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REVIEW ARTICLE

Insulin Resistance in Patients with Endometrial Polyps and its Relationship with the Expression of InR, IGF-1R, and IRS in the Endometrium

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Abstract

Objective: This study investigates the insulin resistance status of patients with endometrial polyps (EP) and its relationship with the expression of endometrial insulin receptor (InR), insulin-like growth factor-1 receptor (IGF-1R), and insulin receptor substrate (IRS) to preliminarily explore the potential link between EP and insulin resistance (IR).

Methods: 170 patients who underwent hysteroscopy due to abnormal uterine bleeding or/and ultrasound findings of abnormal intrauterine echoes or space-occupying lesions were divided into Polyp group (endometrial polyps, n = 84) and Control group (normal endometrium, n = 86) based on endometrial pathology results. Clinical data and insulin resistance (IR) related indicators [fasting blood glucose (FG), fasting insulin (FIN), and insulin resistance index (HOMA-IR)] were compared between the two groups. The differences in the expression of InR, IGF-1R, IRS1, and IRS2 in their endometrial tissues were also compared using immunohistochemistry.

Results: In patients with endometrial polyps, FIN and HOMA-IR were significantly elevated compared to the control group, while the incidence of IR was slightly higher, but the difference was not statistically significant. There were no statistically significant differences in the expression of InR, IGF-1R, TRS1, and TRS2 among endometrial polyps, peri-polyp endometrium, and normal endometrium. There were no significant differences in the expression of the four antibodies between the proliferative and secretory phases in the polyp group and the control group respectively. In both the polyp group and the control group, there were no significant differences in the expression of the four antibodies in the endometrium between insulin-resistant patients (IR group) and non-insulin-resistant patients (NIR group).

Conclusion: Patients with endometrial polyps tend to have insulin resistance, but the expression of InR, IGR-1R, IRS1 and IRS2 in the polyp tissue is not significantly different from that in the adjacent endometrium and normal endometrium. The occurrence of endometrial polyps may be related to abnormalities in the post-insulin-receptor signaling pathway, which requires further research to confirm.

Keywords

Endometrial polyps, Insulin resistance, Insulin receptor, Insulin-like growth factor-1 receptor, Insulin receptor substrate

Introduction

Endometrial polyps (EP) are one of the most common benign diseases among women of reproductive age [1]. They can cause abnormal uterine bleeding and infertility, and are prone to recurrence and have a certain tendency to become malignant [2]. The cause of EP is currently unclear, but it may be related to factors such as genetics, estrogen and progesterone receptor dysregulation, cell proliferation/apoptosis imbalance, and immune inflammatory stimulation [3,4]. Current data suggest that patients with obesity, impaired glucose tolerance, diabetes, hyperlipidemia etc. are high-risk groups for EP [5,6]. The core patho-physiological feature of metabolic diseases mentioned above is insulin resistance, therefore insulin resistance plays an important role in the development of EP. Previous studies have suggested that insulin signaling pathway first requires insulin/insulin-like growth

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factor-1 to bind to its corresponding receptor (InR/IGF-1R), and then phosphorylate insulin receptor substrate (IRS) to form a tightly linked trimer. Phosphorylated IRS acts as a docking protein to reactivate a series of proteins containing Src homology domain 2 (SH2), causing corresponding biological effects [7]. Given this, the occurrence of endometrial polyps may be related to abnormalities at key nodes in the insulin signaling pathway. Therefore, this study aims to examine the expression of insulin receptors (InR), insulin-like growth factor-1 receptors (IGF-1R), and insulin receptor substrates (IRS) in the endometrium of EP patients to preliminarily explore the potential link between EP and insulin resistance (IR).

Materials and Methods

Subjects

Clinical data of patients who underwent hysteroscopy at the Department of Obstetrics and Gynecology, Kiangwu Hospital, Macau, from October 2024 to March 2026 were collected.

Inclusion criteria:

1. Patients with indications for hysteroscopy and no contraindications;
2. Endometrial pathology confirmed the diagnosis of normal endometrium or endometrial polyps.

Exclusion criteria:

1. Already diagnosed diabetes or impaired glucose tolerance, hyperlipidemia, or polycystic ovary syndrome;
2. Use of hormonal drugs within the past 3 months;
3. Contraindications to hysteroscopy;
4. Recurrence of endometrial polyps;
5. Pathological examination indicating endometrial hyperplasia, endometrial cancer, submucosal fibroids, or endometritis. Informed consent forms were signed by all included subjects. This study was approved by the ethics committee of hospital (approval number 2024-003).

Serum measurement and IR-related indicators

All patients fasted for more than 8 hours before the operation. Elbow venous blood was collected on the morning of admission. Serum fasting insulin (FIN) levels were measured using a chemiluminescence immunoassay analyzer, and fasting plasma glucose (FPG) was measured using a Toshiba automated biochemical analyzer. Insulin resistance-related indicators were calculated using the formula: a homeostatic model assessment-insulin resistance index (HOMA-IR) [(homeostatic model assessment-insulin resistance) = FINxFPG/22.5] was established to assess the patients' IR status. In this study, the diagnostic criteria for IR were: FIN ≥ 10 mIU/L or HOMA-IR ≥ 2.14.

Histopathological and immunohistochemical analysis

After specimen collected during the hysteroscopic procedure, fixation, dehydration, paraffin embedding, and sectioning of paraffin blocks were performed. HE staining and immunohistochemical staining were conducted.

HE staining and routine morphological observation: Sections were routinely dewaxed, stained with hematoxylin and eosin, dehydrated using a routine gradient of alcohols, cleared with xylene, and mounted with neutral resin for microscopic observation of tissue morphology to determine histological stage.

Immunohistochemical staining methods: The EnVision two-step method with DAB staining was used. The entire process was performed on a fully automated immunoassay system (Ventana Benchmark Ultra). Rabbit anti-human polyclonal antibody InR, rabbit anti-human polyclonal antibody IGF-1R, rabbit anti-human polyclonal antibody IRS-1, and rabbit anti-human monoclonal antibody IRS-2 were purchased from ABCAM Company (USA). Insulin, IGF-1R, TRS1, and TRS2 positive expression were all localized in the cytoplasm.

Result evaluation: The staining scoring criteria of Yu et al. were used as a reference, combining staining intensity and distribution range. Staining intensity was scored as follows: negative staining (0 point), weak staining but stronger than the negative control (1 point), clear staining (2 points), and strong staining (3 points). Distribution range was scored as follows: positive cells < 10% (0 point), 10%-30% (1 point), 31%-60% (2 points), and > 60% (3 points). The two scores are added together: 0-1 point is (-), 2 points is (+), 3-4 points is (++), and 5-6 points is (+++).

Statistical processing

SPSS 22.0 statistical software was used for data statistical analysis. Quantitative data were expressed as mean ± standard deviation ($\bar{x} \pm s$) and analyzed using t-tests or one-way ANOVA. Categorical data were expressed as percentages (%) and analyzed using χ^2 tests. $P < 0.05$ was considered statistically significant.

Results

Comparison of clinical data between two groups

Based on endometrial pathology results, enrolled patients were divided into Polyp group (endometrial polyp patients, n = 84) and Control group (normal endometrium group, n = 86). As table 1 shown, the FIN and HOMA-IR levels were significantly higher in endometrial polyp patients than in the control group, while the incidence of IR was slightly higher, but the difference was not statistically significant. Furthermore, there were no significant differences between the

Table 1: Comparison of clinical data between two groups.

Item	Category	Polyps group (n = 84)	Control group (n = 86)	t/χ^2	P
Age (years)		39.04 ± 8.11	37.95 ± 7.23	0.92	0.36
Gravidity	≤ 1 time ≥ 2 times	38 46	41 45	0.101	0.75
Parity	≤ 1 time ≥ 2 times	59 25	62 24	0.071	0.79
Menstrual cycle	Regular Irregular/Amenorrhea	58 26	68 18	2.22	0.136
High blood pressure (mmHg)	Yes No	4 80	4 82	0.108	0.74
BMI (kg/m^2)		23.03 ± 3.02	21.86 ± 5.41	1.786	0.076
FPG (mmol/L)		5.41 ± 0.84	5.30 ± 0.69	0.936	0.351
FIN (mIU/L)		8.59 ± 2.08	7.37 ± 1.96	12.43	< 0.001
HOMA-IR		2.01 ± 1.44	0.96 ± 0.75	6.33	
IR prevalence (%)		23.8 (20/84)	15.1 (13/86)	2.05	< 0.001 0.15
Endometrial staging	Proliferative phase Secretory phase	45 39	55 31	1.89	0.17

Table 2: Comparison of the expression of four antibodies in the polyp group and control group.

	Polyps group		Control group (n = 33)
	Polyps (n = 52)	Peripolyp endometrium (n = 52)	
InR	2.27 ± 0.56	2.40 ± 0.57	2.15 ± 0.57
IGF-1R	2.25 ± 0.52	2.29 ± 0.61	2.03 ± 0.53
IRS-1	2.25 ± 0.52	2.40 ± 0.53	2.06 ± 0.61
IRS-2	2.23 ± 0.61	2.35 ± 0.59	2.12 ± 0.65

Table 3: Comparison of the expression of four antibodies in polyp group and control group at different endometrial stages.

	Polyps group		Control group	
	Proliferative phase (n = 28)	Secretory phase (n = 24)	Proliferative phase (n = 21)	Secretory phase (n = 12)
InR	2.18 ± 0.55	2.38 ± 0.58	2.14 ± 0.57	2.17 ± 0.58
IGF-1R IRS-1	2.29 ± 0.54 2.14 ± 0.45	2.21 ± 0.51 2.38 ± 0.58	2.05 ± 0.50 2.10 ± 0.54	2.00 ± 0.60 2.00 ± 0.74
IRS-2	2.25 ± 0.52	2.21 ± 0.721	2.10 ± 0.70	2.17 ± 0.58

Table 4: Comparison of the expression of four antibodies in patients with different insulin resistance status in Polyp group and Control group.

	Polyp group		Control group	
	IR group (n = 20)	NIR group (n = 32)	IR group (n = 13)	NIR group (n = 20)
InR	2.25 ± 0.64	2.27 ± 0.52	2.23 ± 0.44	2.10 ± 0.64
IGF-1R	2.30 ± 0.57	2.24 ± 0.50	1.95 ± 0.49	2.10 ± 0.55
IRS-1	2.30 ± 0.57	2.24 ± 0.50	2.08 ± 0.76	2.05 ± 0.51
IRS-2	2.15 ± 0.59	2.27 ± 0.63	2.08 ± 0.76	2.15 ± 0.59

two groups in terms of age, parity, menstrual cycle, hypertension, BMI, FG, and endometrial stage.

Expression of four antibodies and differences between different groups

InR, IGF-1R, TRS1, and TRS2 are expressed in both glandular epithelial cells and stromal cells, with staining occurring in the cytoplasm and cell membrane, while expression is weaker in the interstitium.

Comparison of the expression of four antibodies in the polyp group and control group: The expression of InR, IGF-1R, TRS1 and TRS2 showed no statistically significant differences among endometrial polyps, peripolyp endometrium and normal endometrium (P > 0.05), as detailed in table 2.

Comparison of the expression of four antibodies in polyp group and control group at different endometrial stages: There was no significant difference in the expression of the four antibodies between the polyp group and the control group during the proliferative and secretory phases (P > 0.05). See table 3 for details.

Comparison of the expression of four antibodies in patients with different insulin resistance status

in polyp group and control group: In both Polyp group and Control group, there were no significant differences in the expression of the four antibodies in the endometrium between insulin-resistant patients (IR group) and non-insulin-resistant patients (NIR group). See table 4 for details.

Discussion

Previous epidemiological data and clinical studies have shown that high-risk factors for endometrial polyps include advanced age, menopause, hypertension, overweight or obesity, dyslipidemia, polycystic ovary syndrome (PCOS), impaired glucose tolerance, and diabetes [8]. Most of the factors above are abnormal glucose and lipid metabolism diseases, which are closely related to metabolic syndrome. Our previous research found that patients with endometrial polyps have the following characteristics compared with those with normal endometrium: 1) a higher proportion of irregular menstruation or amenorrhea; 2) a wider waist circumference; 3) higher blood FIN; 4) a higher HOMA-IR index. According to the results of logistic regression analysis, FIN ≧ 10mIU/L, HOMA-IR ≧ 2.14, waist circumference ≧ 80cm, irregular menstrual cycle or amenorrhea are risk factors for endometrial polyps [6]. In this study, it was also found that under similar BMI conditions, the FIN and HOMA-IR of EP patients were significantly higher than those of the control group, while the incidence of IR was slightly higher than that of the control group. The above results remind us that clinicians need to pay attention to the role of IR in the occurrence of EP.

During the natural menstrual cycle, the endometrium undergoes proliferative and secretory phase changes in sequence with the changes in estrogen and progesterone secreted by the ovary, and sheds periodically. During pregnancy, the endometrium undergoes decidual-like changes and receives embryo implantation. The endometrium itself does not have the ability to synthesize glucose, but the above physiological processes all require a large amount of glucose [9]. Endometrial cells exhibit steroid-dependent periodic changes, transporting glucose to the uterine cavity for energy. Therefore, the endometrium is also considered to be insulin-sensitive tissue. Previous studies have shown that insulin receptor (InR) and insulin-like growth factor I/II (IGF-I/II) expression can be seen in normal endometrium in both the proliferative and secretory phases [10]. The peak values of InR and IGF-II occur in the luteal phase, while IGF-I occurs in the follicular phase. IGF-1 in peripheral blood binds to and is activated by its receptor IGF-IR in target organs, playing a role in regulating cell proliferation and differentiation. Endometrial tissue itself can synthesize IGF-1 and its receptor [11]. Studies have shown that the trend of IGF-1 expression in EP tissue is consistent with the trend of IGF-1R expression. Increased IGF-1 expression is closely related to cell proliferation and plays an important role in the pathogenesis of endometrial polyps [12]. Doria et al. [13] found that the imbalance between IGF-1 and its binding proteins and gene polymorphism may be one of the links in the pathogenesis of EP. In this study, InR and IGF-1R were expressed in normal endometrium, but no difference was shown between the proliferative and secretory phases. Furthermore, there was no significant difference in the expression of InR and IGF-1R in polyp tissue and adjacent endometrial tissue at different stages of endometrium, and there was no significant difference compared with normal endometrium either. Given that this study did not select patients according to the sub-stages of the endometrial cycle, it could not show the changing trends of InR and IGF-1R expression with the endometrial cycle, which may be the reason for the difference from other study results.

Although IRS does not possess the activity of kinases or other endogenous enzymes, it can act as an adaptor protein to bind to transmembrane receptors, forming a signal complex that coordinates the transmission of cell signals from the extracellular to the intracellular space, thereby regulating biological processes such as cell growth, metabolism, survival, and proliferation [14]. Currently, six types of IRS have been identified, from IRS-1 to IRS-6. Their distribution shows obvious tissue specificity. IRS-1 and IRS-2 are widely distributed in various human tissues, and their research is the most thorough. Previous studies have suggested that insulin signaling activated by IRS-1 promotes the expression of mitotic kinases in estrogen-induced uterine epithelial cells, thereby promoting cell mitosis [15]. IRS-1 is overactivated in endometrial cancer and dysplasia. The activation of IRS-1 in endometrial cancer is associated with adverse clinicopathological features and may be a prognostic predictor of this tumor [16]. The IRS-2 G1057D gene polymorphism may be associated with the occurrence of endometrial cancer [17]. Currently, there are no reports on the expression of IRS in endometrial polyps. In this study, there were no significant differences in the expression of IRS1 and IRS2 among normal endometrium, uterine polyp tissue and adjacent endometrial tissue.

Insulin resistance originates from defects in insulin receptor function, including pre-receptor, receptor-in-itself, and post-receptor defects. At present, it is generally believed that post-receptor defects may be an important mechanism leading to the development of EP, which is a series of metabolic abnormalities caused by the impaired transmission of signals from the insulin receptor to the cell after binding with insulin. Li et al. [18] found that the expression scores and positive expression rates of PI3K and Akt proteins in EP patients were significantly higher than those in normal endometrium ($P < 0.05$). With the increase of HOMA-IR value, the expression scores of PI3K and Akt proteins in endometrial tissue also increased. There

was a high positive correlation between HOMA-IR value and the expression of PI3K and Akt proteins ($P < 0.01$). The authors believe that the abnormal activation of this signaling pathway may be a potential pathogenesis mechanism in the process of EP. As the starting stage of the insulin signaling pathway, the abnormal activation of downstream signaling molecules PI3K and Akt proteins of the insulin receptor trimer has not yet been reported.

In summary, patients with endometrial polyps tend to have insulin resistance, but the expression of InR, IGR-1R, IRS1 and IRS2 in polyp tissue is not significantly different from that in the adjacent endometrium and normal endometrium. The occurrence of endometrial polyps may be related to abnormalities in the post-insulin-receptor signaling pathway, which requires further research to confirm.

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Ethical Statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study.

Conflict of Interest Statement

The authors have no proprietary, financial, professional, or other personal interest of any nature in any product, service, or company.

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