The value of melatonin supplementation in postmenopausal women with Helicobacter pylori-associated dyspepsia

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Research article

Keywords: menopause, dyspepsia, Helicobacter pylori, melatonin

Posted Date: November 5th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-31148/v3

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Version of Record: A version of this preprint was published on November 26th, 2020. See the published version at https://doi.org/10.1186/s12905-020-01117-z.
Abstract

Background Dyspeptic syndrome is particularly common in postmenopausal women in the form of epigastric pain. The aim of the study was to assess the role of melatonin in chronic dyspepsia in this group of women, and examine the role of Helicobacter infection.

Methods The study comprised 152 subjects including 30 healthy women (Group I), 60 women with asymptomatic H. pylori infection (Group II), and 64 women with H. pylori infection with chronic dyspepsia (Group III). Endoscopic examination was performed, as well as histological assessment of gastric and duodenal mucosa, urease breath test (UBT-13C), and immunoenzymatic assessment of serum 17β-estradiol, follicle stimulating hormone and melatonin, and urinary 6-sulfatoxymelatonin. In Group III, 14-day antibacterial treatment was introduced with pantoprazole, amoxicillin and levofloxacin followed a six-month treatment with placebo in 32 women (Group IIIa), and melatonin 1 mg/morning and 3 mg/night in the other 32 women (Group IIIb).

Results No significant differences were found between serum level of female hormone. Serum melatonin levels were similar between Group I (12.5 ± 2.72 pg/ml) and Group II (10.5 ± 3.73 pg/ml; p>0.05). The level was significantly lower in Group III (5.72 ± 1.42 pg/ml; p<0.001). Eradication of H. pylori was obtained in 75.0% women in Group IIIa, and in 84.3% in Group IIIb (p>0.05). After six months, dyspeptic symptoms resolved in 43.7% patients in Group IIIa and 84.3% in Group IIIb (p<0.001).

Conclusion Melatonin supplementation is useful in treating H. pylori-associated dyspepsia, particularly in postmenopausal women with lower levels of this hormone.

Trial registration: NCT04352062, date of registration: 15.04.2020.

Background Following the menopause, many women can demonstrate range of psychosomatic disorders. The severity of climacteric symptoms, typically hot flushes, excessive sweating, sleep disorders, irritability, depressive mood, fatigue, headache, vertigo, myalgia, palpitation and formication, can be assessed using the Menopause Rating Scale [1]. However, this index does not take into account the gastrointestinal disorders which frequently cause chronic dyspepsia. Dyspeptic syndrome, in the form of epigastric pain, hunger, nocturnal pain and appetite disorders is particularly frequent. These symptoms are caused by a fall in estrogen level, which exerts a protective effect by inhibiting the secretion of hydrochloric acid and pepsin [2] and motor activity [3], as well as stimulating the secretion of mucus and bicarbonates [4]. Furthermore, estradiol exerts antioxidant activity [5,6] and modulates visceral sensation [7].

However, dyspeptic problems are not relieved by hormone replacement therapy [8]. This may be due to the fact that in addition to estrogens, the postmenopausal period is characterized by a deficiency of various hormones, including melatonin [9,10]. Experimental studies have shown that like estrogens, melatonin has an inhibitory effect on the secretion of hydrochloric acid [11] and stimulates the secretion of bicarbonates in the upper gastrointestinal tract [12]. It also demonstrates antioxidant [13], cytoprotective [14], myorelaxant [15] and analgesic [16] properties. Simultaneous estrogen and melatonin deficiency may create adverse conditions in the stomach and trigger dyspeptic discomfort. This assumption is supported by the results of earlier studies, which found reduced melatonin secretion in patients with functional dyspepsia [17]. The expression of melatonin-synthesizing enzymes in the gastric mucosa [18,19] and the concentration of melatonin in gastric juice [20] may also be reduced.

The aim of the present study was to assess the role of melatonin in the pathogenesis of chronic dyspepsia in postmenopausal women, and to examine the effect of Helicobacter pylori infection.

Methods The study comprised 152 women aged 49-64 years (mean age 56.3 ± 8.3 years). The group included 62 women who developed dyspeptic problems for the first time after menopause. The study took place in the years 2011-2018.

Three groups were distinguished: Group I - 30 women without dyspeptic complaints and without Helicobacter pylori infection; Group II - 60 women with asymptomatic Helicobacter pylori infection; Group III - 62 women with chronic dyspepsia and Helicobacter pylori infection.

Diagnosis of H. pylori – associated dyspepsia was based on the Kyoto Global Consensus [21].

Inclusion criteria The main symptoms reported in Group III were epigastric pain of a hunger nature and pain at night, as well as increased appetite. The severity of dyspeptic symptoms was evaluated using the Visual Analogue Scale. All subjects underwent endoscopic examination of the upper gastrointestinal tract and histological assessment was performed using hematoxylin-eosin and Giemsa staining. To confirm Helicobacter pylori infection, the UBT-13C urea breath test was performed using FANci-2 System (Fisher Instrumente, GmbH, Hamburg, Germany).

Exclusion criteria The following women were excluded from the study: those with other functional or inflammatory diseases of the gastrointestinal tract, liver and pancreas; those with metabolic, allergic or mental illness; those who were receiving hormone replacement therapy.

Laboratory tests
The following routine laboratory examinations were performed: blood cell count, C-reactive protein, glycosylated hemoglobin, bilirubin, alanine and aspartate aminotransferase, amylase, lipase, urea, creatinine, cholesterol HDL and LDL, triglyceride assay.

Immunoenzymatic assay of 17-β-estradiol (antibodies Ortho-Clinical Diagnostics, Inc., Raritan, NY, USA) and follicle-stimulating hormone (FSH – Vitros Product antibodies – Ortho-Clinical Diagnostics, Inc., Rochester, NY, USA) was also performed. Serum melatonin level and urinary 6-sulfatoxymelatonin level were measured by ELISA with IBL antibodies (RE-54021 and RE-54031, IBL International GmbH, Hamburg, Germany) and Expert 99 MicroWin 2000 Reader (GmbH, Labtech, Offenburg, Germany).

Blood samples were drawn from the antecubital vein at 9:00 a.m. and were frozen at minus 70°C. On the same day, samples of urine were taken over 24 hours. Next morning 20ml volume of urine samples were frozen at minus 70°C.

The subjects followed the same diet for seven days prior to the evaluations. On the day of the study, all patients consumed the same liquid diet (Nutridrink – Nutricia), containing 18.9 g carbohydrate, 6.0 g protein and 5.8 g lipid per ml. Three 400 ml meals were taken, with a total caloric value of 1800 kcal, together with 1500 ml of isotonic water.

Therapeutic procedure

In group III, the following 14-day antibacterial treatment was introduced: pantoprazole (2x40 mg), amoxicillin (2x1000 mg) and levofloxacin (2x500 mg).

Afterward, the patients were randomly divided into two equally-sized groups. Group IIIa (n = 32) was administered placebo (LEK – KAM, Poland) as two tablets a day, and Group IIIb (n = 32) received melatonin at a dose of 1 mg/morning and 3 mg/at bedtime, for six months. In this period, the patients applied the same balanced diet with a total caloric value of 1600 kcal.

Follow-up clinical examinations were performed after one, three and six months, and the UBT-13C test was performed after three and six months.

Statistical analysis

Normally distributed data was compared using Student’s t-test, and non-normal data by the Kruskal-Wallis and post hoc tests. Data were expressed as mean and standard deviation. Therapeutic effects after melatonin supplementation were evaluated using the chi-square test. A p-value of < 0.05 was considered statistically significant. Statistica 13.3 (StatSoft, INC, USA) and MS Excel (Microsoft Co., USA) were used for statistical calculations.

Results

The general characteristics of the investigated women are shown in Table 1. The groups did not differ in terms of age, body mass index, aminotransferase levels or renal filtration index. However, the result of the UBT-13C test excluded *H. pylori* infection in the control group.

| Feature               | Group I (n = 30) | Group II (n = 40) | Group III (n = 64) |
|-----------------------|------------------|-------------------|-------------------|
| Age (years)           | 54.6 ± 7.2       | 57.4 ± 8.2        | 56.8 ± 7.9        |
| BMI (kg/m²)           | 23.8 ± 1.6       | 24.1 ± 2.3        | 25.6 ± 6.1        |
| UBT - 13 C (ppm)      | -                | 18.4 ± 4.6        | 21.0 ± 6.1        |
| ALT (IU/L)            | 21.6 ± 6.2       | 26.3 ± 4.4        | 24.2 ± 6.1        |
| AST (IU/L)            | 20.6 ± 4.0       | 25.1 ± 3.8        | 22.8 ± 6.9        |
| GFR (ml/min)          | 98.5 ± 11.8      | 97.6 ± 12.1       | 102.4 ± 11.3      |

BMI – body mass index, UBT-13C- urease breath test, ALT – alanine aminotransferase, AST – aspartate aminotransferase, GFR – glomerular filtration rate; differences between groups no statistically significant, p>0.05.

The serum levels of 17-β-estradiol were 15.1±4.64 pg/ml in Group I, 14.4±5.27 pg/ml in Group II and 11.9±3.72 pg/ml Group III. These differences were not statistically significant (Figure 1).

Similarly, no significant differences in serum follicle-stimulating hormone levels were found between the groups: Group I – 72.7±23.6 IU/ml; Group II – 82.3±17.5 IU/ml; Group III – 89.7±16.9 IU/ml (Figure 2).

Similar serum melatonin levels were observed in Group I (12.5±2.72 pg/ml) and Group II (10.5±3.73 pg/ml; p > 0.05). However lower levels were found in women with symptomatic *H. pylori* infection: 5.27±1.42 pg/ml (p< 0.001, Figure 3).

Interestingly, significant differences were observed between the groups with regard to urinary 6-sulfatoxymelatonin excretion over 24 hours: 19.3±6.18µg in Group I, 13.2±4.80 µg in Group II – (p < 0.001), and 7.93±2.27 µg/ml in Group III (p<0.001, Figure 4).
Eradication of Helicobacter pylori was obtained in 24 women (75.0%) in Group IIIa, and in 27 women (84.3%) in Group IIIb (p > 0.05).

After six months, dyspeptic symptoms resolved in 14 women (43.7%) in Group IIIa, and in 27 (84.3%) in Group IIIb (p < 0.001, Table 2).

Table 2. The results of Helicobacter pylori eradication and dyspeptic symptom improvement in patients receiving placebo (Group IIIa) or melatonin (Group IIIb)

| Patients | Group IIIa | Group IIIb | X² - value | P-value |
|----------|------------|------------|------------|---------|
|          | N=32       | N=32       |            |         |
| n        | %          | n          | %          |         |
| Without H. pylori |          |            |            |         |
| 3 months | 24         | 26         | 0.366      | 0.545   |
| 6 months | 23         | 27         | 1.459      | 0.227   |
| Without symptoms |          |            |            |         |
| 3 months | 12         | 16         | 1.014      | 0.314   |
| 6 months | 14         | 27         | 11.489     | 0.0007  |

Melatonin was well tolerated: only four women (12.5%) reported increased fatigue in the morning, and two patients (6.2%) headache in the first week of the treatment. No cases required discontinuation of therapy or dose reduction.

**Discussion**

In humans, melatonin secretion decreases with age [22]. These changes are particularly apparent in perimenopausal women [23,24]. Some researchers believe that the reduction in melatonin secretion in women begins around the age of 40 years and may initiate menopause [25]. In this period of life, dyspeptic symptoms are frequently observed. The obtained results indicate that lowered melatonin levels may be one of reason of dyspeptic symptoms. Interestingly, while women with relatively normal melatonin levels tended to demonstrate asymptomatic H. pylori infection, those with both H. pylori infection and with low melatonin levels were more likely to suffer from dyspepsia. In the latter cases, there were indications for antibiotic therapy; however, eradication of H. pylori only eliminated complaints in some patients. Hence, it appears that dyspeptic symptoms may be associated with low secretion of melatonin in the gastric mucosa, and melatonin may have a protective effect in asymptomatic infections. Many studies have shown that even asymptomatic infection induces destructive changes in the gastric mucosa [26,27] and the presence, or absence, of symptoms depends on many factors. The presence of gastrotoxic factors and absence of enteroprotective factors can trigger dyspeptic symptoms and can hasten the development of peptic ulcers and stomach cancer [28,29].

Melatonin demonstrates many beneficial effects in the combined therapy of many gastrointestinal diseases, such as esophageal reflux disease [30], functional dyspepsia [31], ulcer disease [32], irritable bowel syndrome [33,34] and ulcerative colitis [35,36]. However, the optimal doses needed for therapeutic effectiveness and good tolerance remain unknown. A review of 392 previous studies found that the applied dose ranged from 0.3 mg to 1000 mg/daily [37], while another indicated from 0.1 to 50 mg/daily [38]. In order to control sleep, the most frequently recommended dose was 1 mg to 5 mg at night, while most treatments of alimentary tract disease [30-35] or climacteric disorders in women were based on doses of 3 mg or 5 mg per day [39,40]. A dose of 8 mg per day was found to be an effective treatment of metabolic syndrome [41], and a dose of 50 – 100 mg daily has been proposed for the regulation of inflammatory and metabolic disorders [42].

Melatonin demonstrates good tolerability and safety, due to its pharmacokinetic properties. Oral administration of 10 mg melatonin resulted in a maximum serum concentration of 3550 pg/ml at T½ 53.7 minutes [43]. Similar results pharmacokinetics were obtained by other researchers following oral doses of 0.4 mg or 4 mg [44] and 80 mg [45]. Thus, the administration of a single dose of melatonin raises its serum level for a few hours. Therefore, to take the best advantage of its effect in postmenopausal disorders, melatonin should be administered in divided doses (1 mg/morning and 3 mg/at bedtime); nevertheless, its dose should be related to age, severity of symptoms and concomitant disease.

Our study has same limitations. The most significant one was the small size of the study group; even so, the population was relatively homogeneous and well characterized.

**Conclusion**

Melatonin supplementation can play a significant role in complex therapy of H. pylori-associated dyspepsia, particularly in patients with reduced melatonin secretion, such as postmenopausal women.

**Abbreviations**
aMT6s - 6-sulfatoxymelatonin
BMI - Body Mass Index
ALT - Alanine aminotransferase
AST - Aspartate aminotransferase
FSH - Follicle-stimulating hormone
GFR - Glomerular filtration rate
UBT-13C - Urease breath test

Declarations

Acknowledgments
The authors thank Janina Grycewicz, for proofreading the manuscript.

Funding
This study was supported by the grant of the Ministry of Science and Higher Education of Poland (NN- 4025437/40).

Availability of data and materials
All data is available from the corresponding author on reasonable request.

Authors' contributions
CC: Conceived the study and carried out the clinical procedures. MM-S: Participated in clinical trials and biochemical procedures. PK: Contributed to the study protocol. JC: Designed and realized the study. AB: Carried out the clinical procedures, collected and analysed the data, wrote and revised the manuscript; AB also acted as study coordinator and Principal Investigator. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study was performed in accordance with the Declaration of Helsinki and with the principles of Good Clinical Practice. Written consent was informed and obtained from each subject enrolled onto the study and the protocol was approved by the Bioethics Committee of the Medical University of Lodz (RNN/596/11/KB).

Consent for publication
Not applicable.

Competing interests
The authors declare no conflict of interests. The sponsors had no role in the design, execution, interpretation, or writing of the study.

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Figures

![Figure 1](https://example.com/figure1.png)

**Figure 1**

The serum level of 17-β-estradiol in healthy women (group I) and in women with asymptomatic H. pylori infection (group II) and in patients with H. pylori infection and chronic dyspepsia (group III); differences between group statistically no significant, p>0.05.
Figure 2
The serum level of follicle-stimulating hormone (FSH) in healthy women (group I), in women with asymptomatic H. pylori infection (group II), and in patients with H. pylori infection and chronic dyspepsia (group III); differences between groups statistically not significant, p>0.05.

Figure 3
The serum level of melatonin in healthy women (group I), in women with asymptomatic H. pylori infection (group II), and in patients with H. pylori infection and chronic dyspepsia (group III); differences between groups I and II – p> 0.05, I and III – p<0.001, II and III – p<0.001.
Figure 4

Urinary 6-sulfatoxymelatonin excretion in health women (group I), in women with symptomatic H. pylori infection (group II), and in patients with H. pylori infection and chronic dyspepsia (group III); differences between all groups statistically significant – p<0,001.