Published in final edited form as:
Gynecol Endocrinol. 2013 June ; 29(6): 551–555. doi:10.3109/09513590.2013.788634.

Cigarette smoking, nicotine levels and increased risk for metabolic syndrome in women with polycystic ovary syndrome

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Abstract

Women with polycystic ovary syndrome (PCOS) are at risk for metabolic syndrome, which may be exacerbated by smoking. We hypothesized that smoking worsens androgen levels and the metabolic profile in women with PCOS. PCOS smokers (n = 47) and non-smokers (n = 64) and control smokers (n = 30) and non-smokers (n = 28), aged 18–45 years, underwent anthropomorphic measurements, pelvic ultrasound and blood sampling. Smokers had higher cotinine (801 ± 83 versus <11 nmol/L; smokers versus non-smokers, respectively; $p < 0.001$) and nicotine levels (37 ± 4 versus <12 μmol/L; $p < 0.001$). Triglyceride levels were higher in women with PCOS who smoked compared to non-smokers (1.55 ± 0.18 versus 0.95 ± 0.08 mmol/L; $p < 0.001$), even when adjusted for BMI. Metabolic syndrome was more common in smokers with PCOS compared to non-smokers with PCOS and smokers who were controls (28.6 versus 3.6%; $p = 0.02$). There were no differences in reproductive parameters including androgen levels. Cotinine ($r = 0.3$; $p < 0.001$) and nicotine levels ($r = 0.2$; $p = 0.005$) correlated with triglycerides. Nicotine levels also correlated with pulse rate ($r = 0.2$; $p = 0.02$) and waist:hip ratio (WHR; $r = 0.2$; $p = 0.02$). Taken together, smoking may worsen the already high risk for metabolic syndrome in women with PCOS.

Keywords

Cotinine; hyperandrogenism; insulin resistance; testosterone; triglycerides

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age, affecting 5% to 7% [1]. It is characterized by irregular menstrual cycles, hyperandrogenism and polycystic ovary morphology [2]. In addition, women with this disorder have a predisposition for obesity and insulin resistance with increased risk of type 2 diabetes, metabolic syndrome and other cardiovascular risk factors [2–6]. Therefore, modifying any adverse lifestyle factor is critical [7].

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Declaration of interest
The authors report no declarations of interest.

While smoking rates have decreased overall in the United States, rates have not changed much recently among reproductive age women [8], and smoking effects may be particularly devastating for reproductive-aged women with PCOS. Smoking not only increases cardiovascular risk, it may have adverse effects on cholesterol levels and reproductive hormones. Smokers have higher levels of serum cholesterol, triglycerides, very low density lipoproteins (VLDL) and low density lipoproteins (LDL) and lower levels of high density lipoproteins (HDL) than non-smokers [9]. Studies suggest that nicotine and smoking can decrease estrogen levels by inhibiting aromatase activity [10]. Other studies demonstrate higher androgen levels in reproductive age women who smoke [11]. Therefore, smoking has the potential to increase both metabolic syndrome and hyperandrogenism in women with PCOS.

We hypothesized that smoking would increase cholesterol levels and hyperandrogenism in women and that these effects would be more pronounced in women with PCOS than in controls who smoked. To test the hypothesis, reproductive, metabolic and anthropomorphic parameters were examined in smokers and non-smokers with PCOS and controls. These parameters were also examined in association with nicotine and cotinine levels.

Materials and methods

Subjects

All subjects were women between the ages of 18 and 45 years. Subjects were a subset of those who had participated in a previous study [12]. There were fewer subjects who smoked in the control group, making the control group slightly smaller. Subjects with PCOS (smokers: $n = 47$; passive smokers: $n = 8$; non-smokers: $n = 64$) had oligomenorrhea (<9 menstrual periods/yr) and clinical and/or biochemical evidence of hyperandrogenism, fulfilling the NIH criteria [12,13]. Clinical hyperandrogenism was defined by: 1) an elevated Ferriman–Gallwey score >9 or 2) acne on the face or back. Biochemical hyperandrogenism was defined as testosterone >63 ng/dL (2.2 nmol/L), DHEAS >430 μg/dL (11.6 μmol/L) or androstenedione levels >3.8 ng/dL (13.3 nmol/L) [12]. Control subjects (smokers: $n = 30$; passive smokers: $n = 4$; non-smokers: $n = 28$) had regular menstrual cycles, 21 to 35 days, and no clinical or biochemical hyperandrogenism. All subjects had normal thyroid function and prolactin levels, a follicular phase FSH level in the premenopausal range, and subjects with late-onset congenital adrenal hyperplasia were excluded as previously described [12]. Subjects were on no hormonal medication except for stable thyroid hormone replacement.

Protocol

The study was approved by the Institutional Review Board of the Massachusetts General Hospital, and all subjects provided written informed consent. Study procedures were described previously [12]. Subjects underwent a detailed history; physical exam including measurement of waist circumference at the umbilicus and hip circumference at the widest diameter; a pelvic ultrasound (ATL HDI 1500, 5MHz convex array transducer); and fasting blood samples for lipid, glucose, insulin, gonadotropin, sex-steroid, cotinine and nicotine levels were measured. An oral glucose tolerance test was performed with blood sampling 2 hours after a 75 gm glucose load. Nicotine and cotinine were assayed using liquid

chromatography-tandem mass spectrometry (Mayo Medical Laboratory, Rochester, MN). The other assays used are previously described [12].

Classification of subjects

All subjects were classified as active or passive smokers or non-smokers based on their self-reported smoking status, cotinine and nicotine levels. Active smokers were subjects who smoked at least one cigarette in the previous 5 days and had a cotinine level greater than 85 nmol/L or nicotine level greater than 12 μmol/L. Passive smokers were regularly exposed to second-hand smoke and had detectable cotinine levels less than 85 μmol/L [14]. Of note, cotinine is a nicotine metabolite present at 10 times the nicotine level and with a longer half-life [15]. Therefore, nicotine levels were not used to identify passive smokers as it is difficult to detect in passive smokers. Non-smokers were subjects who never smoked, had no regular exposure to second-hand smoke in the previous 6 months and had undetectable serum cotinine and nicotine levels. Women who had stopped smoking for at least 2 years and who had undetectable serum cotinine and nicotine levels were classified as non-smokers, based on epidemiologic evidence that many reproductive abnormalities are normal in former smokers [16]. Metabolic syndrome was defined using the ATP III criteria when three out of the five following criteria are present: waist circumference >88 cm, triglycerides ≥150 mg/dL, HDL <50 mg/dL, blood pressure ≥135/≥85mm Hg and fasting glucose ≥110 mg/dL [17].

Statistical Analysis

Hormone levels were log transformed for analysis. Comparisons between PCOS, controls and smoking status were made using two-way ANOVA or chi square as appropriate. Multiple linear regression was subsequently used to control for the effects of age and BMI. Based on the small number of passive smokers in the PCOS and control groups, the passive smokers were not included in the two-way ANOVA or chi-square analyses, but were included in the correlation analyses. However, the complete data analysis is presented in the Supplementary Data (Supplementary Table 1). The relationship between cotinine and nicotine levels and measured parameters were examined using Spearman correlations. A p value <0.05 was considered significant.

Results

The anticipated differences between the PCOS cases and controls were present (Table 1). Weight, BMI, pulse, waist and hip circumference and the waist:hip ratio (WHR), Ferriman–Gallwey score, testosterone, androstenedione, 17OH progesterone, LH, LH:FSH ratio, triglycerides, HbA1C, 2-hour glucose, fasting and 2-hour insulin levels, HOMA, ovarian volume and follicle number were higher in women with PCOS than in controls. However, the relationship between PCOS status and waist circumference, HOMA and fasting insulin were no longer significant when controlled for BMI. Sex hormone binding globulin (SHBG) and HDL levels were lower in women with PCOS than in controls, even after correcting for age and BMI.

Cotinine and nicotine levels were higher in smokers (846 ± 85 and 45 ± 5) than in passive smokers (36 ± 5 and 14 ± 1.2) and non-smokers (<11 and <12), by definition (all $p < 0.001$; Table 1). WHR was higher in smokers compared to non-smokers ($p = 0.02$), but was no longer significant when controlled for BMI and age. Triglyceride levels were higher in women with PCOS who smoked compared to control smokers and women with PCOS who were non-smokers, and the effect of smoking remained significant when controlled for BMI and age ($p = 0.02$). HbA1C was higher in smokers than in non-smokers with both PCOS and controls, but the effect was no longer significant when controlled for BMI and age ($p = 0.1$). There were no differences in sex steroids, gonadotropin levels or ovarian parameters between smokers and non-smokers, even after adjusting for age and BMI.

The rate of metabolic syndrome was higher in women with PCOS than in controls (14.7 versus 3.4%; $p = 0.03$). The prevalence of metabolic syndrome was also higher in smokers compared to non-smokers, overall (17.5 versus 6.3%; $p = 0.04$). However, the rate of metabolic syndrome was higher in women with PCOS who smoked than controls who smoked (28.6 versus 3.6%; $p = 0.02$). The rates of metabolic syndrome were not controlled for age and BMI as the definition is dependent on waist circumference, which is highly linked to BMI.

Triglyceride levels correlated with cotinine and nicotine levels (Table 2). There was also a correlation between nicotine levels and pulse rate and nicotine levels and WHR.

Discussion

Women with PCOS have an increased risk of diabetes, metabolic syndrome and other cardiovascular risk factors [2–5]. Smoking is not only a cardiovascular risk factor, but appears to exacerbate the components of metabolic syndrome. Smoking was associated with higher triglyceride levels in women with PCOS. Further, cotinine and/or nicotine levels correlated with triglyceride levels, pulse rate and WHR. Finally, smokers, particularly those with PCOS, had the highest rate of metabolic syndrome. However, there was no difference in androgen levels in smokers. Thus, smoking exacerbates the already increased risk of metabolic syndrome in women with PCOS and the effect is independent of changes in androgen levels.

The data expand evidence demonstrating an association between smoking and metabolic risk factors to women with PCOS. A meta-analysis of epidemiological studies in smokers demonstrated a dose–response relationship between smoke exposure and higher total cholesterol, triglyceride and LDL levels and lower HDL levels [9]. Similarly, the current study demonstrated a correlation between both nicotine and cotinine and triglyceride levels, supporting the possibility that a direct relationship exists between cigarette smoking and lipid levels. The mechanism for increased triglyceride levels in smokers has been demonstrated to involve decreased skeletal muscle lipoprotein lipase activity, which may be affected by insulin resistance [18,19], and smaller LDL particle size, which favors triglyceride production [20]. Higher triglycerides were not demonstrated in control smokers compared to non-smokers, perhaps because of smaller numbers than in epidemiological

studies and less variation in triglyceride levels in women controls compared to those with PCOS.

Despite demonstrating higher triglyceride levels, the current study did not demonstrate greater insulin resistance in smokers. However, the evaluation using only fasting glucose and insulin may not have been sufficiently sensitive. Insulin resistance was demonstrated in male smokers using a euglycemic hyperinsulinemic clamp [18]. Further, a previous study demonstrated higher fasting insulin levels in smokers with PCOS compared to nonsmokers [21]. There was a correlation between nicotine levels and WHR in the current study as has been demonstrated in large, epidemiological studies [22]. The higher WHR and BMI may contribute to insulin resistance seen in smokers [18,21]. Finally, there was a relationship between smoking and higher HbA1C in the current study, similar to findings in diabetic smokers who had higher fasting glucose levels [23], although the relationship was not independent of BMI.

The current study demonstrated a relationship between nicotine levels and pulse rate. It is likely that increased sympathetic activity accounts for these findings [24]. Interestingly, the same relationship was not demonstrated with cotinine levels, likely because nicotine levels more immediately reflect cigarette smoke exposure [14].

Although women with PCOS were hyperandrogenic with elevated levels of testosterone and lower levels of SHBG, there were no associations between smoking status and increased androgen levels. One previous study demonstrated a higher free androgen index in women with PCOS who smoked compared to those who did not [21]. It is likely that the different definitions of PCOS used in the two studies account for the differences in testosterone findings, because the previous study used the Rotterdam criteria to define PCOS, and there was a trend toward higher BMI and greater hirsutism in the smoking compared to the non-smoking group. In contrast, the current study used the NIH criteria for PCOS, resulting in a comparison of women with higher androgen levels at baseline in both the smoking and non-smoking groups, and thus less difference between smokers and non-smokers [2,13].

The current study had the advantage that nicotine and cotinine levels were directly measured. Therefore, there was improved accuracy in classifying smoking status, which can be inaccurate by history. Further, the relationships between cotinine and nicotine levels and metabolic parameters could be determined because they were measured as continuous variables. The study was limited by small numbers, particularly in the passive smoking group, although significant relationships were demonstrated despite the small sample size.

The data demonstrate that smokers with PCOS had higher triglyceride levels than non-smokers and control women. Women with PCOS also have higher rates of metabolic syndrome, including higher triglyceride levels, larger waist circumference and lower HDL levels compared to controls, and smoking was associated with even higher rates of metabolic syndrome. There was no relationship between smoking and androgen levels. Thus, smoking worsens the already high risk for metabolic syndrome in women with PCOS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial Support: This work was supported by the National Institutes of Health 1R01HD065029 (CKW), ADA 1-10-CT-57 (CKW), 1 UL1 RR025758 Harvard Clinical and Translational Science Center, M01-RR-01066 from the National Center for Research Resources and the Flight Attendant Medical Research Institute.

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Table 1

Hormone and anthropomorphic parameters in women with PCOS and controls.

	PCOS			Control					
	All PCOS	**Smokers (*n* = 47)**	**Non-Smokers (*n* = 64)**	**All Control**	**Smokers (*n* = 30)**	**Non-smokers (*n* = 28)**	**PCOS versus controls *p* value**	**Smoking status *p* value**	**Interaction PCOS and smoking *p* value**
Age (yrs)	**27.4 ± 0.6**[*]	27.9 ± 0.9	27.0 ± 0.7	**27.6 ± 0.8**	27.7 ± 1.0	27.5 ± 1.2	0.8	0.5	0.8
Cotinine (nmol/L)	**329 ± 50**	801 ± 83	11	**477 ± 110**	909 ± 178	11	0.2	<0.001	0.2
Nicotine (μmol/L)	**22 ± 2**	37 ± 4	12	**35 ± 6**	46 ± 9	12	0.3	<0.001	0.3
Height (cm)	**1.64 ± 0.01**	1.65 ± 0.01	1.64 ± 0.01	**1.65 ± 0.01**	1.65 ± 0.01	1.64 ± 0.01	0.4	0.4	0.9
Weight (kg)	**83.0 ± 2.2**	87.6 ± 3.8	79.9 ± 2.5	**70.3 ± 2.5**	73.3 ± 4.1	67.1 ± 2.9	<0.001	0.08	0.9
BMI (kg/m^2)	**30.9 ± 0.8**	32.2 ± 1.3	30.0 ± 1.0	**25.8 ± 0.8**	26.7 ± 1.4	24.8 ± 0.9	<0.001	0.1	0.8
Systolic blood pressure (mm Hg)	**114 ± 1**	116 ± 2	113 ± 2	**111 ± 2**	112 ± 2	110 ± 1	0.2	0.2	0.8
Diastolic blood pressure (mm Hg)	**70 ± 1**	71 ± 2	69 ± 1	**71 ± 1**	73 ± 2	69 ± 2	0.6	0.06	0.6
Pulse	**74.9 ± 1.0**	74.0 ± 1.4	75.4 ± 1.3	**69.4 ± 1.2**	70.9 ± 1.6	67.7 ± 1.8	<0.01	0.5	0.1
Waist circumference (cm)	**98.2 ± 1.8**	101.1 ± 2.9	96.0 ± 2.2	**86.1 ± 2.4**	89.5 ± 4.0	82.5 ± 2.3	<0.001	0.06	0.8
Hip circumference (cm)	**108.7 ± 1.4**	111.0 ± 2.3	107.0 ± 1.7	**102.0 ± 1.7**	103.4 ± 2.8	100.5 ± 0.8	0.03	0.2	0.8
Waist:hip ratio	**0.90 ± 0.01**	0.91 ± 0.01	0.89 ± 0.01	**0.84 ± 0.01**	0.86 ± 0.02	0.82 ± 0.01	<0.001	0.04	0.4
Ferriman–Gallwey score	**14 ± 1**	15 ± 1	13 ± 1	**4 ± 0.5**	4 ± 1	4 ± 1	<0.001	0.8	0.2
Testosterone (nmol/L)	**2.30 ± 0.13**	2.50 ± 0.26	2.17 ± 0.14	**1.47 ± 0.10**	1.54 ± 0.14	1.38 ± 0.15	<0.001	0.2	0.3
Androstenedione (nmol/L)	**13.2 ± 0.5**	13.8 ± 0.8	12.7 ± 0.6	**11.3 ± 1.0**	11.5 ± 1.2	11.0 ± 1.6	0.02	0.2	0.9
SHBG (nmol/L)	**37.5 ± 2.1**	34.7 ± 2.6	39.5 ± 3.2	**61.5 ± 4.0**	63.5 ± 6.3	59.2 ± 4.8	<0.001	0.8	0.6
DHEAS (nmol/L)	**5.6 ± 0.3**	5.6 ± 0.5	5.7 ± 0.4	**6.1 ± 0.4**	6.2 ± 0.6	6.0 ± 0.6	0.4	0.6	0.9
17OH progesterone (nmol/L)	**4.44 ± 0.24**	5.02 ± 0.45	3.96 ± 0.21	**2.80 ± 0.24**	2.75 ± 0.33	2.87 ± 0.36	<0.001	0.5	0.2
LH (IU/L)	**25.5 ± 1.5**	26.0 ± 2.5	25.0 ± 1.9	**17.9 ± 2.6**	18.8 ± 3.8	17.0 ± 3.6	<0.001	0.6	0.9
FSH (IU/L)	**9.7 ± 0.3**	9.5 ± 0.5	9.9 ± 0.4	**11.2 ± 1.1**	10.2 ± 0.6	12.3 ± 2.2	0.1	0.4	0.8
LH:FSH ratio	**2.6 ± 0.1**	2.7 ± 0.2	2.5 ± 0.2	**1.6 ± 0.2**	1.8 ± 0.2	1.5 ± 0.2	<0.001	0.2	0.7
Cholesterol (mmol/L)	**4.70 ± 0.10**	4.77 ± 0.16	4.66 ± 0.12	**4.69 ± 0.11**	4.70 ± 0.13	4.69 ± 0.18	1.0	0.5	0.8
Triglycerides (mmol/L)	**1.21 ± 0.09**	1.55 ± 0.18[‡]	0.95 ± 0.08	**0.86 ± 0.06**	0.86 ± 0.07	0.86 ± 0.09	0.002	0.008	0.04[†]
HDL (mmol/L)	**1.37 ± 0.04**	1.33 ± 0.08	1.40 ± 0.05	**1.59 ± 0.04**	1.60 ± 0.06	1.57 ± 0.06	<0.001	0.6	0.1
LDL (mg/dL)	**2.87 ± 0.08**	2.91 ± 0.14	2.84 ± 0.11	**2.65 ± 0.10**	2.67 ± 0.14	2.64 ± 0.14	0.1	0.8	0.8

	PCOS			Control					
	All PCOS	**Smokers (*n* = 47)**	**Non-Smokers (*n* = 64)**	**All Control**	**Smokers (*n* = 30)**	**Non-smokers (*n* = 28)**	**PCOS versus controls *p* value**	**Smoking status *p* value**	**Interaction PCOS and smoking *p* value**
HbA1c (%)	**5.38 ± 0.04**	5.43 ± 0.05	5.39 ± 0.03	**5.20 ± 0.05**	5.29 ± 0.07	5.00 ± 0.10	0.002	0.04‡	0.5
Fasting glucose (mmol/L)	**4.73 ± 0.08**	4.60 ± 0.09	4.81 ± 0.12	**4.57 ± 0.06**	4.63 ± 0.09	4.50 ± 0.07	0.2	0.9	0.2
Glucose 120 min (mmol/L)	**5.56 ± 0.18**	5.40 ± 0.24	5.65 ± 0.24	**4.60 ± 0.20**	4.31 ± 0.24	4.91 ± 0.31	<0.001	0.1	0.5
Fasting insulin (pmol/L)	**80.4 ± 6.5**	91.0 ± 11.8	73.6 ± 7.6	**50.9 ± 11.7**	61.8 ± 22.2	39.6 ± 4.2	<0.001	0.5	0.6
Insulin 120 min (pmol/L)	**476.5 ± 50.1**	489.6 ± 78.5	468.8 ± 65.3	**174.6 ± 20.4**	149.3 ± 24.3	200.0 ± 32.6	<0.001	0.3	0.4
HOMA	**2.67 ± 0.30**	3.14 ± 0.60	2.35 ± 0.28	**1.76 ± 0.45**	2.18 ± 0.89	1.30 ± 0.42	<0.001	0.4	0.7
Maximum ovarian volume (mL)	**15.6 ± 0.6**	16.1 ± 1.1	15.1 ± 0.7	**9.3 ± 0.7**	9.8 ± 1.1	8.8 ± 0.8	<0.001	0.5	0.9
Maximum follicle number	**13.8 ± 0.4**	14.6 ± 0.7	13.3 ± 0.4	**10.0 ± 0.5**	10.0 ± 0.7	9.9 ± 0.8	<0.001	0.3	0.5

*Data are expressed as mean ± SE.

†Triglyceride levels are higher in women with PCOS who smoke than in control smokers and PCOS non-smokers.

‡The relationship between smoking and HbA1C was no longer significant when controlled for BMI

Table 2

Correlation of cotinine and nicotine with triglycerides and anthropometric measurements.

	Correlation coefficient (r)	*p* Value
Cotinine and Triglycerides	0.30	<0.001
Nicotine and Triglycerides	0.23	0.005
Nicotine and Resting Pulse Rate	0.18	0.02
Nicotine and WHR	0.16	0.03