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Sterol regulatory element binding protein-1 *(SREBP1)* gene expression is similarly increased in polycystic ovary syndrome and endometrial cancer

Running Head: *SREBP1* in PCOS and endometrial cancer

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Abstract

Introduction: Women with polycystic ovary syndrome (PCOS) have a 3-fold higher risk of endometrial cancer (EC). Insulin resistance and hyperlipidaemia may be pertinent factors in the pathogenesis of both conditions. The aim of this study was to investigate endometrial Sterol Regulatory Element Binding Protein-1 gene *(SREBP1)* expression in PCOS and EC endometrium, and to correlate endometrial *SREBP1* expression with serum lipid profiles. *Material and methods:* A cross-sectional study was performed at Nottingham University Hospital, United Kingdom. A total of 102 women (PCOS, EC and controls; 34 participants in each group) were recruited. Clinical and biochemical assessments were performed before endometrial biopsies were obtained from all participants. Taqman real-time PCR for endometrial *SREBP1* and its systemic protein expression were analysed. *Results:* The BMI of women with PCOS (29.28 (±2.91) kg/m^2) and controls (28.58 (±2.62) kg/m^2) was not significantly different. Women with EC had a higher mean BMI (32.22 (±5.70) kg/m^2). *SREBP1* gene expression was significantly increased in PCOS and EC endometrium compared to controls ($p<0.0001$). *SREBP1* gene expression was positively correlated with BMI ($r=0.017$, $p=0.921$) and waist-hip ratio ($r=0.023$, $p=0.544$) in PCOS, but this was not statistically significant. Similarly, statistically insignificant positive correlations were found between endometrial *SREBP1* gene expression and BMI in EC ($r=0.643$, $p=0.06$) and waist-hip ratio ($r=0.096$, $p=0.073$). *SREBP1* expression was significantly positively correlated with triglyceride in both PCOS and EC ($p= 0.028$ and $p=0.027$). Quantitative serum SREBP1 correlated with endometrial gene expression ($p<0.05$). *Conclusions: SREBP1* gene expression is significantly increased in the endometrium of PCOS and EC women compared with controls and positively correlates with serum triglyceride in both PCOS and EC.

Keywords

Endometrial cancer, PCOS*, SREBP1*, Regulatory Element Binding Protein-1,

Key Message

Women with PCOS are at a higher risk of developing endometrial cancer, due to increased endometrial lipogenesis, resulting from increased *SREBP1* expression.

List of abbreviations

ACTB: beta actin gene

BMI: body mass index

EC: endometrial cancer

FSH: Follicle stimulating hormone

G1: Grade 1 (well differentiated)

G2: Grade 2 (moderately differentiated)

G3: Grade 3 (poorly differentiated)

HDL: high density lipoprotein

HOMA-IR: homeostatic model assessment of insulin resistance

IGF1: insulin-like growth factor-1

IGFBP1: insulin-like growth factor binding protein 1

PTEN phosphatase and tensin homolog

LH: leutinizing hormone

PCOS: polycystic ovary syndrome

SREBP1: sterol regulatory element binding protein-1gene

WHR: waist-hip ratio

Introduction

Polycystic ovary syndrome (PCOS) is a complex hormonal and metabolic disorder that affects women of reproductive age. It is estimated that about 5-10% (1) of women of reproductive age, are diagnosed with this condition. Other than being associated with a poor fertility outcome and an increased risk of cardiovascular disease, PCOS has also been associated with an increased risk of endometrial cancer (EC). Women with PCOS have a 3 to

4 fold increased risk of EC compared with women without PCOS, the large majority of which being type 1 EC (2,3). The exact molecular mechanisms linking PCOS and EC remain unclear (4), however similar clinical and metabolic mechanisms appear to be involved in the pathogenesis of PCOS and EC. These include obesity, unopposed estrogen, hyperandrogenism and hyperinsulinaemia (5). Recent studies linking aberrant regulation of intracellular lipogenesis in EC, (6) through up-regulation of Sterol Regulatory Element Binding Protein-1 *(SREBP1)*, suggest that this pathway might also play a role in modulating the risk of EC in women with PCOS. There have however been no previous studies investigating endometrial expression of *SREBP1* in women with PCOS.

SREBP is a gene that regulates lipogenesis. Its expression is regulated by the insulin and sterol levels in the cell. In mammalian cells, three isoforms of *SREBP* have been identified, namely *SREBP1a, SREBP1c* and *SREBP2*. Although there is some overlap in their function and pathways, studies have shown that *SREBP1* plays a role in fatty acid synthesis and metabolism, whereas *SREBP2* is involved in cholesterol regulation (7,8). A recent study revealed that the expression of Silent Information Regulator-1 (*SIRT1*) and *SREBP1* were up-regulated in the endometrium of EC women compared to normal endometrium (9). This *de novo* lipogenesis is known to be pathognomonic in cancer cell growth (10). Interestingly, the role of *SREBP1* is not only confined to lipid synthesis but this gene has also been found to activate the Phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) pathway, which synergistically promotes cell proliferation and growth (11). Prior to commencing the recruitment for our study, we identified one published study investigating *SREBP1a* and *SREBP 1c* genetic variation in blood from women with PCOS, which found no association (12). There had however, been no study investigating endometrial *SREBP1* expression in PCOS and clinical or biochemical correlations with its endometrial expression. Our study therefore aimed to investigate the association between PCOS and EC by measuring endometrial *SREBP1* gene expression in PCOS and EC women compared with controls. We also evaluated clinical and biochemical correlations with endometrial *SREBP1* gene expression levels. This was considered an important additional building block to increase our understanding of the complex web of molecular interactions that increase EC risk in women with PCOS. Understanding these interactions could also justify the facilitation of EC prevention strategies by suppression of lipid synthesis in women with PCOS.

Material and methods

A cross sectional study was performed at Nottingham University Hospital, in the UK following Research Ethics (institutional review board) approval from the National Research Ethics Service, East Midlands-Northampton committee (13/EM/0119). Part of this project investigating the insulin signaling pathways has been published (13).

As published (13), a total of 102 participants were recruited into three groups (women with PCOS, women with EC and controls) with 34 participants, in each group. Women with PCOS were diagnosed using the Rotterdam criteria (14) and aged between 18 to 45 years. In the EC group, the endometrial histology results confirmed endometroid adenocarcinoma (type 1), before they were recruited in this study. Women with any evidence of metachronous/ synchronous tumour and/ or previous chemo/ radiotherapy were excluded prior to recruitment. The control group consisted of women without PCOS and without EC who were scheduled for elective gynecological or a pelvic surgical procedure for benign (non-malignant) indications.

Participants were assessed clinically with measurements taken of their blood pressures, weight (kilograms), height (metres), body mass index (BMI), and waist-hip circumference. Hormonal and biochemical profiles (testosterone, sex hormone binding globulin (SHBG), follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, thyroid hormones, fasting blood sugar, high density lipoprotein (HDL), low density lipoprotein (LDL) and triglycerides) were measured following a venipuncture. Endometrial tissue biopsy for PCOS group was obtained using a Pipelle® endometrial catheter for histology and gene expression analysis. The samples were snap frozen in liquid nitrogen at minus 80 degrees Celsius and stored in freezer at minus 160 degrees Celsius until analysis. For the EC tissue sampling, the whole surgical specimen following hysterectomy was transferred to the histology pathology laboratory immediately, where a designated pathologist performed a gross examination of the specimen. The uterus was bisected and endometrial surface inspected. Following that, a small cut of the endometrial tissue (0.5x0.5cm) was performed and the sample was handed to the researcher in a 1.5 ml tube. The tube was immersed in liquid nitrogen at minus 80 degrees Celsius. The sample was then transported to the laboratory for storage in a freezer at minus 160 degrees Celsius until future analysis.

The control group consisted of women who were identified and recruited from the outpatient gynecology clinics, at Queen's Medical Centre, Nottingham. They were diagnosed with benign gynecology disorders (for example uterine fibroids, ovarian cysts or were scheduled for bilateral tubal ligation for contraception), and endometrial samples were obtained during the planned operative procedure following their consent. Prior to surgery, venepunctures, for endocrine and biochemical assays were also performed.

The Cobas 8000® System by Roche (West Sussex, UK) was used for the measurement of fasting blood sugar level and lipid profiles. For hormonal analysis (FSH, LH and testosterone), an immunoassay method was used using the Architect 12000SR® equipment by Abbott (Chicago, USA). Various verification methods which included precision, accuracy, linearity and method comparison studies were performed to ensure validity of the results.

The tissue samples obtained during the operative procedures were fixed in 10% buffered formalin. Then, the tissues were cut into thin sections. The sections were later paraffin-embedded after graded ethanol dehydration process and paraffin infiltration. Thin tissue sections ranging between 3 to 10 microns in thickness were cut from the paraffin block using a microtome. The slices of tissue sections were then stained with hematoxylin and eosin (H&E), and mounted on a glass slide. The slices were covered with a thin glass cover to seal the preparation. The sections were examined using a Carl Zeiss light microscope (Oberkochen, Germany).

The QIA shredder kit, Qiagen® (Hilden, Germany) was used for endometrial tissue disruption and homogenization, for RNA extraction. Following that, the RNA was purified using the QIAamp Mini-kit, Qiagen® (Hilden, Germany). The Superscript® III First-Strand Synthesis System, Invitrogen ^{TM} (California, USA) was utilized for reverse transcription process (13). Real-time q-PCR was performed using Taqman® qPCR Gene Expression Master Mix (Life Technologies) (California, USA) as described in our previous publication (13). The life cycler 480® (California, USA) machine was used to perform the q-PCR analysis. Beta-actin (*ACTB*) was selected as a housekeeping gene (13) to normalize differences in the quantity of RNA in each sample in comparison to the gene of interest (*SREBP1)*. To ensure a high degree of precision, every sample was made in triplicate. The ratio of gene expression was calculated using this formula, (E target) $^{\Delta Ct\ target\ (control\text{-}treated)}$/ (E ref) $^{\Delta Ct\ ref\ (control\text{-}treated)}$

Statistical analyses

GraphPad Prism 6® (GraphPad Software, San Diego, CA, USA) and SPSS version 21 (IBM Corp., Armonk, NY, USA) were used for statistical calculation. The normality test was checked using the Shapiro normality test. A one-Way-ANOVA test or independent T-test was performed to compare demographic data for any statistically significant differences between the groups. Confounding factors (e.g. age and weight) were adjusted to ensure a reliable correlation test. Means ± standard deviations were used to summarize normally distributed continuous variables, whilst medians ± range, were used for variables that were not normally distributed. The Spearman correlation coefficient test was used to correlate independent variables. A p-value of less than 0.05 was set as statistical significance.

Results

Participant characteristics

Although the mean BMI of women with PCOS (29.28 (±2.91) kg/m^2) and controls (28.58 (±2.62) kg/m^2) was not significantly different, women with EC had a higher mean BMI (32.22(±5.70) kg/m^2). The mean age for PCOS was however younger (31.8 (±5.97) years) compared to women with EC (63.44 (±10.07) years) and controls (43.68 (±13.12) years). Although PCOS participants were recruited during their proliferative menstrual phase (based on their menstrual history), histologically two women had secretory phase endometrium and eight samples were inadequate. However majority (24 PCOS women) were in the proliferative phase. All EC participants had endometroid adenocarcinoma, with moderately differentiated (G2) most prevalent, 44.1%, followed by poorly differentiated (G3) (29.4%) and well differentiated (G1) (26.5%). The waist-hip ratio (WHR) was positively correlated with insulin resistance (homeostatic model assessment of insulin resistance (HOMA-IR)) with p=0.011, in EC however it was not significant in PCOS (p=0.245) (13).

SREBP1 Expression

The expression of *SREBP1* gene in the endometrium was significantly increased in PCOS and EC women (p<0.0001) compared to controls. Even though in EC the expression was lower compared to PCOS this was not statistically significant (p=0.067) (Figure 1). The Spearman correlation coefficient test was performed to determine the correlation between *SREBP1* expression with clinical and biochemical parameters. *SREBP1* gene expression was positively correlated with BMI in PCOS (r=0.289, p=0.336) and EC (r=0.643, p=0.006) but

this was only statistically significant in EC women. WHR was also not significantly correlated with *SREBP1* expression in PCOS and EC with p=0.544 and p=0.086 respectively. HOMA-IR was significantly correlated with *SREBP1* gene expression in PCOS but not EC.

Correlation between SREBP1 expression and lipid profiles

Apart from HDL cholesterol levels, all serum lipid parameters had a positive correlation with endometrial *SREBP1* gene expression in both PCOS and EC. However, only triglyceride levels were significant correlated with *SREBP1* gene expression in both PCOS and EC ($p<0.05$). Table 1 illustrates these findings.

SREBP1 serum validation using ELISA immunoassay

Serum SREBP1 protein concentration was significantly higher in PCOS compared to controls (p=0.046). Similarly, the protein concentration was higher in EC compared to controls (p=0.008). There was no significant difference in serum SREBP1 protein concentrations between PCOS and EC (p=0.346). Figure 2 illustrates the concentration of *SREBP1* protein in the serum of PCOS and EC compared to controls.

Discussion

This study investigates endometrial *SREBP1* gene expression (a gene that regulates lipid synthesis) in women with EC, PCOS and controls. This gene expression has been shown to be independent of menstrual cycle phase and estrogen levels in circulation (15). We find that endometrial *SREBP1* gene expression is markedly increased in PCOS and EC women compared to endometrium in women without EC and without PCOS. The hypothesis that endometrial *SREBP1* gene expression level is raised in women with PCOS and EC compared to controls is based on the observation that hyperlipidaemia, metabolic syndrome and insulin resistance are pertinent risk factors present in EC and in the majority of women with PCOS (16).

Previous studies have found that *SREBP1* gene is up-regulated and supports cell growth and proliferation in cancer cells (17). *SREBP1* has not only been found to be highly expressed in EC cells and atypical endometrial hyperplasia (18) but also in hepatocellular cancer (19). Knocking down *SREBP1* by shRNA achieved almost complete reduction of colonies in their

clonogenic assays of endometrial tumour and inhibition of this gene leads to cell death and apoptosis (18,20). Increased *SREBP1* gene expression may therefore be associated with an increased risk of EC in PCOS.

As far as we know, our study is the first study that investigates endometrial gene expression of *SREBP1* in PCOS endometrium. A previous study has however investigated genetic variations in *SREBP1* gene obtained from whole blood samples, in a cohort of 153 PCOS women in order to explain different PCOS phenotypes, but did not identify any variations (12).

In our study, although the BMI of women with PCOS and controls are not significantly different, women with EC have a higher mean BMI. A significant positive correlation of *SREBP1* expression to BMI and triglyceride in EC is also present. These findings are consistent with the finding of a 6.25 fold increased risk of EC among obese compared non-obese women (21). A previous study (22) investigating the correlation of WHR (instead of BMI alone), a marker of abdominal fat distribution, with the risk of EC found that after adjusting for BMI, a waist circumference of more than 88 cm was a significant risk of EC. *SREBP1* expression is therefore probably associated with central obesity and insulin resistance as found in PCOS rather than BMI alone. In our study however, although *SREBP1* gene expression is positively correlated with WHR, this correlation is not statistically significant. On the other hand, *SREBP1* gene expression is significantly correlated with triglyceride and insulin resistance (HOMA-IR) in PCOS women. In a study of insulin-like growth factor-1 (*IGF1),* insulin-like growth factor binding protein 1*(IGFBP1)* and phosphatase and tensin homolog *(PTEN)* genes which are involved in the insulin signaling pathway, in endometrial biopsies taken from the women recruited into our study (13), we found that the pattern of over expression of *IGF1, IGFBP1* and *PTEN* also mirrored the over expression of *SREBP1* outlined in this paper. These interactions between fatty acid metabolism, insulin resistance, obesity and EC risk in PCOS clearly require more detailed evaluation.

The indirect effect of *SREBP1* on the *IGF1* pathways and the promotion of cell growth and proliferation is an interesting observation. Experiments on sebaceous cell line models reveal that *IGF1* stimulates the expression of both *SREBP1* protein and lipogenesis (23,24). It is also well documented that *IGF1* is crucial in the development of many cancers and its expression

is related to the cancer grade and poor prognostic outcome (25, 26, 27). Therapeutic strategies to prevent EC risk in PCOS should therefore ideally explore not only *IGF1* but strategies synergistically blocking *SREBP1* receptors as well. However the effect of lipid lowering drugs in PCOS for EC prevention or concurrent use of lipid lowering agents and agents targeting *IGF1* in preventing EC in PCOS has not previously been investigated. This is particularly important, given increasing evidence on the use of insulin sensitizing agent (metformin) to regulate *IGF1* in EC cells (28).

The strengths of our study are in its originality, the rigorous phenotyping of patients and the robust endocrine, metabolic and gene expression experiments. It would have been ideal to possibly explore genome-wide, proteomic and metabolomics expression studies in parallel, to facilitate a more robust pathway analysis of molecules, possibly involved in modulating EC risk in PCOS including the specific role of *SREBP1* in this pathway. This was however not considered feasible in the context of the available resources.

In conclusion, in our study, *SREBP1* gene expression is significantly increased in the endometrium of women PCOS and EC compared with controls, although the BMI of women with PCOS and controls are not significantly different. Women with EC however have a higher mean BMI than women with PCOS and EC. Although this can be interpreted as evidence that elevated *SREBP1* in our study is independent of obesity, an association between *SREBP1* gene expression and BMI, WHR, HOMA-IR, and lipid profiles is present. These interactions between intra-cellular lipogenesis, insulin resistance, obesity and EC risk in PCOS clearly require more detailed evaluation. There may also be a role for using lipid lowering drugs (alone in combination with agents targeting insulin resistance) to prevent EC in women with PCOS. More studies are however required to validate these findings and test these hypotheses.

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Figure legends

Table 1: Spearman correlation coefficient test with *p value <0.05 is significant. PCOS, polycystic ovary syndrome; EC, endometrial cancer; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglyceride; Total Chol, total cholesterol.

Figure 1: Relative *SREBP1* and *ACTB* expression in polycystic ovary syndrome (PCOS) and endometrial cancer (EC) compared to controls.

Figure 2: The concentration of serum SREBP1 in the controls, polycystic ovary syndrome (PCOS) and endometrial cancer (EC).

Groups/ Parameters	PCOS		EC	
	r value	P-value	r value	P-value
LDL	0.79	0.008	0.045	0.855
HDL	-0.143	0.587	0.09	0.705
TG	0.757	0.004*	0.539	0.027*
Total Chol	0.176	0.562	0.196	0.441

Table 1: Spearman correlation coefficient test with *p value <0.05 is significant. LDL: Low density lipoprotein; HDL: High density lipoprotein; TG: Triglyseride; Total Chol: Total cholesterol.

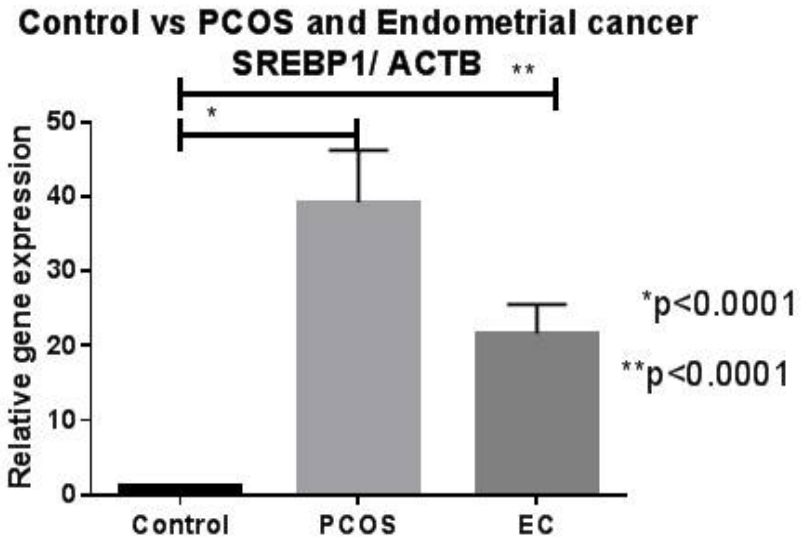

Figure 1: Relative SREBP1 and ACTB gene expression in PCOS and EC vs control

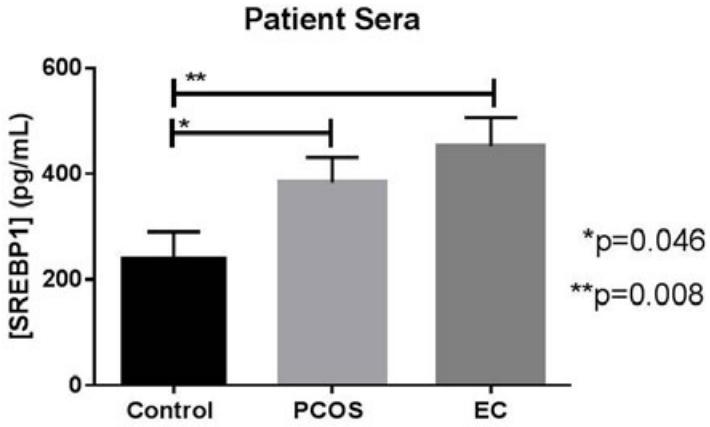

Figure 2: The concentration of serum SREBP1 in controls, PCOS and EC