INTRODUCTION

Prolactin is known as a multifunctional pituitary hormone presented by a non-glycosylated protein which contains a simple polypeptide chain of 198 amino acids. Prolactin is synthesized and secreted by lactotropic pituitary cells in diurnal rhythm, with its highest levels early in the morning. The expression of its receptor is present in most peripheral organs. The most prominent physiological role of prolactin is the maintenance of lactation, but the effect of this hormone also manifests itself in metabolic, osmotic and immunoregulatory mechanisms [1].

Experimental studies conducted even 30 years ago showed that prolactin has positive chronotropic and vasoconstrictor effects [2]. In subsequent years, some reports suggested a discrete role of prolactin in cardiovascular system depending on its concentration in the blood. High normal prolactin levels correlated with parameters associated with hypertension, while high or very high levels of prolactin (above reference values) might adversely affect endothelial function and perhaps other markers of atheromatosis [3]. The level of prolactin in the blood is higher in men with a significant increase of blood pressure (BP), while reducing of its concentration may benefit the BP control. According to Georgiopoulos et al., prolactin levels correlate with BP values, possibly by the mechanism of increasing of arterial stiffness, with no correlation with other traditional factors of cardiovascular risk. According to the evaluation of many surrogate markers, for example, endothelial and micrcirculatory function, BMI, and the fact of existence of atherosclerotic plaques, there was no association between prolactin levels and atherosclerosis in women in early menopause, while men were not included into the study [4]. In studies of next years, prolactin receptors were discovered in atherosclerotic lesions of the coronary arteries [5], which further indicates the probable role of prolactin in atherosclerosis. A recent analysis of Georgiopoulos et al. showed that in women below 55 years of age prolactin is an independent predictor of changes in the pulse wave velocity (PWV) over time, and a high normal level of circulating prolactin suggests changes in hemodynamic parameters and deterioration of endothelial function in healthy postmenopausal women [6].

PROLACTIN IN HYPERTENSIVE MEN WITH ANDROGEN DEFICIENCY: AN ÉMINENCE GRISE?

PROLAKTYNA U MĘŻCZYZNA Z NADCIŚNIENIEM TĘTNICZYM I NIEDOBOREM ANDROGENÓW: SZARA EMINENCJA?

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ABSTRACT

Introduction: Considering significant gap of convincing knowledge in the field of cardiovascular effects of prolactin and its role as a stress hormone in men precise investigations of these peculiarities has become necessary.

The aim of this study was to find out the relationship of prolactin concentration with parameters of arterial stiffness in hypertensive men with low testosterone.

Materials and methods: In total 83 men were examined including 27 apparently healthy individuals as the control group. Physical examination, ABPM, non-invasive evaluation of arterial stiffness and central hemodynamics parameters, answering AMS questionnaire, evaluation of total testosterone and prolactin levels using ELISA were performed.

Results: Initially 56 hypertensive patients were divided into 2 groups with regard to their total testosterone level: group 1 included 31 hypogonadal men, group 2 - 25 male patients who had their testosterone concentrations within the normal range. Prolactin levels appeared to be significantly higher in hypertensive men with lower testosterone, they had more unfavorable parameters of arterial stiffness and the difference between 1 and 2 group in terms of central aortaSBP and aortaPWV became statistically significant. Prolactin concentration was not related with RWTT and index Aix% 75, a significant correlation was observed between prolactin and aortaPWV. A strong correlation was found between prolactin concentration and psychological symptoms in AMS.

Conclusion: Our study suggests the positive association of prolactin concentration with psychological domain of andropause symptoms and worse parameters of arterial stiffness among hypertensive men with androgen deficiency.

KEY WORDS: hypertension, androgen deficiency, prolactin, arterial stiffness
The given data for women disagree with the results obtained in the investigation of male population. It was noted by Corona et al. that in a large number of men who had been consulted about sexual dysfunction, the decrease in plasma level of prolactin was associated with a worse lipid profile and glycemic parameters, as well as a higher incidence of metabolic syndrome and erectile dysfunction [7]. According to the data of Reuwer et al. the systemic concentration of prolactin did not appear to be different in apparently healthy men from such women characterized by development of coronary artery disease during the observation period and those who did not suffer from cardiovascular diseases, patients with higher levels of prolactin did not show to have notably increased risk of CAD [5]. The association of daily fluctuations of circulating prolactin with decreased endothelial function in men with arterial hypertension was also described [8]. Subsequently, Haring et al. found an independent positive association of prolactin concentration with a higher 10-year cardiovascular and total mortality [9]. A similar result was obtained by Corona et al. - prolactin level was considered as an independent predictor of cardiovascular events in men with erectile dysfunction [10]. In spite of the previous data, later Therkelsen et al. using the information from the analysis of 4053 participants of the Framingham Study did not find any association of prolactin with certain cardiovascular risk factors [11].

Prolactin was also suggested to be a stress hormone which could alter BP level but its correlation with anxiety and depressive symptoms were clearly described mostly for female population [12]. Although the numerous studies show the negative impact of prolactin elevation in cardiovascular diseases (CVD), the global assessment of prolactin levels in patients with CVD, particularly in males, was not performed.

THE AIM
Since the previous studies were not gender-specific and did not describe in detail the characteristics of vascular remodelling depending on the level of circulating prolactin, the aim of this study was to find out the relationship of prolactin concentration with parameters of arterial stiffness in hypertensive men with low testosterone.

MATERIALS AND METHODS
To accomplish the aim of the study after obtaining written informed consent, 83 men were examined including 27 apparently healthy individuals who were included into the control group. All the study participants including the control group were comparable by age and anthropometric parameters, and were subjected to physical examination, daily blood pressure monitoring, non-invasive evaluation of arterial stiffness and central hemodynamics parameters using the BPLab VasoTens system. The following parameters were studied: the aortic pulse wave velocity (aoPWV), the reflected wave transit time (RWTT), function (dP/dt), aortic augmentation index (AIXao), Aix% 75 (normalized for the heart rate of 75 bpm), ambulatory arterial stiffness index (AASI), central aortic systolic blood pressure (central aoSBP). Blood samples were obtained from study subjects in the morning hours (8 am-10 am). Levels of serum prolactin and total testosterone were assessed using a set of reagents «Accubind», USA. All the study participants filled in the AMS (Aging Male's Symptoms) questionnaire which is a 17-item self-report questionnaire for identifying middle-aged and older men with androgen deficiency. The results of the study were statistically analyzed using software packages Microsoft Excel 2016 and Statistica 6.0 (license number AXR712D33214FAN5). The results were considered as statistically significant if p-value was less than 0.05. The data is presented as the median and interquartile interval.

RESULTS
Initially 56 hypertensive patients were divided into 2 groups with regard to their total testosterone (TT) level: group 1 included 31 hypogonadal men, while remaining 25 male patients had their TT concentrations within the normal range and were grouped together as the group 2. The mean age of participants was 57.4 ± 7.2, 55.5 ± 7.2 and 53.1 ± 8.0 for group 1, group 2 and control subjects respectively. Statistically significant difference between group 1 and group 2 regarding office systolic BP, office diastolic BP and heart rate was not found.

As it was mentioned before, all study participants were interviewed for symptoms of possible androgen deficiency using AMS questionnaire. According to calculations of total AMS score, patients’ symptoms were evaluated in psychological, somatovegetative and sexual domains [13]. A total score was calculated based on Lickert scale for each question. Total AMS scores of 37–49 and >49 points which are classified as “moderate symptoms” and “severe symptoms” respectively, were peculiar for 90.3% of patients of 1st group and 64% of patients of 2nd group, besides the strongest correlation was seen between total testosterone level and sexual domain (Table I). In addition, a strong correlation was found between prolactin concentration and psychological symptoms. Somatic items did not correlate significantly with named hormones.

The main characteristics of study groups are shown in the Table I.

Seeing the contributing role of prolactin level in the development of predominantly psychological symptoms of androgen deficiency arises the need for the evaluation of its possible role in clinical settings with reference to the course of hypertension in these patients. Parameters of 24h ABPM and indicators of arterial stiffness were assessed for this purpose.

The group of patients with low testosterone level were characterized by higher values of mean 24 h SBP compared to men with normal testosterone level. It was also noticed that more patients of group 1 have non-favourable
circadian pattern of BP (69% of non-dippers in 1st group vs. 45% in 2nd). The correlation of prolactin with these parameters turned out to be non-significant. Prolactin levels appeared to be significantly higher in hypertensive men with lower testosterone (median 12.62 [10.55; 15.49] versus 10.45 [9.18; 12.61] ng/mL (P = 0.037) in group 2 and 10.26 [5.11; 12.11] ng/mL (P = 0.0007) in control group). However, the correlation of prolactin with testosterone was insignificant (P = 0.1).

In the matter of central aortic SBP, it appeared to be significantly higher in patients with lower values of total testosterone compared to those without androgen deficiency and control subjects. There were also notable differences in parameters of arterial stiffness (Table II).

Table I. Characteristics of study groups.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group 1 (hypertensive men with low TT)</th>
<th>Group 2 (hypertensive men with normal TT)</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT, ng/mL</td>
<td>1.56 [1.27; 1.82]*#</td>
<td>3.08 [2.55; 3.72]*</td>
<td>4.25 [2.89; 4.83]</td>
</tr>
<tr>
<td>AMS score:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-total score</td>
<td>41 [38; 46]*#</td>
<td>33 [28; 37]*</td>
<td>28 [22; 30]*#</td>
</tr>
<tr>
<td>-somatovegetative domain</td>
<td>7 [4; 9]</td>
<td>6 [4; 8]</td>
<td>5 [4; 8]</td>
</tr>
<tr>
<td>-psychological domain</td>
<td>13 [9; 17]*#</td>
<td>10 [8; 13]*#</td>
<td>9 [7; 12]*#</td>
</tr>
<tr>
<td>-sexual domain</td>
<td>13 [8; 17]*#</td>
<td>11 [8; 14]*#</td>
<td>9 [6; 13]*#</td>
</tr>
</tbody>
</table>

Note: * - p<0.05 compared to control group, # - p<0.05 compared to group 2; TT – total testosterone, AMS – Aging Male’s Symptoms Score

Table II. Parameters of central hemodynamics and arterial stiffness of study participants

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group 1 (hypertensive men with low TT)</th>
<th>Group 2 (hypertensive men with normal TT)</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central aoSBP, mm Hg</td>
<td>128 [122; 134]*#</td>
<td>124 [121; 132]*</td>
<td>116 [114; 119]</td>
</tr>
<tr>
<td>aoPWV, m/s</td>
<td>11.2 [9.1; 11.8]*#</td>
<td>10.1 [9.4; 10.6]*</td>
<td>8.1 [7.6; 8.6]</td>
</tr>
<tr>
<td>RWTT, ms</td>
<td>128 [126; 135]*</td>
<td>125 [123; 137]*</td>
<td>118.5 [106.3; 130.8]</td>
</tr>
<tr>
<td>Aix %75</td>
<td>-28.5 [-36.8; -18.5]*</td>
<td>-27.5 [-36.4; -19.0]</td>
<td>-34 [-37.5; -30.5]</td>
</tr>
<tr>
<td>AASI</td>
<td>145.5 [129.8; 167.3]</td>
<td>140.5 [115.3; 165.8]</td>
<td>135.5 [119.3; 147.8]</td>
</tr>
</tbody>
</table>

Note: * - p<0.05 compared to control group, # - p<0.05 compared to group 2

Figure 1. Correlation between prolactin level and aoPWV.

y = 0.3685x + 5.9303
R² = 0.6888
As demonstrated in Table II, men with low testosterone level who were also characterized by higher prolactin level had more unfavorable parameters of arterial stiffness and the difference between 1 and 2 group in terms of central aoSBP and aopPWV became statistically significant.

Further analysis showed that prolactin concentration was not related with RWTT (r=0.172; P=0.24 and index Aix% 75 (r=0.907; P=0.87). In contrast, a significant correlation was observed between prolactin and aopPWV (r=0.87; P=0.017) (Figure 1).

DISCUSSION
The question about the consequential role of prolactin in processes of vascular remodelling in CVD has recently arisen and lead to the continuing of in-deep investigation of mechanisms of action of this hormone in the development of cardiovascular pathology. Most studies concentrate on prolactin level as a contributor to atherosclerosis in women in menopause, and the same data for men are not widely available. The notable finding of the current study is the demonstration of significant correlation of prolactin level with parameters of arterial stiffness, that is aopPWV and AASI, as well as with indicators of central hemodynamics (central aoSBP). Central BP is determined among others by stroke volume, peripheral resistance and arterial stiffness, emphasizing the role of the last as a key antecedent factor for BP elevation. Thereby, adverse cardiovascular effects of excess or upper boundary values of prolactin can be argued [4].

Several possible ways of the impact of prolactin levels in vascular remodelling were suggested, among them influence on vascular tone, mediation of low-grade inflammation and induction of smooth muscle cell proliferation are well described [14, 15].

Previous studies have described the association of prolactin with an increase in BP, especially among postmenopausal women [4, 16]. Similar results have been shown in our study conducted among men.

Numerous studies conducted predominantly on male population have shown the regulating role of prolactin in acute psychological stress response but the type of hormonal reaction on stress in these studies are inconsistent. Our data correspond to the results received by Lennartsson et al., who demonstrated hormonal response among others by stroke volume, peripheral resistance and arterial stiffness, emphasizing the role of the last as a key antecedent factor for BP elevation. Thereby, adverse cardiovascular effects of excess or upper boundary values of prolactin can be argued [4].

REFERENCES

Authors’ contributions:
According to the order of the Authorship.

Conflict of interest:
The Authors declare no conflict of interest.