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Estrogen metabolites and hydrogen peroxide - Missing elements in the pathophysiology and possible treatment of treatment-resistant depression?

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ABSTRACT

The pathogenesis of depression is complex and heterogeneous, and the management of this disease remains unsatisfactory, so mechanisms and therapeutic strategies are constantly being sought. This study aimed to determine the potential role of estrogen metabolites in the pathogenesis of treatment-resistant depression (TRD) based on the determination of concentrations of estrogens and their metabolites and hydrogen peroxide (H_20_2) in the biological material of patients with TRD.

In this study, we observed for the first time an association between unbalanced estrogen metabolism and elevated H_20_2 levels in TRD patients. Reduced concentrations of 2-methoxyestradiol (2-ME2), 17α-estradiol (α-E2) and 17β-estradiol (β-E2) may be due to abnormal estrogen metabolism toward neurotoxic semiquinones and quinones which are a potential as yet undescribed mechanism responsible for generating oxidative stress (OS) in TRD.

1. Introduction

Depression is a heterogeneous disease with a complex multifactorial background [1,2]. It is believed that it is the interactions between etiological mechanisms that affect both the variability of symptom manifestation and the effectiveness of the response to the included treatment [2]. In addition to the genetic aspect, the role of psychological, environmental, as well as biological factors is emphasized in the pathophysiology of depression [3]. However, the well-established monoamine theory of depression referring to reduced levels of neurotransmitters (serotonin, norepinephrine, dopamine) does not fully explain the pathomechanism of the disease [4]. Reduced volume of the hippocampus and prefrontal cortex as well as an alteration in the signaling of brain-derived neurotrophic factor (BDNF) and its receptor, tropomycin receptor kinase B (TrkB) are observed [3,5]. The current emphasis is on the role of OS in the etiology of depression, as elevated reactive oxygen species (ROS) levels have been linked to disruptions in neurotransmission, impaired neuroplasticity and neurogenesis, dysregulation of the hypothalamic-pituitary-adrenal axis (HPA) and the development of neuroinflammation, which are mechanisms underlying the pathophysiology of depression [3,6].

Estrogens receptors (ERα and Erβ) are widely distributed in the brain, including the hippocampus and hypothalamus - structures associated with mood regulation [7,8]. Estrogens are widely known for their neuroprotective, as they can prevent the accumulation of hydrogen peroxide (H_2O_2) in brain structures, including the hippocampus [9,10], reduce lipid peroxidation in central nervous system (CNS) cells [11] and through modulation of gene expression can affect serotonergic pathways and regulate serotonin (5-HT) transmission in the CNS [12]. Numerous studies confirm that a sharp decline in β-E2 levels during the peri-menopausal period, among others, is associated with worsened mood in women [13]. Women's entry into the cyclical hormonal fluctuation related to the menstrual cycle correlates with increased vulnerability to depression in some of them [12]. Finally, estrogens can

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affect not only the incidence of depression, but also the response to drug treatment or the severity of depressive symptomatology [12,14]. β-E2 and estrone (E1) undergo multi-step metabolic transformations that lead to metabolites with different biological activities [15]. However, the catecholoestrogen metabolism stage can also produce unstable semi-quinone and quinone derivatives that generate ROS including H202 [16]. (Fig. 1).

In the first step, E1 and E2 are converted to catechol derivatives by aromatic hydroxylation at positions 2 and 4: 2-hydroxy-estradiol, 4-hydroxy-estradiol [16]. In the next stage, catecholoestrogens with the participation of catechol-*O*-methyltransferase (COMT) are metabolized to methoxy-derivatives: 2-methoxyestradiol and 4-methoxyestradiol (2-ME2, 4-ME2) [17,18]. At the stage of peroxidation of semiquinones to quinones, superoxide anion radical is released, which is converted to H_20_2 by the action of superoxide dismutase (SOD), and hydroxyl radicals of outstanding reactivity are generated in the next stage in the Fenton reaction [16] Quinone derivatives have a high electrophilic potential, which is associated with a possibly increased risk of spontaneous reactions with nucleophilic cell structures, i.e. the side chains of proteins or the polar heads of certain lipids of the cell lipid bilayer, as well as glutathione (GSH) [19]. Estrogen quinone derivatives lead to an increase in reactive oxygen species, which lead to the destruction of the double cell membrane but are also involved in the process of ferroptosis [19–21]. Quinone derivatives have a high electrophilic potential, which is associated with a possibly increased risk of spontaneous reactions with nucleophilic cell structures, i.e. the side chains of proteins or the polar heads of certain lipids of the cell lipid bilayer, as well as glutathione (GSH) [19]. ROS lead to altered cell membrane functionality through peroxidation of unsaturated lipid bonds and formation of lipid hyperoxides [22], and the brain, due to its high levels of lipids, including unsaturated fatty acids, and concomitant high oxygen turnover, is particularly susceptible to oxidative damage [4].

It has been suggested that in women with premenstrual syndrome (PMS), catechol estrogens generating oxygen free radicals may lead precisely to the peroxidation of neuronal cell membrane lipids, which in turn may negatively affect the GABA-ergic system and contribute to the development of PMS psychiatric symptoms [23]. Excess of ROS damage cell DNA and increases OS correlated with the development of depressive disorders [3,24]. In depression, an increase in the oxidation biomarkers such as malondialdehyde (MDA), 8-hydroxy-2-deoxyguanosine (8-OHDG), and F2-isoprostane is observed [25,26] with concomitantly decreased indices of total antioxidant status (TAS) [4]. OS induces neuroinflammation through various mechanisms, including activation of the NF-κB pathway, as well as inflammasomes (like NLRP6, NLRP3, NLRC6) involved in promoting pyroptosis - the so-called conscious cell death closely associated with depression [27–30].

Estrogen quinones leading to an increase in reactive oxygen species (ROS) can also activate the process of ferroptosis, a programmed cell death linked to the pathogenesis of depression, which is becoming a potential target for antidepressant therapies [20]. Ferroptosis is closely related to OS as a result of excessive accumulation of ROS in cell membrane lipids, phospholipid hydroperoxides are generated and damage to the lipid bilayer occurs [31]. A study on the mouse hippocampal neuron cell line model (HT22) showed that catechol estrogens (hydroxy derivatives, i.e., 2-hydroxyestrone, 2-hydroxyestradiol, 4-hydroxyestrone and 4-hydroxyestradiol) had a protective effect against HT22 by preventing chemically induced ferroptosis [32]. This seems to support our hypothesis of redirected metabolism of estrogens, in these catecholoestrogens toward neurotoxic quinone derivatives being a ROS donor can contribute to the process of ferroptosis. Patients with major depression and inflammation exhibit diminished responses to antidepressant treatment, indicating that the co-occurrence of major depression and low-grade inflammation may increase resistance to pharmacotherapy [33,34]. Analysis of the above mechanisms leads to the hypothesis that altered estrogen metabolism with concomitantly elevated H_2O_2 levels may represent a new, as yet undescribed pathway playing a key role in exacerbating OS in patients with TRD.

In contrast, 2-methoxyestradiol (2-ME2) is a compound with anticancer properties, the activity of which has been studied experimentally [35–39]. In a study on a non-small cell lung cancer cell line, it was shown that the compound inhibited the growth of cancer cells and reduced their viability. Moreover, it was significantly lower in patients with non-small cell lung cancer (NSCLC) compared to healthy controls, indicating 2-ME2 as a potential predictor of cancer development [19]. The fact above prompts the question of whether there is a link between TRD and predisposition to cancer.

2. Material and methods

2.1. Study group

The study group consisted of 19 patients (4 men and 15 women) with a mean age of 46 years (range 31–65) who were diagnosed with TRD. The following criteria were used for inclusion: according to the International Neuropsychiatric Interview v. 5.0 (MINI), a verified diagnosis of TRD on the Montgomery MDD: Asberg Depression Rating Scale (MADRS), which was completed by the patient; the Inventory of Depressive Symptomatology (IDS-30); Clinical Global Impression (CGI)

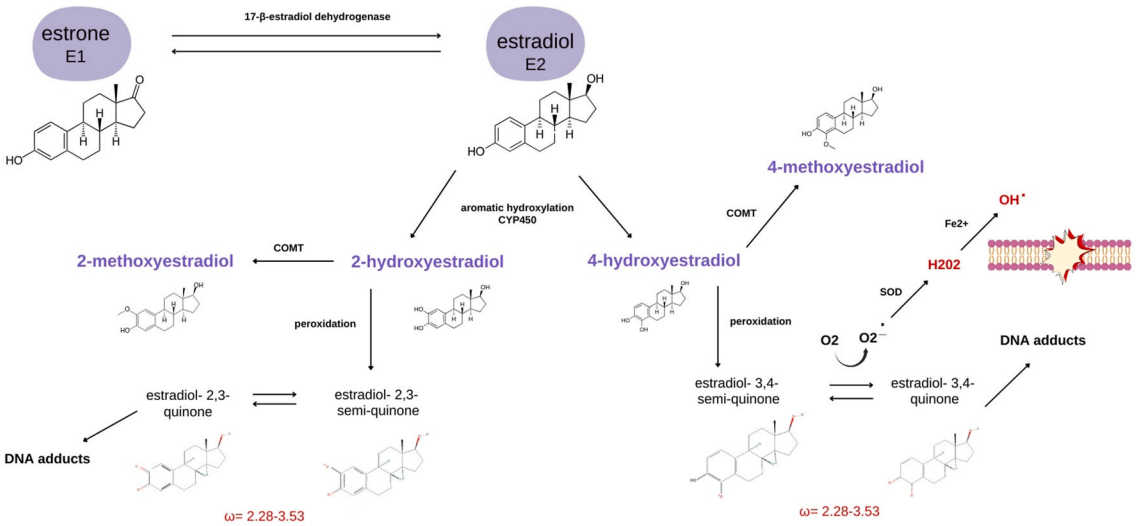

Fig. 1. The multi-step cycle of estrogen metabolism.

to assess general functioning; the Columbia Suicide Severity Rating Scale (C-SSRS) to assess suicide safety and propensity; the Snaith-Hamilton Pleasure Scale (SHAPS) to assess anhedonia; age 18–65 and antidepressant therapy. The selected group aged 18–65 is homogeneous in terms of age range, as there are cut off extremes in the form of the elderly and children. It is also the largest group of patients who are professionally and socially active, which makes it possible to collect samples with biological material for testing [40]. The exclusion criteria were hormonal contraception so as not to disrupt physiological estrogen concentrations [41]. The control group consisted of 8 volunteers, including 2 men and 6 women, with a mean age of 40 years (range 23–57).

The Independent Commission on Bioethics for Research of the Medical University of Gdansk approved this study (permission number: 85/2023). Each subject gave written consent to participate in the study.

2.2. Collection of biological material from patients and control subjects

The biological material was collected from healthy volunteers and patients diagnosed with TRD at the Department of Psychiatry of Medical University of Gdansk (Gdansk, Poland). Each study participant signed a voluntary consent before the study.

Twenty milliliters of blood were drawn from each patient with TRD and healthy volunteers. The blood was centrifuged for 10 min at 1200 rpm to separate plasma from red blood cells. The red blood cells were discarded. The collected plasma was used to examine E2 metabolites and quantify H_20_2 levels. H_20_2 concentration was determined using a special stopped-flow technique [42,43] while the content of estrogens and their metabolites in plasma was measured by LC-MS/MS [15,44].

2.3. LC/MS/MS instrumentation and analytical conditions and sample preparation

The concentrations of estrogens: E1, α-E2, β-E2 and their methoxy-derivative 22-ME2 were determined by liquid chromatography combined with tandem mass detection–LC–MS/MS as previously described [15,44].

2.4. Hydrogen peroxide (H2O2) detection

After blood collection and separation of red blood cells, plasma was collected and centrifuged (200×*g*, for 5 min). Cell pellets were washed twice with PBS and then resuspended in 3 ml of extraction buffer (150 mM NaCl, 5 mM EDTA, 1 % Triton X-100, 10 mM Tris-HCl pH 7.4). Insoluble cellular debris was centrifuged (500×*g*, for 10 min). The supernatants were then analyzed by the stopped-flow method. H2O2 concentration was determined by the stopped-flow method as previously described [42,43].

2.5. A statistical analysis of the data

The statistical analysis was carried out using GraphPad Prism (GraphPad Software, Inc., version 8, USA). When comparing two groups —TRD patients and a healthy control group—the Mann-Whitney *U* test was used. p-value less than 0.05 was the threshold for statistical significance.

3. Study results

3.1. Analysis of plasma from patients with TRD

The concentrations of estrogens were determined in the plasma of TRD patients by the LC–MS/MS method (Table 1 and Fig. 2a).

The concentration of 2-ME-2 in TRD patients decreased (Me = 0.014) compared to that in healthy subjects (Me = 0.0865). Moreover, the 2-ME2 level in TRD was reduced in comparison to E1 (0.289), α-E2 (0.343) and β-E2 (0.382) (Fig. 2A). The median concentration of H_2O_2 in the blood plasma of TRD patients was 5,79 × 10^{-6} mol/dm^3 (min = 1.09 × 10^{-6}; max = 9.35 × 10^{-5}), while the level of H_2O_2 in healthy control was below the quantification threshold, i.e. below 10^{-7} mol/

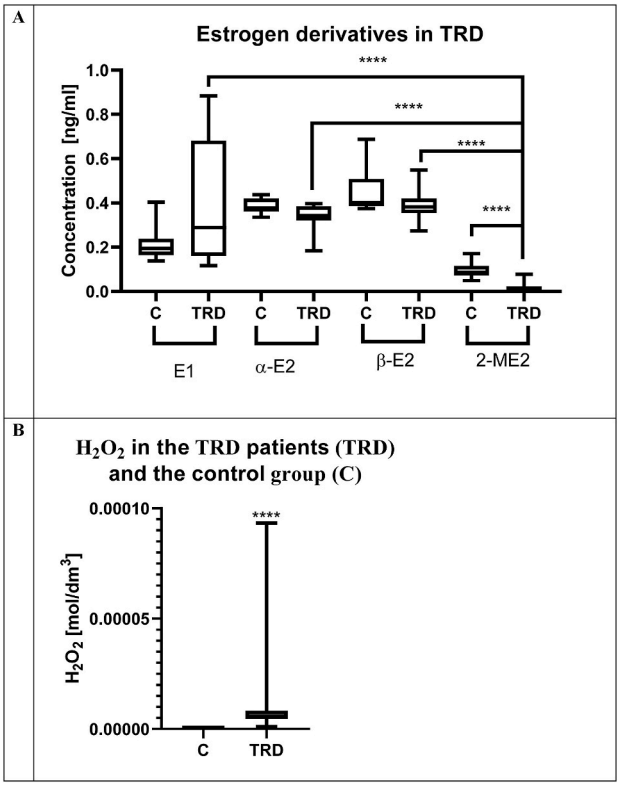

Fig. 2. A. The level of estrogens E1, α-E2 β-E2 and 2-ME- in the blood plasma of TRD patients compared to the healthy control. Determination by LC/MS. Statistical analysis was performed with Mann– Whitney *U* test. ****$p < 0.001$. B. The comparison of serum H2O2 levels in TRD patients with healthy controls using stopped-flow analysis. Statistical analysis was performed with Mann–Whitney *U* test. ****$p < 0.001$.

Table 1
Descriptive statistics of the analyzed metabolites in the blood plasma of TRD patients (TRD) compared to the healthy control (C) in ng/mL. Determination by LC–MS/MS. Statistical analysis was performed with Mann–Whitney *U* test. The value of $p < 0.05$ was considered statistically significant and is presented in bold.

	E1		α-E2		β-E2		2-ME2	
	C	TRD	C	TRD	C	TRD	C	TRD
Min	0.138	0.117	0.335	0.184	0.375	0.274	0.049	0.000
Q1	0.1643	0.161	0.3615	0.322	0.3863	0.355	0.0725	0.000
Me	0.1935	0.289	0.3765	0.343	0.401	0.382	0.0865	0.014
Q3	0.238	0.681	0.42	0.384	0.5075	0.42	0.1153	0.022
Max	0.404	0.883	0.437	0.397	0.688	0.549	0.171	0.078
Statistical test result	U = 57.5; p = 0.3389		U = 40.5; p = 0.0602		U = 40; p = 0.0583		**U = 3.50; p < 0.0001**	

dm^3 (Fig. 2B).

4. Discussion

TRD affects up to 30 % of people treated for a major depressive episode, in whom therapeutic success is not achieved after two or more attempts at antidepressant drug therapy [45]. Moreover, TRD is characterized by significantly increased OS, and interventions targeting lipid peroxidation and activation of immune-inflammatory pathways have been identified as novel treatments [46]. Given the significant role of OS in the development of inflammation in major depression, which is associated with poorer response to drug treatment, in the present study for the first time we focus on the analysis of unbalanced estrogen metabolism and its correlation with elevated H_20_2 levels, which may represent a distinct, as yet undescribed pathway involved in the exacerbation of OS in patients with TRD. To date, the literature lacks data on the involvement of quinone derivatives of estrogens in the pathogenesis of TRD, which, through induction of H_20_2 synthesis, may potentiate OS and exacerbate the development and symptomatology of depressive disorders in TRD patients.

An imbalance in estrogen metabolism may be involved in the excessive production of oxygen free radicals, which promotes the development of OS elevated in depression [47–49]. In the present study, the estrogen metabolic pathway was indeed unbalanced in TRD patients-lower levels of 2-ME2 were noted, while at the same time H_20_2 levels were elevated in TRD patients compared to healthy controls. The lower concentrations of α-E2 were also noted but without statistical significance. This may suggest that the estrogen metabolic pathway is tuned toward neurotoxic quinone derivatives associated with ROS production. The study by Gaikwad et al. seems to support the hypothesis, as according to their results as long as the estrogen metabolic pathway was balanced the oxidation of catecholoestrogens to quinone derivatives was minimized [50]. However, when the estrogen metabolic pathway is disrupted, endogenous synthesis of quinone derivatives may increase, resulting in, among other things, overproduction of oxygen free radicals, thereby potentiating OS [50]. Disturbed homeostasis of estradiol metabolism may result from polymorphisms within COMT (which may result in redirection of catecholoestrogen metabolism to quinone derivatives instead of methoxyestrogens), as well as polymorphisms in quinone reductase, which in turn reduces conversion to hydroxy derivatives supporting high concentrations of quinones [51–53].

Analysis of samples in above study indicated high H_20_2 levels in TRD patients compared to healthy controls. Similar conclusions were reached by other researchers, where high H_20_2 levels were also demonstrated in patients with recurrent major depression [54]. Other work indicates that reduced serum SOD levels in major depressive disorder (MDD) patients were directly related to endogenous H_20_2 synthesis, which may confirm depletion of SOD resources due to persistent OS [55,56]. Notably, significant differences in SOD activity have been shown depending on the severity of depression [49]. Tayeb et al. also alluded to differences in levels of oxidative damage products-a more severe course of MDD was correlated with higher levels of 8-OHdG compared to a milder course of MDD [49]. In addition, the total oxidant status (TOS) was positively correlated with the severity of the depressive disorder, while for total antioxidant capacity (TAC) this correlation is negative [57].

A link between microglia disorders and the development of depression has also been described [58,59]. During severe episodes of MDD, microglial activation was observed in the prefrontal cortex and anterior cingulate cortex [60]. In addition, activation of microglia cells in the anterior cingulate cortex is also correlated with the severity of the depressive episode [60]. There are data indicating an inhibitory effect of 2-ME2 on proliferation, pro-inflammatory responses and activation of microglia cells, which may suggest a protective effect of this metabolite on microglia [61]. Neuroprotective effects of 2-ME2 and its potential in mitigating strokes due to inhibition of hypoxia-inducible factor (HIF-1α) were also specified [62]. In presented study, the reduced levels of 2-ME2 compared to healthy subjects was observed, which may explain the lack of protective effect against microglia cells, and thus the possible development and severity of depressive disorders.

Interestingly, patients with clinically diagnosed depression appear to be at higher risk of developing cancer and exhibit a worse cancer course and higher mortality from cancer and any cause [63]. According to Pitman et al. as many as 20 % of oncology patients struggled with depressive disorders [64]. It is also reported that depression and anxiety were associated with an increased risk of lung cancer, prostate cancer, and breast or colorectal cancer [65]. As mentioned, lower levels of anti-cancer 2-ME were noted in patients diagnosed with NSCLC. Interestingly, among Parkinson's disease (PD) patients, resistance of this group of patients to the development of tumors has also been described [66,67], which may explain the high levels of this metabolite in PD patients compared to healthy controls [44]. Thus, significantly lower levels of 2-ME in TRD patients compared to healthy controls may explain increased risk of cancer due to indicate a "lack of protection" of 2-ME2 against cancer development. It may be one of the mechanisms responsible for the co-occurrence of cancer in patients with depression. The likely antitumor mechanism of 2-ME is due to the induction of neuronal nitric oxide synthase (nNOS) expression, which generates local OS and contributes to the death of rapidly dividing cells [44,68]. In addition, 2-ME appears to activate BCL-2-associated X (BAX), which contributes to mitochondrial breakdown and tumor cell death (sarcoma) [35].

The data attached below are on the co-occurrence of cancer with depression in the Polish population, the first of its kind in the field. Data from the National Health Fund in Poland (POW NFZ, 2022) covering the years 2017–2020 confirmed the correlation between depression and cancer, with prostate cancer, lung cancer, skin cancer and oral cancer being the most frequently mentioned comorbidities (Table 2) [69].

Moreover, α-E2 is widely recognized as the most active form of estradiol. Some research articles point to α-E2 as the predominant ligand in the brain, which can more potently attach to estrogen receptors X (ER-X) and, in addition, activate mitogen-activated protein kinases (MAPKs)/extracellular signal-regulated kinases (ERKs) and phosphatidylinositol 3-kinase-Akt signaling pathways [70,71]. Other data suggest that the neuroprotective effect may not depend on the activation of ER but may be due to the structure of estrogen (a hydroxyl group located at the C3 position in the A ring of the steroid molecule) [9]. Vedder H. et al. indicated that α-E2, like E2, can prevent intracellular accumulation of H_20_2, which may prevent degeneration of hippocampal cells [11]. α-E2 is also showed as a potential neuroprotective compound to promote neuroplasticity and spatial memory suggesting that its reduced levels may negatively affect brain function [71].

However, there are studies contradicting the above data. Although an inhibitory effect of 2-ME2 on the activation of microglia cells has been suggested [60], there are also data indicating its neurotoxicity [72,73]. Bastian et al. described the cytotoxicity of 2-ME2 against the neuroblastoma cell line SH-SY5Y through induction of nitrooxidative stress, which leads to cell death in a cellular model of neurodegeneration [44]. In addition, elevated levels of 2-ME2 have been reported in Parkinson's disease patients compared to healthy controls, which may suggest the involvement of this metabolite in neuronal degeneration in Parkinson's disease [44]. In addition, other work analyzing urine samples from

Table 2
Number of patients with depressive disorders by years and type of cancer; The data was generated from the POW NFZ IT system as of March 9, 2022. POW NFZ explains that the list in question includes the number of patients reported in the years 2017–2020 [69].

L.p.	Type of cancer	2017	2018	2019	2020	Sum
1.	Oral neoplasms	8	8	10	8	34
2.	Skin cancers	8	14	19	12	53
3.	Lung cancer	20	8	12	16	56
4.	Prostate cancer	26	25	23	23	97
5.	Prostate cancer/Lung cancer	2	1	–	–	3

patients with depression (subtype: primary, endogenous and recurrent) indicated increased methylation rates and decreased 4-hydroxylation rates in patients-the ratio of 2-methoxyestrogens to 2-hydroxyestrogens higher in patients and controls [74].

It is worth noting that a limitation of the study is the small group of patients. Designing a future study to include the full range of derivatives would allow for a better understanding of the estrogen metabolic pathway and establish a more accurate pathway. Indeed, in the vitro model suggested that 4-hydroxyestrone is a highly neuroprotective compound, with greater potency than estradiol [75], so the more careful examination of estrogen metabolism in the context of the pathophysiology of depression seems warranted.

5. Conclusions

OS appears to play a significant role in the development of depressive disorders, prompting the search for new mechanisms involved in the pathophysiology of depressive disorders, including TRD being a particularly challenging subtype of depression to treat. Moreover, it has multilevel effects on the biological substrates involved in the development of depression, including induction of mitochondrial abnormalities, as well as dysregulation of the HPA axis, dysfunction on the BDNF/TrkB axis, exacerbation of glutamate excitotoxicity, 5-HT deficiencies in the brain, or disturbances on the microbiota-brain axis [76]. In the present work the impaired estrogen metabolism in TRD patients may imply increased conversion toward quinone derivatives and generation of reactive oxygen species, as evidenced by elevated H2O2 levels in TRD patients.

Also, other work describes new potential pathways associated with the development and progression of depression linked to OS. Ali et al. linked renin-angiotensin system (RAS) dysfunction to mitochondrial dysfunction, OS and neuroinflammation [77]. OS may also be a bridge linking the co-morbidity of depression and type 2 diabetes-2, as their coincidence is twice as high compared to their independent occurrence. Hyperglycemic state as well as lipid disorders inducing OS and inflammation may impair serotonergic transmission and the development of depression [78]. OS and related inflammatory signaling pathways may become a therapeutic target for drugs in the treatment of depressive disorders. Sildenafil, a phosphodiesterase inhibitor used for erectile dysfunction in addition to promoting brain neurotransmission, may also reduce depressive symptoms through its anti-inflammatory effects [79]. Also, intervention with angiotensin receptor blockers and angiotensin-converting enzyme inhibitors can alleviate depressive states by modulating OS, BDNF levels and serotonin neurotransmission [77].

This study verified for the first time the plasma concentrations of estrogens and their metabolites in TRD patients. The results showed reduced levels of estrogenic methoxy derivative 2-ME2 at the same time as elevated levels of H_2O_2 in TRD patients, which is unique data in this area. In addition, the study showed reduced levels 2-ME2 in TRD patients, which could be interpreted as the lack of protective effects of estrogen metabolites on nerve cells. The above results are the first to shed new light on unbalanced estrogen metabolism in TRD, as another source of OS, which is correlated with the severity of depressive symptoms.

In conclusion, the above results point to new, previously undescribed mechanisms related to estrogen metabolism in the context of the pathophysiology of depression. However, there is a need for further research to better understand the interrelationships in estrogen metabolism, which in the future may play a role in diagnosis and therapy design.

CRediT authorship contribution statement

Zofia Winczewska: Writing – original draft, Investigation. **Agnieszka Mechlińska:** Writing – review & editing. **Piotr Radziwiłłowicz:** Writing – review & editing. **Lucyna Konieczna:** Writing – review & editing, Investigation. **Joanna Drzeżdżon:** Writing – review & editing. **Dagmara Jacewicz:** Writing – review & editing, Investigation. **Mariusz Wiglusz:** Writing – review & editing. **Tomasz Bączek:** Writing – review & editing. **Wiesław Jerzy Cubała:** Writing – review & editing. **Magdalena Górska-Ponikowska:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare no conflict of interest.

Data availability

Data will be made available on request.

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