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

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Research article

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Abstract

Background Dyspeptic syndrome in the form of epigastric pain are particularly frequent in postmenopausal women. The aim of the study was to assess the role of melatonin in chronic dyspepsia in this group of women, with consideration 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 H. pylori infected with chronic dyspepsia (group III). Endoscopic examination, histological assessment of gastric end duodenal mucosa, urease breath test (UBT-13C), and serum levels of 17-β-estradiol, follicle stimulating hormone, melatonin and urinary concentration of 6-sulfatoxymelatonin were determined by immunoenzymatic method. In group III – 14-day antibacterial treatment was introduced with pantoprazole, amoxicillin and levofloxacin. Afterward, in 32 women was administered placebo (group IIla), and in 32 women (group IIIb) melatonin at a dose 1 mg/morning and 3 mg/ at bedtime, for six months.

Results No significant differences were assessed between serum level of female hormone. Serum level of melatonin in group I and in group II was similar – 12.5 ± 2.72pg/ml and 10.5±3.73 pg/ml (p>0.05), whereas in group III it was lesser – 5.72±1.42 pg/ml (p<0.001). Eradication of H.pylori was obtained in 75.0% women in group IIla, and in 84.3% in group IIIb (p>0.05). After 6 months dyspeptic symptoms resolved in 43.7% patients in group IIla and in 84.3% in group IIIb (p>0.001).

Conclusion Melatonin supplementation is useful to complex therapy of H. pylori-associated dyspepsia, particularly in postmenopausal women at whom secretion of this hormone is decreased.

Trial registration: NCT04352062, date of registration: 15.04.2020.

Background

Different psychosomatic disorders are observed in postmenopausal women. The severity of climacteric symptoms such as: 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]. This index do not take into account gastrointestinal disorders which frequently cause chronic dyspepsia . Dyspeptic syndrome in the form of epigastric pain, including hunger and nocturnal pain and appetite disorders are particularly frequent. These symptoms are referred to the reduction of estrogen secretion, 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]. Despite this, female sex hormones applied in hormone replacement therapy do not reduce dyspeptic problems [8]. In the postmenopausal period, in addition to estrogens, there is a deficiency of other hormones, including melatonin [9,10]. Experimental studies have shown that melatonin, like estrogens, 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, among others, by the results of earlier studies, which showed that in patients with functional dyspepsia melatonin secretion is reduced [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 with consideration of Helicobacter pylori infection.

Methods

The study comprised 152 women, aged 49-64 years (mean age 56.3 ± 8.3 years), including 62 women who developed dyspeptic problems for the first time after menopause. The research 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

Main symptoms in group III were epigastric pain of a hunger nature and pain at night, as well as increased appetite. Severity of dyspeptic symptoms was evaluated using Visual Analogue Scale. All subjects underwent endoscopic examination of the upper gastrointestinal tract and histological assessment was performed using hematoxylin-eosin and Giemsa staining. In order to confirm Helicobacter pylori urea breath test UBT-13C was performed using FANcl-2 System (Fisher Instrumente, GmbH, Hamburg, Germany).

Exclusion criteria

Women with other functional or inflammatory diseases of the gastrointestinal tract, liver and pancreas, as well as metabolic, allergic and mental disease, and with hormone replacement therapy were excluded from the study.

Laboratory tests
Routine laboratory examinations included: blood cells count, C-reactive protein, glycosylated hemoglobin, bilirubin, alanine and aspartate aminotransferase, amylase, lipase, urea, creatinine, cholesterol HDL and LDL, triglyceride.

Moreover, 17-β-estradiol (antibodies Ortho-Clinical Diagnostics, Inc., Raritan, NY, USA), follicle-stimulating hormone (FSH – Vitros Product antibodies – Ortho-Clinical Diagnostics, Inc., Rochester, NY, USA) were determined by immunoenzymatic methods for the research purposes. Serum melatonin level and urinary concentration of 6-sulfatoxymelatonin were measured by the ELISA method applying 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 then they were frozen at minus 70°C. On the same day, the 24-hour urine collection was performed and the samples with a 20 ml capacity were kept at 4°C. Next morning, the volume of urine was measured and the samples were frozen at minus 70°C.

Seven days prior to the evaluations the subjects were on the same diet. On the day of the study all patients were administered the same liquid diet (Nutridrink – Nutricia) in the amount of 3x400 ml, containing 18,9 g carbohydrate, 6,0 g protein, 5,8 g lipid/ml, of the total caloric value of 1800 kcal, and 1500 ml of isotonic water.

**Therapeutic procedure**

In group III a 14-day antibacterial treatment was introduced with: pantoprazole (2x40 mg), amoxicillin (2x1000 mg), and levofoxacin (2x500 mg).

Afterward, the patients randomly divided into two equal groups. Group IIIa (n = 32) was administered placebo (LEK – KAM, Poland) 2x 1 tablet, and group IIIb (n = 32) melatonin at a dose 1 mg/morning and 3 mg/at bedtime, for six months. In this period the patients applied the same balanced diet of total caloric value 1600 kcal.

Follow-up clinical examinations were performed after 1,3 and 6 months, and UBT-13C test was performed after 3 and 6 months.

**Statistical analysis**

Student t-test was used to compare the means for normal distribution and Kruskal – Wallis and Post-hoc tests to compare the data of case non-normality. Data were expressed as mean and standard deviation. Therapeutic effects after melatonin supplementation was performed using chi-squared 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**

General characteristics of the investigated women is shown in Table 1. The groups did not differ in terms of age, body mass index, aminotransferases levels and renal filtration index, except for the result of the UBT-13C test, which excluded H. pylori infection in 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.

Serum level of 17-β-estradiol in group I was 15.1±4.64 pg/ml, and in group II – 14.4±5.27 pg/ml, and group III – 11.9±3.72 pg/ml; differences between groups statistically no significant (Figure 1).

Similarly, no significant differences were assessed between serum level of follicle-stimulating hormone: group I – 72.7±23.6 IU/ml, in group II – 82.3±17.5 IU/ml, and in group III – 89.7±16.9 IU/ml (Figure 2).

Serum level of melatonin in group I and group II was similar – 12.5±2.72 pg/ml and 10.5±3.73 pg/ml, respectively (p > 0.05), whereas in women with symptomatic H. pylori infection was lesser – 5.27±1.42 pg/ml (p< 0.001, Figure 3).

Then differences between urinary 6-sulfatoxymelatonin excretion were statistically significant – in group I – 19.3±6.18µg/24h, in group II – 13,2±4.80 µg/24h (p < 0.001 ), and in group III – 7.93±2.27 µg/ml (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 6 month 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 symptoms improvement in patients taken placebo (group IIIa) or melatonin (group IIIb)

| Patients | Group IIIa | Group IIIb | χ²-value | P-value |
|----------|------------|------------|----------|---------|
|          | N=32       | N=32       |          |         |
| n        | %          | n          | %        |         |
| Without H. pylori |          |            |          |         |
| 3 mth    | 24         | 81.2       | 0.366    | 0.545   |
| 6 mth    | 23         | 84.3       | 1.459    | 0.227   |
| Without symptom |        |            |          |         |
| 3 mth    | 12         | 50.0       | 1.014    | 0.314   |
| 6 mth    | 14         | 84.3       | 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 but without the need of discontinuation of the therapy or dose reduction.

**Discussion**

Melatonin secretion decreases in humans with age [22]. These changes are observed especially 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 women life dyspeptic symptoms are frequently observed. The obtained results indicate that one of them may be a decrease in melatonin secretion. It is interesting that in women with relatively normal melatonin levels, H.pylori infection was asymptomatic. However, dyspepsia occurred in women in whom H.pylori infection coexisted with low melatonin levels. In these cases, there were indications for antibiotic therapy, but eradication of this bacterium eliminated complaints only in some patients. Thus, it can be assumed that dyspeptic symptoms are associated with low secretion of melatonin also in the gastric mucosa. Whereas, in asymptomatic infections, melatonin has a protective effect. Many studies have shown that asymptomatic infection is not indifferent to the body, as it always leads to destructive changes in the gastric mucosa [26,27] and the presence or absence of symptoms depends on many factors. Both gastrotoxic factors and deficiency of enteroprotective factors can trigger dyspeptic symptoms and predispose to the development of peptic ulcers and stomach cancer [28,29]. The beneficial properties of melatonin are used in the combined therapy of many gastrointestinal diseases as esophageal reflux disease [30], functional dyspepsia [31], ulcer disease [32], irritable bowel syndrome [33,34] and ulcerative colitis [35,36]. However, it has not been determined what doses of melatonin should be used for therapeutic effectiveness and good tolerance. An optimal dose which should be administered in different diseases is a debatable issue. Harpose [37] reviewed 392 literature records and found out that the applied doses were from 0.3 mg to 1000 mg/daily. Similar data (from 0.1 to 50 mg/daily) were found by Vural et al. [38]. In order to control the sleep the most frequently recommended dose 1 – 5 mg at night. The dose of 3 mg or 5 mg/daily were usually used in the treatment of alimentary tract diseases [30-35] as well as climacteric disorders in women [39,40]. Goyal et al. [41] used 8 mg melatonin daily in an effective treatment of the metabolic syndrome. Cardinali and Haderland [42] suggested a melatonin dose 50 – 100 mg daily for the regulation of inflammatory and metabolic disorders. Good tolerability and safety of melatonin result from its pharmacokinetic properties. Anderson et al. [43] administered orally 10 mg of melatonin and found its maximum serum concentration of 3550 pg/ml at T½ = 53.7 min. Similar results of the studies on melatonin pharmacokinetics were obtained by other researchers who used oral dose of 0.4 mg or 4 mg [44] and 80 mg [45]. Thus, the administration of a single dose of melatonin raises its level for a few hours. His justifies the administration of melatonin in divided doses (1mg/morning and 3mg/at bedtime) in order to take good advantage of its effect in postmenopausal disorders in women. Nevertheless, its dose should be related to age, severity of symptoms and concomitant disease.

Our study has same limitations, particularly the number of subjects enrolled is not very impressive, but we had relatively homogeneous and well characterized groups.

**Conclusion**

Melatonin supplementation is useful to complex therapy of H. pylori-associated dyspepsia, particularly in postmenopausal women at whom secretion of this hormone is decreased.

**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

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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 and carried out the clinical procedures. MM-S: Participated in a clinical trials and biochemical procedures. PK: Contributed of the study protocol. JC: Finally designed and realized of the study. AB: coordinator and performed of the study as Principal Investigator. All authors read and approved 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 subjects enrolled into the study and the protocol was approved by the Bioethics Committee of the Medical University in 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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