aguilar-Faisal L, Asbun-Bojalil J. Individualized homeopathic treatment and fluoxetine for moderate to severe depression in peri- and postmenopausal women (HOMDEP-MENOP Study): a randomized, double-dummy, double-blind, placebo-controlled trial. *PLoS ONE* 2015; **10**(3): e0118440 http://dx.doi.org/10.1371/journal.pone.0118440.
24 Pearce SHS, Brabant G, Duntas LH, *et al*. ETA guideline: management of subclinical hypothyroidism. *Eur Thyroid J* 2013; **2013**(2): 215–228 http://dx.doi.org/10.1159/000356507.
25 Pramparo P, Schargrodsky H, Boissonet C, *et al*. Cardiovascular risk factors for heart disease and stroke in women by age and time since menopause, in seven Latin American cities: the CARMELA study. *CVD Prev and Control* 2008; **3**: 181–189 http://dx.doi.org/10.1016/j.cvdpc.2008.08.002.
26 Escobedo de la Peña J, de Jesus-Pérez R, Schargrodsky H, Champagne B. Prevalencia de dislipidemias en la Ciudad de México y su asociación con otros factores de riesgo cardiovascular. Resultados del estudio CARMELA. *Gac Med México* 2014; **150**: 128–136.
27 Blümel JE, Chedraui P, Aedo S, Fica J, Mezones-Holguin E, *et al*. Obesity and its relation to depressive symptoms and sedentary lifestyle in middle-aged women. *Maturitas* 2015; **80**: 100–105.
28 http://www.cenetec.salud.gob.mx/descargas/gpc/CatalogoMaestro/019_GPC_ClimatyMenop/SS_019_08_EyR.pdf.
29 http://www.cenetec.salud.gob.mx/descargas/gpc/CatalogoMaestro/233_GPC_Dislipidemias/GER_Dislipidemia.pdf.
30 Chakraborty D, Samadder A, Dutta S, Khuda-Bukhsh AR. Antihyperglycemic potentials of a threatened plant, Helonias dioica: antioxidative stress responses and the signaling cascade. *Exp Biol Med (Maywood)* 2012; **237**(1): 64–76 http://dx.doi.org/10.1258/ebm.2011.011161. Epub 2011 Dec 14.
31 Kato M, Serretti A. Review and meta-analysis of antidepressant pharmacogenetic findings in major depressive disorder. *Mol Psychiatry* 2010; **15**: 473–500.

32 Mocking RJT, Verburg HF, Westerink AM, *et al*. Fatty acid metabolism and its longitudinal relationship with the hypothalamic—pituitary—adrenal axis in major depression: associations with prospective antidepressant response. *Psychoneuroendocrinology* 2015; **59**: 1–13.

33 Papakostas GI, Öngür D, Iosifescu DV, Mischoulon D, Fava M. Cholesterol in mood and anxiety disorders: review of the literature and new hypothesis. *Eur Neuropsychopharmacol* 2014; **14**: 135–142.