

Alterations in nasal mucociliary activity in polycystic ovary syndrome



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ABSTRACT

Objectives: Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of reproductive age. It can affect various organ systems, and respiratory mucosa has been reported as being hormone responsive.

Study design: A case-control study consisting of 50 women with PCOS and 30 control subjects matched for age and body mass index was conducted, in order to investigate nasal mucociliary clearance time (NMCT) in patients with PCOS. Serum basal hormonal-biochemical parameters and NMCT were evaluated on menstrual cycle days 2–5 for all participants.

Results: The mean NMCT in PCOS and control groups was 10.45 ± 2.88 and 6.92 ± 1.78 , respectively ($p = 0.0001$). A significant positive correlation was found between NMCT and duration of disease ($r = 0.52$; $p = 0.001$), serum total testosterone level ($r = 0.28$; $p = 0.04$), and luteinizing hormone/follicle stimulating hormone ($r = 0.29$; $p = 0.04$).

Conclusions: Our findings indicate that PCOS is associated with altered NMCT. Prolonged NMCT predisposes patients to respiratory tract and middle ear infections, and clinicians should be aware of this.

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Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder, affecting 5–15% of women of reproductive age [1–3], which can affect several organs. Despite the high prevalence of basic and clinical research studies, the underlying mechanisms of PCOS have not been clearly elucidated. Inflammation plays an important role in the pathophysiology of PCOS [4], and insulin resistance is a common characteristic of the syndrome. Insulin acts synergistically with luteinizing hormone (LH) to stimulate the synthesis of androgens by ovarian theca cells [5]. The exaggerated synthesis and secretion of the ovarian and adrenal androgens are the primary defect in PCOS [6], and these sex hormones can have both genital and non-genital organ targets, such as otolaryngological organs [7–9].

Nasal mucociliary activity is the ability of respiratory mucosa to retain moisture throughout the mucosal surfaces and to remove foreign particles by ciliary activity, and nasal mucosa can be influenced by pregnancy, menopause [8], oral contraceptive pill (OCP) use [9] and hormone replacement therapy (HRT) [10]. Mucociliary clearance (MCC) is the initial defense mechanism of the respiratory tract. Dysfunctional ciliary activity causes increased upper and lower respiratory tract infections by affecting the microparticle clarifying function of the airways [11].

The present study was designed to evaluate nasal mucociliary activity in women with PCOS compared healthy controls, by using the saccharin test, which is a non-invasive and commonly used clinical method [8,12,13]. To our knowledge, this is the first study to evaluate nasal mucociliary activity in PCOS patients.

Methods

The study was performed at Dumlupinar University Medical Faculty, Department of Obstetrics and Gynecology and Otolaryngology, Kutahya, Turkey. The participants included in the study were recruited consecutively between September 2015 and January 2016. The study was approved by the Ethics Committee

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at Dumlupinar University and conducted in accordance with the declaration of Helsinki. Informed written consent was obtained from all participants. PCOS was diagnosed based on the Revised Rotterdam consensus on diagnostic criteria for PCOS [14]. At least 2 out of 3 of the following are required for the diagnosis: clinical and/or biochemical signs of hyperandrogenism; oligo- and/or amenorrhea; and polycystic ovaries in ultrasound. *Menstrual periods* with intervals of more than 35 days and 182 days are considered as oligomenorrhea and amenorrhea, respectively. Clinical hyperandrogenism was assessed as the self-reported degree of hirsutism using the modified Ferriman–Gallwey scoring (FGS) method, the presence of acne or androgenic alopecia. The modified FGS is the most common method of grading hirsutism in clinical studies. It scores hair growth in nine androgen sensitive body areas, including chin, the upper lip, chest, upper and lower abdomen, upper arm, thighs, upper and lower back from 0 to 4. The FGS ≥ 8 was considered to have hirsutism [15]. Disorders with a similar clinical presentation, such as congenital adrenal hyperplasia, androgen secreting tumors, Cushing's syndrome, and hyperprolactinemia, were excluded from the study. All subjects had normal renal, hepatic and thyroid functions. Women who received any medication known to affect gonadal or adrenal function in the previous 3 months were excluded from the study. Subjects with a nasal pathology causing nasal obstruction such as nasal septum deviation, sinusitis, or nasal polyposis; with a history of allergy or asthma; with a respiratory tract infection; with a history of nasal or paranasal operation were also excluded from the study.

Each participant underwent ear, nose and throat examination screened by nasal endoscopy, and examined for possible inflammation of the upper airways. Mucociliary transport time was evaluated with the saccharin test. The tests were performed by the same clinician blind to the study groups at the otolaryngology clinic, by application of a $\frac{1}{4}$ saccharin tablet, 1 cm posterior and inferior to the head of the inferior turbinate, while the patient was in the sitting position with the head bent forward. The patients were instructed to swallow every 30 s and not to sniff, sneeze, or wipe their noses until the time they tasted the saccharin. The time from placement to the perception of the sweet taste was recorded as the nasal mucociliary clearance time (NMCT). Serum basal hormonal-biochemical parameters and NMCT were evaluated on menstrual cycle days 2–5 for all participants.

SPSS for Windows 21.0 software (IL, USA) was used for statistical analysis. All data are given as mean $\pm$ standard deviation (SD). Normal distribution of continuous variables was tested with Kolmogorov–Smirnov test. Chi square test was used for comparisons between categorical variables. Mann–Whitney *U* tests were used for continuous variables when comparing the groups. For

correlation analysis, Spearman's correlation test was used. A *p*-value <0.05 was considered as statistically significant.

Results

Eighty participants were recruited, and of these, 76 participants completed the study. Upon otolaryngological examination, 4 participants were excluded from the study due to inflammation and nasal septal deviation. The mean age of the PCOS and control groups was 24.08 ± 5.35 years and 25.40 ± 5.56 years, respectively. The basal serum hormonal and biochemical variables are summarized in Table 1. Among the PCOS patients, 70.02% presented with oligo/amenorrhea. The mean NMCT in the PCOS group was significantly longer than in the control group ($p < 0.001$) (Fig. 1). There was a positive correlation between NMCT and PCOS disease duration ($r = 0.52$; $p = 0.00$), serum total testosterone level ($r = 0.28$; $p = 0.04$), and LH/FSH ($r = 0.29$; $p = 0.04$).

Discussion

PCOS is a syndrome of unknown etiology with hyperinsulinemia having major pathophysiological role in the hyperandrogenism in patients with PCOS independent of obesity [16]. Hyperinsulinemia stimulates ovarian and adrenal androgen secretion and suppresses sex hormone-binding globulin (SHBG) synthesis, causing a surplus of androgens. While previous studies reported that sex hormones can influence nasal physiology [17], the effect of PCOS, the most common cause of hyperandrogenism and anovulation in women of reproductive age, on nasal mucosal functions has not, to date, been investigated. A recent study by Devci et al. demonstrated loss of cilia, edema, vascular engorgement and reduced goblet cell number in larynx mucosa in an experimentally induced PCOS rat model, emphasizing the effect of hyperandrogenism in larynx mucosa [18]. Clinically loss of cilia and goblet cell number causes increased respiratory tract infections. Therefore, we hypothesized that PCOS might affect nasal mucociliary activity in the same way.

MCC, measured by NMCT, is the primary defense mechanism of the respiratory tract, whereby inhaled particles recognized as harmful are trapped by mucus and removed from the nasal cavity toward the nasopharynx by cilia. Any change in mucosal or ciliary activity can therefore alter this function [19]. NMCT can be affected by many factors [20,21]. As such, patients with cardiovascular disorders, diabetes mellitus, hematological disease, autoimmune disease, acute or chronic systemic inflammatory disease, malignancy, asthma, cystic fibrosis, metabolic disease, and smokers were excluded from the study.

PCOS may result in alterations in several different organ systems, including the pancreas, liver, brain, eye, ear, and

Table 1
Demographic, clinical, and laboratory data of the groups.

Characteristics	PCOS group (n = 47) (mean $\pm$ SD)	Control group (n = 29) (mean $\pm$ SD)	p-Value
Mean age (years)	24.08 ± 5.35	25.40 ± 5.56	0.24
BMI (kg/m ²)	24.4 ± 6.0	24.8 ± 4.6	0.53
Mucociliary clearance time (minutes)	10.45 ± 2.88	6.92 ± 1.78	0.0001
FGS	7.41 ± 4.45	3.60 ± 2.99	0.0001
LH (mIU/ml)	7.57 ± 5.52	5.10 ± 1.04	0.04
LH/FSH	1.27 ± 0.98	0.76 ± 0.19	0.03
Total testosterone (ng/dl)	0.58 ± 0.54	0.40 ± 0.18	0.12
HOMA index	2.62 ± 3.11	1.84 ± 1.43	0.54
17OHP	1.66 ± 2.79	0.75 ± 0.37	0.16
DHEAS	21.27 ± 30.91	18.75 ± 11.64	0.52
CRP	5.94 ± 9.54	1.75 ± 2.13	0.04

BMI = body mass index; FGS = ferriman gallwey score; LH = luteinizing hormone; FSH = follicle stimulating hormone; 17OHP = 17-hydroxy progesterone; DHEAS = dehydroepiandrosterone sulphate; CRP = C-reactive protein.

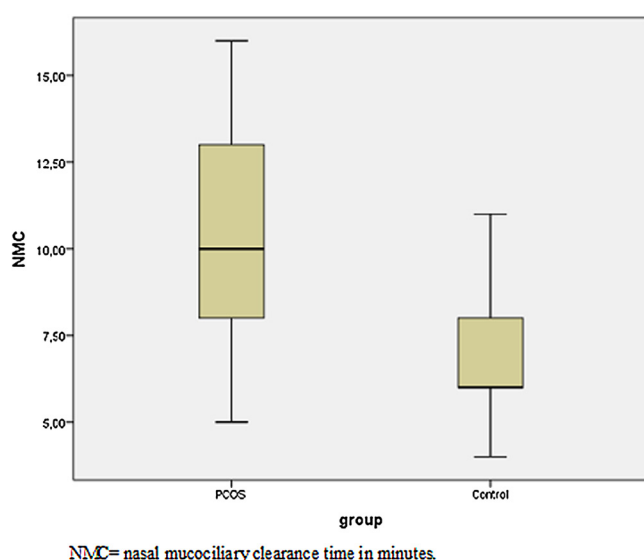


Fig. 1. The mean nasal mucociliary clearance time of the study and control group.

cardiovascular system [7,22,23]. Nasal mucosa has been reported to be an estrogen target along with vaginal epithelial cells in postmenopausal women under HRT [24], and a recent study reported longer NMCT in postmenopausal women compared to premenopausal controls [8]. This was also shown to be positively correlated with menopause duration. Similarly, a study by Nappi et al. reported an increased mucociliary clearance time which was reversed by HRT in postmenopausal women, emphasizing the effect of estrogens on nasal mucosa [10] although a further study by Wild et al. failed to demonstrate this [12]. Similar to menopause, PCOS alters reproductive hormones. In the present study, women with PCOS were found to have significantly longer NMCT which was positively correlated with LH/FSH and serum testosterone level. A recent experimental study reported decreased number of goblet cells in larynx mucosa in PCOS [18]. The changes in the content and volume of nasal mucus, which is related to goblet cell number, might be a mechanism by which NMCT is altered in PCOS in our study. There are a few studies with conflicting results about the effect of gender on nasal mucociliary activity. Some studies have found no sex differences [25], while the other reported NMC to be faster in women [26].

PCOS is a proinflammatory state. A meta-analysis of the most comparable studies indicates that circulating CRP level is elevated in PCOS reflective of the chronic low-grade inflammation present in the disorder. They also found that elevated circulating CRP in PCOS is independent of obesity. The reported prevalence of obesity varies from 30 to 75% in PCOS and most, but not all, women with PCOS are overweight or obese [27]. The participants were recruited consecutively from Obstetrics and Gynecology outpatient clinic, near to the University campus where most of the patients are young university students whose positive body image is important for them. This might explain the relatively lower BMI (24.4) of the study group in the current study. Herein the presenting study, CRP level of the PCOS patients was significantly higher [28]. Besides, the mean FGS was significantly higher in PCOS group ($p < 0.01$). Although the pathophysiology of PCOS is not clearly elucidated, insulin resistance which is associated with inflammation and hyperandrogenism seen in PCOS, is shown to have a critical role [29].

The potential limitations of the current study include a relatively small sample size and the absence of pathophysiological evaluation of the nasal mucosa due to ethical issues. However, this is the first clinical study to evaluate NMC activity in PCOS patients.

In the current study, we identified prolonged NMCT in women with PCOS compared to healthy eumenorrheic women. The results of this study suggest that hyperandrogenism can alter NMC functions, and further studies with histopathological confirmation will be informative for a more comprehensive understanding of the underlying mechanisms. As discussed, prolonged NMCT predisposes patients to frequent airway and middle ear infections, and clinicians should be aware of this.

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Conflict of interest

The authors declare that they have no conflict of interest.

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