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# Salivary monoaminergic biomarkers and item performance of the Hamilton Rating Scale for Depression in major depression: an exploratory study

## Biomarkery aktywności monoaminergicznej oceniane w ślinie u chorych z większym zaburzeniem depresyjnym, w odniesieniu do wymiarów psychopatologicznych skali depresji Hamiltona

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**ABSTRACT**

**Objectives.** Central monoaminergic dysfunction with autonomic nervous system dysregulation are reported in major depressive disorder (MDD). Salivary α-amylase (sAA) activity and salivary 3-methoxy-4-hydroxy-phenylglycol (sMHPG) are adopted as markers of central noradrenergic activity with salivary 5-hydroxyindole acetic acid (s5-HIAA) being indicative of central serotonin turnover. No data is available on baseline sAA, s5-HIAA and sMHPG in MDD being interrelated to the specific psychopathological dimensions and item performance of the Hamilton Rating Scale for Depression (HAMD-17) in MDD.

**Material and methods**. The basal sMHPG and s5-HIAA concentrations and sAA activity as correlated with HAMD-17 psychometric assessment were studied in this exploratory study of 20 adult, treatment-naïve MDD patients.

**Results.** The negative correlations between sMHPG and HAMD-17 items 7 (work and activities) ($r = -0.56$, $p = 0.01$) and 4 (early insomnia) ($r = -0.45$, $p = 0.049$) were found post hoc. On exploration the correlations between sAA and items 7 (work and activities) ($r = -0.47$, $p = 0.04$) and 12 (gastrointestinal symptoms) ($r = 0.49$, $p = 0.03$) were also observed with no such observation with regard to s5-HIAA.

**Conclusions.** On exploratory analysis, in basal, non-stimulated conditions baseline sAA, sMHPG levels in MDD were found to be correlated with HAMD-17 items representing clinical symptoms attributable to primary noradrenergic dysfunction at the early stage of major depression. Saliva is a promising source of monoaminergic biomarkers in MDD research. However, further systematic studies are needed to contribute consistent results to aid standardization, in particular with psychometric measures.

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KEYWORDS

- salivary alpha-amylase
- 3-methoxy-4-hydroxy-phenylglycol
- salivary 5-hydroxyindole acetic acid
- major depressive disorder
- Hamilton Rating Scale for Depression

SŁOWA KLUCZOWE

- α-amylaza ślinowa
- 3-metoksy-4-hydroksyfenyloglikol
- kwas 5-hydroksyindolooctowy
- duże zaburzenie depresyjne
- skala depresji Hamiltona

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**STRESZCZENIE**

**Cel pracy.** W dużej depresji (MDD, *major depressive disorder*) obserwuje się ośrodkową dysfunkcję monoaminergiczną z towarzyszącą dysregulacją autonomicznego układu nerwowego. Aktywność α-amylazy ślinowej (sAA) oraz stężenie 3-metoksy-4-hydroksyfenyloglikolu w ślinie (sMHPG) przyjmuje się jako markery centralnej aktywności noradrenergicznej, z kolei stężenie kwasu 5-hydroksyindolooctowego w ślinie (s5-HIAA) wskazuje na centralny obrót serotoniny. Nie ma danych na temat wartości wyjściowych sAA, s5-HIAA i sMHPG w MDD, które są powiązane ze specyficznymi wymiarami psychopatologicznymi i wynikami w Skali oceny depresji Hamiltona (HAMD-17) w MDD.

**Materiał i metody.** Podstawowe stężenia sMHPG i s5-HIAA oraz aktywność sAA, skorelowane z oceną psychometryczną HAMD-17 zostały przeanalizowane w tym badaniu eksploracyjnym w grupie 20 dorosłych, nieleczonych uprzednio pacjentów z MDD.

**Wyniki.** *Post hoc* stwierdzono negatywne korelacje między sMHPG a HAMD-17 w pozycji 7 (praca i aktywność) ($r = -0{,}56$, $p = 0{,}01$) i 4 (wczesne budzenie się) ($r = -0{,}45$, $p = 0{,}049$). Podczas eksploracji zaobserwowano również korelacje między sAA a pozycjami 7 (praca i aktywność) ($r = -0{,}47$, $p = 0{,}04$) i 12 (objawy żołądkowo-jelitowe) ($r = 0{,}49$, $p = 0{,}03$) bez takiej obserwacji w odniesieniu do s5 -HIAA.

**Wnioski.** W analizie eksploracyjnej stwierdzono, że na wczesnym etapie dużej depresji (MDD), w podstawowych, niestymulowanych warunkach wyjściowe poziomy sAA i sMHPG są skorelowane z pozycjami HAMD-17 reprezentującymi objawy kliniczne przypisywane pierwotnej dysfunkcji noradrenergicznej. Ślina jest obiecującym źródłem biomarkerów monoaminergicznych w badaniach MDD. Konieczne są jednak dalsze systematyczne badania w celu uzyskania spójnych wyników oraz standaryzacji, w szczególności w zakresie pomiarów psychometrycznych.

## Objectives

Altered monoamine neurotransmission plays a key role in psychopathology and pharmacotherapy of major depressive disorder (MDD). There is evidence for salivary markers being indicative of central monoaminergic function and offering a non-invasive and stress-free sampling method (Martí-Álamo *et al.* 2012).

Salivary α-amylase (sAA) activity and salivary 3-methoxy-4-hydroxy-phenylglycol (sMHPG) are adopted as a marker of central noradrenergic activity being sensitive to physiological stressors and found low in MDD (Martí-Álamo *et al.* 2012, Schumacher *et al.* 2013, Cubała and Landowski 2014, Cubała *et al.* 2014). There is also some evidence for salivary 5-hydroxyindole acetic acid (s5-HIAA) being adopted as an index of central serotonin turnover (Cubala *et al.*2014).

A number of methodological considerations exist in MDD studies with regard to salivary biomarkers of central monoaminergic activity with inconsistent results attributable elevation to the illness stage, severity, specific dimensions of depression and measures of distress. There is also a considerable inconsistency in the results, attributing biomarkers to specific psychopathological dimensions of MDD, where noradrenergic activity is hypothesized, being associated with psychomotor drive, alertness and cognition, while serotonergic dysfunction plays a role in emotional processing.

Recently, we demonstrated low baseline sAA and sMHPG with unaltered s5-HIAA levels in drug-naïve patients with short-illness-duration first episode MDD (Cubała *et al.* 2014), being in line with Schildkraut's catecholamine hypothesis of depression (Schildkraut 1965, Blier and Briley 2011). The sAA activity, sMHPG and s5-HIAA concentrations were not significantly correlated neither with duration nor the severity of depressive symptoms as measured by the total HAMD-17 score.

This exploratory study was undertaken to examine whether and to what extent sAA, sMHPG and s5-HIAA levels in baseline non-stimulated conditions are interrelated to the item performance of the Hamilton Rating Scale for Depression in MDD. It was hypothesized that the sAA and sMHPG decline would be correlated with the severity of items associated predominantly with noradrenergic function with s5-HIAA levels being associated with emotional dimension of depression.

## Material and methods

The study population and protocol has been exhaustively reported elsewhere (Cubała *et al.* 2014). Briefly, twenty first-episode and drug-naïve MDD patients were diagnosed using the Structured Clinical Interview for DSM-IV Axis I Disorders (First *et al.* 1997). Subjects with a 17-item Hamilton Rating Scale for Depression (HAMD-17) (Hamilton 1960) score of ≥ 20, an episode duration ≤ 24 weeks, free from any current or past suicidality and psychotic symptoms, were eligible for inclusion in the study.

All study subjects underwent routine physical examination. Current or evidence of any previous unstable medical condition, any history of endocrine, inflammatory, autoimmune, oral/dental health problems, including salivary gland disorders, neurological disease,

inflammatory responses in the previous two weeks, pregnancy or lactation, alcohol or drug abuse in the past 12 month, tobacco smoking exceeding 25 cigarettes a day, Body Mass Index (BMI) ≤ 18 and ≥ 30, and age < 18 and > 55 years were exclusion criteria for this study, and the women included had not received hormonal contraception for at least 12 months.

The study was performed in agreement with the Declaration of Helsinki, following the approval of the Ethic Research Committee of the Institution. For each study participant, written consent was obtained.

The study followed a case-control design. As previously described (Cubała *et al.* 2014), saliva was sampled and processed with subsequent batch sAA activity and s5-HIAA concentration analyses by means of an enzyme-linked immunoassay using an ELISA kits with sMHPG concentration being measured using HPLC-ECD.

The total HAMD-17 score was analysed followed by the exploratory analysis based on the hierarchical Cole and Motivala model (Cole *et al.* 2004) with core depression, insomnia, anxiety and somatic psychopathological dimensions.

Statistical procedures were performed using StatsDirect v2.7.9. The Pearson's correlation coefficient was used to assess correlations between the obtained variables in post hoc analysis. All tests were two-tailed with an alpha = 0.05.

## Results

The levels of sAA, sMHPG and s5-HIAA in MDD subjects were not significantly correlated neither with duration nor severity of depressive symptoms as measured by the total HAMD-17 score nor analysed subscales scores. There were no significant associations between gender, age, BMI or WHR (Waist-Hip Ratio) and sAA, sMHPG and s5-HIAA. Additional information can be found in prior reports (Szarmach *et al.* 2017, Cubała *et al.* 2014).

Post hoc HAMD-17 analyses revealed correlations between sMHPG concentration and items 7 (work and activities) ($r = -0.56$, $p = 0.01$) and 4 (early insomnia) ($r = -0.45$, $p = 0.049$). On exploratory analysis significant correlations between sAA and items 7 (work and activities) ($r = -0.47$, $p = 0.04$) and 12 (gastrointestinal symptoms) ($r = 0.49$, $p = 0.03$) were also observed. No such an exploratory observation was identified with regard to s5-HIAA concentration (Table 1).

**Table 1** Pearson's correlation coefficient between sMHPG, sAA and s5-HIAA levels and psychometric variables in MDD

| | Median (IQR) | Salivary MHPG | | Salivary α-amylase | | Salivary 5-HIAA | |
|---|---|---|---|---|---|---|---|
| | | *R* | *p* | *R* | *p* | *R* | *p* |
| HDRS1(depressed mood) | 3 (3, 3) | –0.03 | 0.91 | 0.04 | 0.85 | 0.17 | 0.46 |
| HDRS2 (feeling of guilt) | 2 (2, 2) | –0.14 | 0.54 | –0.09 | 0.71 | 0.13 | 0.58 |
| HDRS3 (suicie) | 0 (0, 0) | 0.08 | 0.72 | –0.27 | 0.25 | –0.01 | 0.96 |
| HDRS4 (insomnia-early) | 1.5(1, 2) | **–0.45** | **0.049** | –0.34 | 0.14 | - 0.35 | 0.13 |
| HDRS5 (insomnia-middle) | 1 (1, 2) | 0.23 | 0.33 | 0.11 | 0.63 | –0.03 | 0.91 |
| HDRS6 (insomnia-late) | 1 (0, 2) | 0.26 | 0.26 | 0.22 | 0.35 | 0.33 | 0.16 |
| HDRS7 (work & activities) | 3 (3, 3) | **–0.56** | **0.01** | **–0.47** | **0.04** | 0.25 | 0.28 |
| HDRS8 (retardation) | 1 (1, 2) | 0.23 | 0.33 | 0.04 | 0.87 | 0.08 | 0.75 |
| HDRS9 (agitation) | 1 (1, 2) | –0.02 | 0.94 | –0.16 | 0.50 | 0.06 | 0.79 |
| HDRS10 (ankiety-psychic) | 2 (1, 2) | 0.19 | 0.41 | 0.15 | 0.52 | 0.25 | 0.28 |
| HDRS11 (anxiety-somatic) | 2 (1.5, 2) | –0.09 | 0.72 | 0.02 | 0.94 | 0.16 | 0.50 |
| HDRS12 (gastrointestinal) | 1 (0, 1) | –0.21 | 0.36 | **0.49** | **0.03** | –0.05 | 0.83 |
| HDRS13 (somatic-general) | 1 (1, 1) | 0.16 | 0.50 | –0.12 | 0.61 | 0.20 | 0.40 |
| HDRS14 (genital) | 1 (0.5, 2) | –0.09 | 0.69 | 0.34 | 0.14 | 0.26 | 0.27 |
| HDRS15 (hypochondriasis) | 0 (0, 1) | –0.13 | 0.58 | –0.04 | 0.86 | –0.12 | 0.62 |
| HDRS16 (loss of weight) | 1 (1, 2) | 0.09 | 0.70 | –0.02 | 0.93 | 0.17 | 0.48 |
| HDRS17 (insight) | 0.5 (1, 2) | 0.21 | 0.37 | 0.15 | 0.53 | –0.15 | 0.53 |
| HDRS-total | 22.5 (21, 24) | –0.05 | 0.83 | 0.16 | 0.50 | 0.28 | 0.23 |
| Core depression | 5 (5, 5) | –0.05 | 0.84 | –0.22 | 0.35 | 0.18 | 0.44 |
| Insomnia | 3 (3, 4) | 0.18 | 0.45 | 0.06 | 0.79 | 0.12 | 0.61 |
| Anxiety | 7 (6, 7) | –0.03 | 0.92 | 0.26 | 0.26 | 0.19 | 0.42 |
| Visceral | 7 (6, 8) | –0.10 | 0.67 | 0.09 | 0.71 | 0.32 | 0.16 |

## Discussion

The exploratory analysis of HAMD-17 items with sMHPG level revealed significant negative correlations with items 4 (early insomnia) and 7 (work and activities). Also, post hoc analysis of HAMD-17 items with sAA level revealed significant negative correlation with item 7 (work and activities) and positive correlation with item 12 (gastrointestinal symptoms). However, no correlations were observed with regard to s5-HIAA concentration. The depressive episode duration and global severity of depressive symptoms as measured by the total HAMD-17 score were not found to be significantly correlated with sAA, sMHPG and s5-HIAA.

The negative correlation between sAA and sMHPG as related to HAMD-17 'work & activities' item may hypothetically be indicative of low central noradrenergic function associated with specific dimension of depression related to the impairment in activities. The reduced noradrenergic neurotransmission is linked to decreased alertness, low energy, problems of inattention, concentration, and cognitive performance constituting debilitating cluster of symptoms (Blier and Briley 2011). The negative correlation found for early insomnia with sMHPG seems to demonstrate the decrease of noradrenergic levels at the early stage of the disease associated with sleep dysregulation. The finding corroborates with urinary MHPG study in MDD subjects on clinical symptomatology with HAMD-17 with regard to sleep and work and activities items being proposed to characterize endogenomorphus depression traits (Samson *et al*. 1994, Agren 1982, Blier and Briley 2011). Alternatively, the positive sAA correlation with HAMD-17 'gastrointestinal symptoms' item may correspond to the autonomic nervous system (ANS) activation being related to hypophagia (Schumacher 2013, Blier and Briley 2011). Thus, that exploratory finding may represent two disease dependent interrelated mechanisms representing noradrenergic and ANS activities in MDD. No correlations found for s5-HIAA and clinical symptoms is attributable to hypothesised serotonergic dysfunction appearance at latter stage of the disease with initial noradrenergic decline as it is postulated by original catecholamine hypothesis of depression (Schildkraut 1965, Szarmach *et al.* 2017). The explorative study design is the key study limitation. The results apply to drug-naïve patients with short-illness-duration first episode MDD who were free of comorbid Axis I and II conditions, current suicidality and suicide history with no reference to normal population per HAMD-17 scoring convention (Hamilton 1960). Besides, the study explores items in MDD subjects only as per rating scale practice principle indicating its applicability to subjects diagnosed with major depression only and being rater-based outcome measure.

## Conclusions

On exploratory analysis, in basal, non-stimulated conditions baseline sAA, sMHPG levels in MDD were found to be correlated with HAMD-17 items representing clinical symptoms attributable to primary noradrenergic dysfunction at the early stage of major depression. A cross-sectional analysis adds to the evidence linking salivary monoaminergic biomarkers with psychopathological features, including item performance in MDD.

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AW – input in the concept and draft of the paper, data collection and interpretation, statistical analysis, literature collection / wkład w koncepcję i projekt pracy, zebranie danych i ich interpretacja, analiza statystyczna i przygotowanie wyników badań do analizy, zebranie piśmiennictwa;

WJC – input in the concept and draft of the paper, critical review in terms of substantial intellectual content, acceptance of the final draft to be published / wkład w koncepcję i projekt pracy, krytyczne zrecenzowanie pod kątem istotnej zawartości intelektualnej, akceptacja ostatecznej wersji do opublikowania;

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