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Does Hyperandrogenism Affect the Otoacoustic Emissions and Medial Olivocochlear Reflex in Female Adults?

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Hypothesis: To evaluate the effects of hyperandrogenism on otoacoustic emission levels and the medial olivocochlear reflex in adult female subjects.
Background: Women have a hearing advantage over men. Otoacoustic emission levels tend to be higher in female subjects, in both newborns and adults. This discrepancy has been presumed to result from prenatal androgen exposure in male subjects.
Methods: The study involved 37 polycystic ovary syndrome patients who were referred from the endocrinology department and 26 healthy volunteers. All participants who showed normal otoscopic findings, hearing thresholds, and acoustic admittance were included. All polycystic ovary syndrome patients showed biochemical signs of hyperandrogenism. Cochlear activity of participants was evaluated by means of distortion product otoacoustic emissions and transient otoacoustic emissions. The medial olivocochlear reflex was evoked with contralateral acoustic stimulation and recorded with distortion product otoacoustic emissions and transient otoacoustic emissions.
Results: Neither distortion products nor transient otoacoustic emission levels showed a statistically significant difference between the right and left ears ($p > 0.05$). Comparisons of distortion products and transient otoacoustic emission levels between the patient and control groups showed no statistically significant difference ($p > 0.05$). Comparison of the medial olivocochlear reflex response between the 2 groups also revealed no statistically significant difference ($p > 0.05$).
Conclusion: Hyperandrogenism did not seem to influence otoacoustic emission levels or the medial olivocochlear reflex response in adult female subjects. **Key Words:** Distortion product otoacoustic emission—Hearing—Hyperandrogenism—Medial olivocochlear reflex—Polycystic over syndrome—Transiently evoked otoacoustic emission.
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Female subjects have an advantage in hearing over male subjects. Epidemiologic studies have shown that women have better high-frequency thresholds than men in virtually all age groups (1,2).

This advantage may be explained by lack of prenatal androgen exposure for the human female fetus and circulating estrogen in women (3,4). Studies also have shown that female subjects have greater otoacoustic emission levels in newborns and adults (3). This difference is more pronounced in click-evoked otoacoustic emissions (CEOAEs) and less in distortion product otoacoustic emissions (DPOAEs) (3). It has been proposed that a difference in the strength of the efferent influence by the medial olivocochlear (MOC) system on the outer hair cells of the cochlea may be responsible for the observed male-female differences in OAEs (5).

MOC fibers synapse on outer hair cells (OHCs), and activation of these fibers inhibits basilar membrane responses to low-level sounds. This MOC-induced decrease in the gain of the cochlear amplifier is reflected in changes in OAEs. Any OAE can be used to monitor MOC effects on the cochlear amplifier (6). Medial olivocochlear system activation can be achieved through acoustic stimulation, the so-called medial olivocochlear reflex. This reflex can be activated with ipsilateral and/or contralateral acoustic stimuli. The medial olivocochlear system has 2 possible effects on the auditory system: improvement of low-frequency detection and sound discrimination from background noise (7) and a protective effect against acoustic trauma to the cochlea (8). Estrogen seems to protect hearing through the MOC efferent system (9).

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McFadden (10) has suggested the ''prenatal-androgen-exposure'' hypothesis as an explanation for the discrepancy of OAEs between the sexes. He speculated that prenatal exposure of androgens during embryonic development creates this discrepancy. Female spotted hyenas, which were exposed to high levels of androgens during prenatal development, were seen to possess male characteristics. Spotted hyenas who were exposed to flutamide (androgen receptor blocker) and finasteride (blocking the breakdown of testosterone into dihydrotestosterone) prenatally showed strengthened CEOAE responses in both sexes (11). An experiment conducted in rhesus monkeys (Macaca mulatta) revealed that CEOAEs of female monkeys are stronger than male subjects. The magnitude of this sex difference fluctuates: weaker during breeding season when male androgens are high and stronger during birthing season when male androgens are low. In female subjects, CEOAEs were slightly stronger (more feminine) in the fall, when sex steroids are elevated in female subjects (and male subjects), than in the summer when rhesus monkeys are reproductively quiescent. Some monkeys of both sexes had been treated with additional testosterone or the antiandrogen flutamide during prenatal development. Prenatal androgen treatment weakened CEOAEs in female subjects, and prenatal flutamide treatment strengthened CEOAEs in male subjects. For DPOAEs, the differences between treated and untreated groups were mostly small and often inconsistent (12).

The discrepancy in hearing levels between sexes can be investigated in animals, and several hormonal manipulations can be accomplished. With the ethical considerations kept in mind, it is not an easy task to investigate the effect of these hormones (androgens, estrogen) in humans. There are anecdotal reports and epidemiologic studies reporting these effects. McFadden et al. (13) reported strengthened OAEs in an adult male subject taking high levels of estrogens to suppress his androgens before sex-change surgery. A recent study has shown that the menopause appears to act as a trigger of a relatively rapid age-related hearing decline in healthy women, starting in the left ear (14).

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age (15). Hallmarks of the syndrome include anovulation, androgen excess, and insulin resistance. The biochemical reproductive phenotype in PCOS consists of increased luteinizing hormone (LH) relative to follicle-stimulating hormone (FSH) secretion, and hyperandrogenism (elevated dehydroepiandrosterone sulfate (DHEA-S), elevated free and total testosterone levels) (16,17).

As previously mentioned, estrogen seems to protect hearing through MOC reflex system and enhances OAE levels. The scope of this study was to evaluate the effects of hyperandrogenism on otoacoustic emissions and the medial olivocochlear reflex, in female adults. Therefore, we selected a special group of subjects with hyperandrogenism: specifically, patients with PCOS. To our knowledge, this is the first study to investigate the effects of hyperandrogenism on OAEs and medial olivocochlear reflex in adult female subjects.

MATERIALS AND METHODS

This prospective study involved 37 PCOS patients who were referred from the endocrinology department and 26 healthy volunteers. The mean age of the PCOS group was 27.2 years (range, 18–49 yr), and that of the control group was 28.1 years (range, 19–36 yr).

The study was performed in accordance with Helsinki Committee requirements and was approved by the ethics committee of İzmir Katip Çelebi University. Written informed consent was obtained from all participants before the study.

All PCOS patients met each of the criteria of the revised 2003 Rotterdam ESHRE/ASRM PCOS Consensus Workshop Group diagnostic criteria (17). PCOS was diagnosed when 2 of the following 3 features were present: oligoovulation and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries on ultrasound examination (the presence of 12 or more follicles of 2–9 mm in diameter and/or ovarian volume greater than 10 cm^3). Importantly, the study group all showed biochemical signs of hyperandrogenism (patients without biochemical hyperandrogenism were excluded). Hormone levels of the patient group compared with normal reference levels are presented in Figures 1 and 2. F1 F2

The health of the control group was determined on the basis of medical history, physical otolaryngologic examination, blood chemistry, and audiologic evaluations. None of these women, PCOS or controls, were on any medication for at least 1 month before the study(newly diagnosed patients or PCOS patients that do not use any medication for at least 1 month who were admitted to endocrinology department), including oral contraceptives; glucocorticoids; ovulation induction agents; antidiabetic and antiobesity drugs; or estrogenic, antiandrogenic, and ototoxic drugs. Patients who had previously had otologic surgery, chronic otorrhea, and chronic tinnitus were excluded.

All participants who showed normal otoscopic findings, hearing thresholds, and acoustic admittance were included. Normal hearing thresholds were defined as being less than 20 dB HL at 500, 1,000, 2,000, 4,000, 5,000, 6,000, 7,000, and 8,000 Hz (Interacoustics AC40 Audio Electronics Inc., Austin, TX, U.S.A.). DPOAE measurements at the frequencies used in the main experiments—0.5, 1, 2, 2.5, 3,4, 5, 6, 7, and 8 kHz—and TOAE measurements at the frequencies used in the main experiments—1,

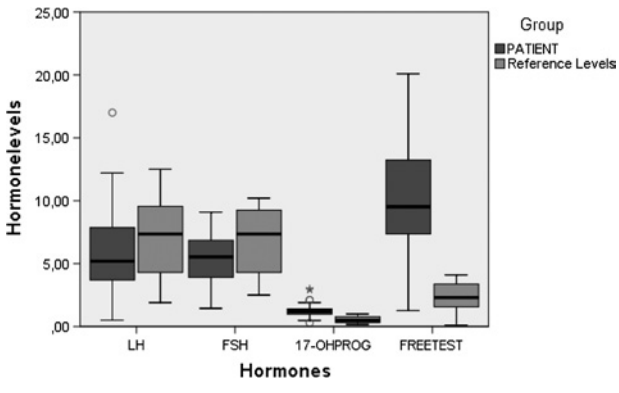

FIG. 1. Hormone levels in patients with hyperandrogenism compared with normal reference levels. FSH indicates follicle-stimulating hormone; LH, luteinizing hormone; 17-OHProg, 17-hydroxyprogesterone; Free Test, free testosterone. (Reference ranges: FSH, 2.5–10.2 [IU/L]; LH, 1.9–12.5 [IU/L]; 17-0 H-Prog, 0.2–1 [ng/ml]; Free Test, 0.1–4.1 [pg/ml], respectively.) Left bar represents patient group; right bar represents normal reference levels.

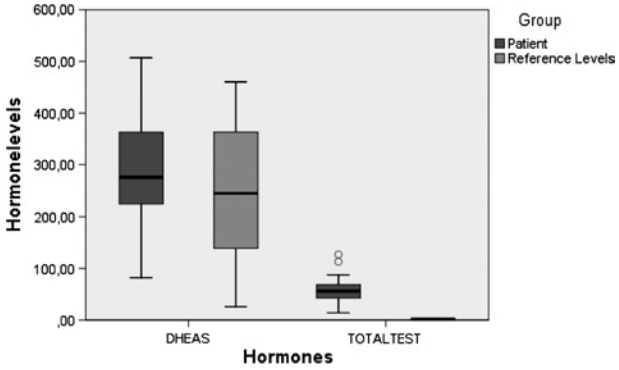

FIG. 2. Hormone levels in patients with hyperandrogenism compared with normal reference levels. DHEAS indicates dehydroepiandrosterone; Total Test, total testosterone. (Reference ranges: DHEAS, 25.9–460.2 [μg/dl]; Total Test, 0.5–2.6 [nmol/L], respectively.) Left bar represents patient group; right bar represents normal reference levels.

2, 3, and 4 kHz—were recorded using a Vivosonic integrity K500 (Vivosonic Inc., Ontario, Canada) measurement system. DPOAEs were recorded with stimulus levels of L1 = 65 and L2 = 55 dB SPL and f2/f1 = 1.22. Emissions were considered to be normal when signal-to-noise ratio levels exceeded 3 dB.

The effects of contralateral acoustic stimulation were investigated delivering contralaterally a continuous, broadband white noise (bandwidth, 50–8,000 Hz) presented at 60 dB SPL, corresponding to 30 dB SL, to minimize interaural transmission and activation of the stapedial reflex. Reduction/suppression may be defined numerically as the amplitude difference of the otoacoustic emission response without and with contralateral acoustic stimulation; the value of this difference shows the degree of reduction/suppression quantitatively. Reduction is present when the difference is positive with a decrease in the response amplitude of TEOAE/DPOAE with contralateral acoustic stimulation; suppression is present when TEOAE/DPOAE responses are extinguished. TEOAE reduction/suppression is absent when the difference is zero or negative. When the difference is zero or negative, DPOAE enhancement is present.

Tympanometric measurements were recorded using an Interacoustics AZ26 (Audio Electronics Inc.) middle-ear analyzer with a 226-Hz probe tone. Compliance peak values within the range of 0.30 to 1.50 ml were considered to be normal. Acoustic reflex thresholds, using steady-state broadband noise, were also recorded with the Interacoustics AZ26 (Audio Electronics Inc.). All participants with an acoustic reflex threshold lower than 80 dB HL were excluded in an effort to exclude middle ear muscle activity as a potential cause of OAE level changes and MOC reflex suppression.

A Shapiro-Wilk test was used to assess the normal distribution of the data. If data were normally distributed, a *t* test was used; otherwise, the Mann–Whitney *U* test and Wilcoxon's signed rank test were used. Statistical analyses were conducted using the SPSS software (version 16 for Windows). The statistical significance level was established at $p < 0.05$, and confidence intervals were 95%. A power analysis was computed with G*Power 3.1.1 (18).

RESULTS

Three patients in the PCOS group and 5 subjects in the control group had perforated tympanic membranes and hearing loss, and 2 patients in the PCOS group had hearing threshold greater than 20 dB, so they were dismissed from the study. The number of valid OAEs and the achieved power of statistical analysis in patient and control group are presented in Tables 1 and 2. T1 T2

All groups are compared based on left, right sides, and mean value of both ears. A comparison of DPOAE levels at all 10 frequencies between patient and control groups revealed no significant difference ($p > 0.05$). We found no significant side difference in emission levels ($p > 0.05$). In both groups, suppression or enhancement of emission levels was observed as a result of contralateral acoustic stimulation (the medial olivocochlear reflex). Intergroup comparison of the medial olivocochlear reflex revealed no statistically significant difference. The amplitude values of the DPOAEs are presented in Figures 3 and 4 F3 F4 (left ear of both groups and right ear of both groups, respectively). Achieved power (d: 0,8) of these analysis ranges between 0.83 and 0.86 except for 0.5 Hz (0.5 Hz achieved power; left, 0.73; right, 0.76).

All groups are compared based on left and right sides and mean value of both ears. A comparison of TEOAE levels at all 4 frequencies between patient and control groups

TABLE 1. *No. of valid otoacoustic emission based on frequency (N1, no. of valid otoacoustic emissions; N2, no. of nonvalid otoacoustic emissions)*

	Patient						Control					
	Left		Right		(Left+ right)/2		Left		Right		(Left+ right)/2	
Distortion product otoacoustic emission (frequency)	N1	N2	N1	N2	N1	N2	N1	N2	N1	N2	N1	N2
0.5	22	10	23	9	28	4	15	6	16	5	17	4
1	30	2	31	1	31	1	19	2	19	2	20	1
2	32	0	32	0	32	0	20	1	21	0	21	0
2.5	32	0	32	0	32	0	20	1	20	0	20	1
3	32	0	32	0	32	0	20	1	21	0	21	0
4	32	0	32	0	32	0	21	0	21	0	21	0
5	32	0	32	0	32	0	21	0	21	0	21	0
6	32	0	32	0	32	0	20	1	21	0	21	0
7	32	0	32	0	32	0	21	0	21	0	21	0
8	30	2	32	0	31	1	21	0	21	0	21	0

TABLE 2. *No. of valid otoacoustic emission based on frequency (N1, no. of valid otoacoustic emissions; N2, no. of nonvalid otoacoustic emissions)*

	Patient						Control					
	Left		Right		(Left+ right)/2		Left		Right		(Left+ right)/2	
Transiently evoked otoacoustic emission (frequency)	N1	N2	N1	N2	N1	N2	N1	N2	N1	N2	N1	N2
1	30	2	30	2	31	1	20	1	17	4	19	2
2	28	4	29	3	30	2	20	1	20	1	20	1
3	29	3	27	5	29	3	18	3	19	2	20	1
4	20	12	13	19	20	12	10	11	12	9	13	8

revealed no significant difference ($p > 0.05$). We found no significant side difference in emission levels ($p > 0.05$). Intergroup comparisons of medial olivocochlear reflex differences showed no statistically significant results. The amplitude values of the TEOAEs are shown in Figures 5 and 6 (left ear of both groups and right ear of both groups, respectively). Achieved power (d: 0.8) of these analysis ranges between 0.81 and 0.84 except for 4 Hz (4 Hz achieved power; left, 0.62; right, 0.59).

DISCUSSION

The current study investigated the effects of hyperandrogenism on OAEs and the medial olivocochlear reflex by comparing a healthy adult female population with adult PCOS patients. A recent study investigating sex differences in young adults showed that women produce more numerous and stronger spontaneous otoacoustic emissions (SOAEs) and CEOAEs with greater response amplitude than men (19). This study is consistent with other reports of sex differences in SOAE numbers in preterm and full-term neonates (20) and infants and children (21), with female subjects typically showing greater numbers of SOAEs than male subjects. However, the prevalence, numbers, and amplitudes of SOAEs have been shown to decrease from neonates to older children (22). A recent study conducted in sheep showed that female animals administered testosterone prenatally have substantially weaker CEOAE than control animals (23). An interesting study by McFadden et al. showed that CEOAE and DPOAE were slightly weaker in female spotted hyenas, not stronger. They explained this discrepancy, the absence of humanlike sex differences in OAE levels, by the fact that the cochlear amplifiers in female spotted hyenas are weakened by the high levels of androgens to which they are naturally exposed prenatally. When spotted hyenas of both sexes were treated with androgen-blocking agents, more powerful CEOAEs were observed (10).

Two interesting studies have tested hypotheses on the effects of androgens on otoacoustic emissions in adults. Oral contraceptives (OCs) are known to reduce bioavailable testosterone levels (24). McFadden et al. suggested that OC use also might affect OAE production and tested this

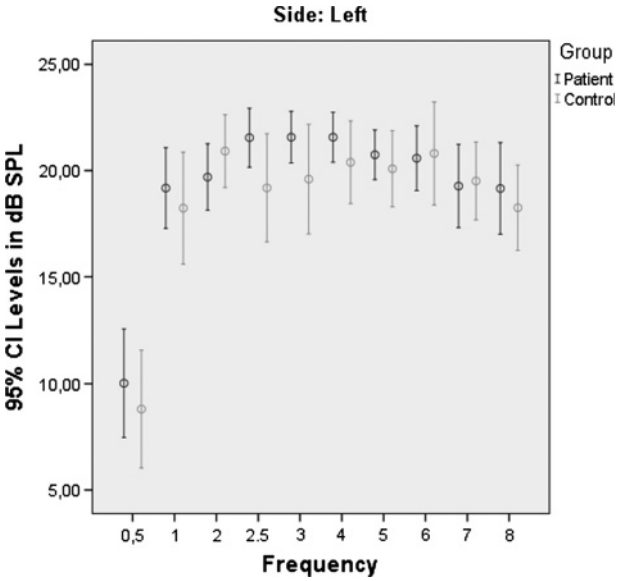

FIG. 3. DPOAEs levels of the left ear of the patient and the control group (first bar of every frequency represents patient group).

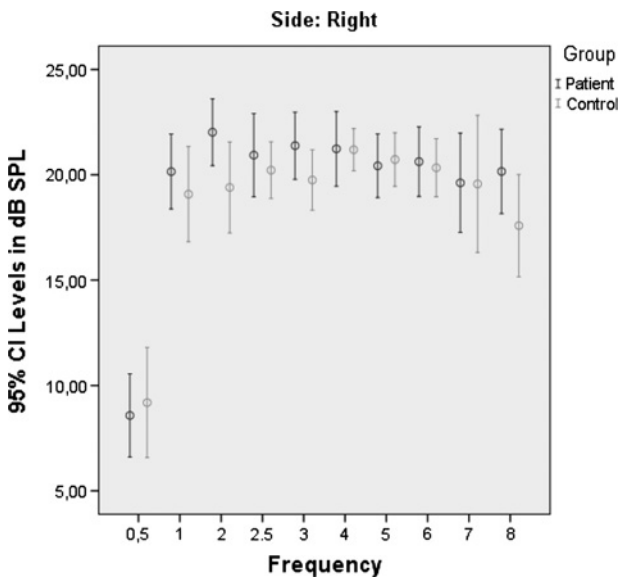

FIG. 4. DPOAEs levels of the right ear of the patient and the control group (first bar of every frequency represents patient group).

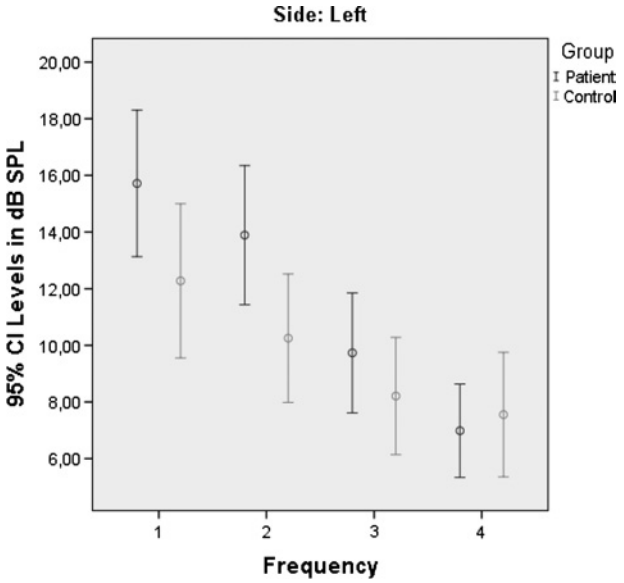

FIG. 5. TEOAEs levels of the left ear of the patient and the control group (first bar of every frequency represents patient group).

hypothesis in a retrospective analysis of SOAE and CEOAE data collected from young women. Modest differences in the means were observed on several OAE measures, but none of these differences were significant (25). Snihur and Hampson (26) demonstrated that women currently using OCs showed a defeminized pattern of OAE production: they produced fewer SOAEs, SOAEs with significantly less power, and smaller CEOAE response amplitudes, compared with naturally cycling women who were tested regardless of the phase of their menstrual cycle. Although most OCs also reduce bioavailable testosterone levels, the authors commented that their results were not explained by low testosterone levels. They proposed that the observed group difference may have been mediated by the interaction of circulating estradiol with estrogen receptor alpha (ERα) or estrogen receptor beta (ERβ) receptors in the cochlea.

Higher otoacoustic emission levels are linked to better hearing. The female advantage in OAEs and hearing might be linked to activation of the medial olivocochlear reflex (8). The main effect of MOC efferents is to inhibit cochlear responses by decreasing the gain of the cochlear amplifier. MOC efferents have been suggested to shift the dynamic range of hearing, reduce masking, protect from acoustic trauma, and aid in selective attention (6). MOC reflex can be assessed with OAEs noninvasively (27). Although studies of the MOC reflex arc and its clinical use in evaluating pathologic states are ongoing, the MOC reflex arc can be abnormal in certain situations, such as vestibular nerve section, tinnitus/hyperacusis, and neuromuscular junction disease (e.g., myasthenia gravis) (28).

Fluctuations in hormone levels during the ovarian cycle might have an impact on the MOC reflex. A recent study involving SOAEs and TEOAEs revealed that MOC suppression changed significantly during the ovarian cycle. The authors stated that the MOC system was involved in modulation of the auditory system during the ovarian cycle, increasing hearing sensitivity around the time of ovulation (29).

An advantage of the right ear has been reported for hearing levels as well as OAE (19). Contrary to the literature, our results showed no such difference between sides. A Brazilian study also reported no such predilection (30).

OAE levels have been found to be higher in female subjects. This difference is presumed to result from prenatal androgen exposure in male subjects. For our study, we investigated whether androgen exposure in adults would result in such a difference. Comparison of DPOAE levels at 0.5, 1, 2, 2.5, 3, 4, 5, 6, 7, and 8 kHz and TEOAE at 1, 2, 3, and 4 kHz frequencies revealed no statistically significant difference between the PCOS and control group. Our suggestion is that the cochlea might be susceptible to effects of androgens only in the prenatal period. The MOC reflex was evaluated in each subject with OAEs by contralateral acoustic stimulation. The MOC reflex is expected to be suppressive when SOAEs are used. Guinan (6) commented that the most important difficulty with using DPOAEs is that the effect can be in either direction and could change greatly with small changes in stimulus parameters, thereby making a single measurement difficult to interpret. As stated, activation of the MOC system can result in either enhancement of OAEs (31) or suppression of OAEs (32). In our study group, activation of the MOC reflex with DPOAEs revealed suppression and enhancement. In our study, a comparison of MOC reflex activity with DPOAEs (amplitude difference in the otoacoustic emissions response with and without contralateral acoustic

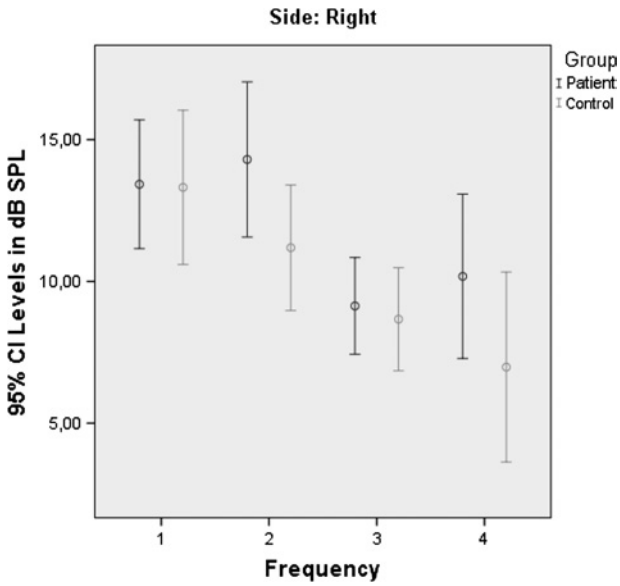

FIG. 6. TEOAEs levels of the right ear of patient and the control group (first bar of every frequency represents patient group).

stimulation) between the PCOS and the control group revealed no statistically significant differences among the 10 frequencies tested ($p > 0.05$). Contrary to some literature reports (6), in our study group, activation of the MOC reflex with TEOAEs also revealed suppression and enhancement. Only 1 report has demonstrated such results (29). In our study, a comparison of the MOC reflex activity with TEOAEs (amplitude difference of the otoacoustic emission response with and without contralateral acoustic stimulation) between the PCOS and control groups revealed no statistically significant differences among the 4 frequencies tested ($p > 0.05$).

Our study has certain limitations. Although the initial sample size was sufficiently large (effect size d, 0.8; achieved power, 0.99) after applying the criteria for audiologic parameters, our results might have suffered from a Type 2 error. Indeed, ovarian cycle seemed to affect OAE levels in MOC reflex amplitude (28). In our study, we did not conduct the audiologic evaluations on the same ovulatory day for each subject. Comparison of OAE levels and MOC reflex amplitude on different days of the ovulatory cycle might have revealed different results. Another limitation we faced is the use of the MOC reflex to assess the status of a disease. To permit clinical use of contralateral acoustic stimulation as a test of the human MOC efferent system, further data must be collected to determine the range of normal and expected results for different disorders.

CONCLUSION

We evaluated the effects of hyperandrogenism on OAEs and the MOC reflex in female adults. We did not find any effect of androgen excess on OAEs and the MOC reflex in female adults. To our knowledge, this is the first report of the effects of hyperandrogenism on OAEs and the MOC reflex in a female adult population.

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