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ORIGINAL RESEARCH

Is Insulin Resistance a High-Risk Factor for Postmenopausal Endometrial Cancer: Insights from the Triglyceride Glucose (TyG) Index and the Metabolic Score for Insulin Resistance (METS-IR)

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Purpose: To evaluate the insulin resistance in patients with menopause who were newly diagnosed with endometrial cancer and its association with disease development.

Methods: The study included 356 patients with menopause who underwent hysteroscopy at Beijing Obstetrics and Gynecology Hospital between September 2013 and July 2018. Data on age, height, weight, menarche and menopausal age, pregnancies, births, and family history of tumors, hypertension, and diabetes were collected. Blood tests provided fasting blood glucose, triglycerides, total cholesterol, high-density lipoprotein, and low-density lipoprotein levels. Pathological testing determined whether patients had endometrial cancer or precancerous lesions. Differences in influencing factors between patients with endometrial cancer or precancerous lesions and those with normal or benign conditions were analyzed using univariate analysis. Quartile grouping of the Metabolic Score for Insulin Resistance (METS-IR) and Triglyceride-Glucose (TyG) index were applied to examine the impact of different insulin resistance on the development of endometrial cancer or precancerous lesions.

Results: Univariate analysis revealed that the proportion of patients with hypertension and diabetes was significantly higher among those with endometrial cancer and precancerous lesions. METS-IR and TyG levels were significantly increased in patients with endometrial cancer and precancerous lesions. The quartile grouping results of METS-IR and TyG suggested that age, BMI, FBG, TG, hypertension, and diabetes prevalence rates increased with an increase in METS-IR or TyG, whereas lipid indicators were negatively correlated and unstable Logistic regression suggested that none of the above influencing factors and METS-IR or TyG were related to the pathological results of the patients.

Conclusion: Patients with endometrial or precancerous lesions showed evidence of insulin resistance compared to others, though this was not directly associated with disease presence. This study provides relevant information for preventing of endometrial cancer in the future. Larger studies are needed to evaluate the role of METS-IR and TyG in endometrial cancer prevention.

Keywords: postmenopausal, endometrial cancer, insulin resistance, METS-IR, TyG

Introduction

Endometrial cancer (EC) is one of the most common gynecological tumors and poses a significant threat to women's health.[1] Metabolic syndrome (MetS) is a group of metabolic disorders including obesity, hypertension, diabetes, hyperlipidemia, and related conditions. Numerous studies have shown that metabolic abnormalities such as obesity, diabetes, and hyperlipidemia are important risk factors for the development of endometrial cancer,[2] intestinal cancer,[3] and heart failure.[4] Some studies have suggested that metabolic syndrome is closely related to more aggressive clinicopathological features of the endometrium. Patients with metabolic syndrome have higher rates of endometrial

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cancer with pathological grades,[2,3] stages II–IV, lymph node metastasis, lymphatic space invasion, and deep myometrial invasion compared to those without metabolic syndrome.[5] Assessing the occurrence of metabolic syndrome, including insulin resistance, is beneficial to the prognosis of patients with endometrial cancer.[6] However, limited studies have examined whether metabolic syndrome could aid in screening for endometrial cancer.

The hyperinsulinemic-euglycemic clamp (HEC) method is considered the gold standard for measuring insulin resistance. However, it is rarely used in patients with endometrial cancer in clinical practice. Therefore, simple formulas that can be used to assess insulin resistance using non-insulin basal markers have been developed for clinical assessment,[7] and have been widely used in clinical observational studies of other diseases.[8,9] Metabolic score for insulin resistance (METS-IR) triglyceride-glucose (TyG) index and triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio is often used as a surrogate index to assess insulin resistance. METS-IR, introduced by Matthews et al[10] in 1985, quantifies the impact of insulin resistance and beta-cell dysfunction on fasting hyperglycemia. Currently, it is widely used to characterize insulin resistance in big data. Some surrogate markers of insulin resistance are elevated in association with endometrial thickening during menopause, and may be used as markers of endometrial lesions.[2]

In this study, the data of patients who underwent endometrial screening using hysteroscopy in our hospital were collected, and the values of surrogate indicators of insulin resistance were calculated to evaluate their ability to predict the results of endometrial screening.

Material and Methods

Patients

We retrospectively analyzed the medical histories, blood test results, and endometrial biopsy findings of patients who underwent hysteroscopy and mobile phone-based examinations at Beijing Obstetrics and Gynecology Hospital, affiliated with Capital Medical University between September 2013 and July 2018.

Inclusion Criteria

Patients were included if they met the following criteria 1. Woman with natural menopause lasting ≥ 1 year; 2. Clinical indications for hysteroscopic examination, such as clinical symptoms of vaginal bleeding or bloody discharge, or abnormal imaging results. Transvaginal ultrasound indicating a maximum anterior-posterior diameter of the uterine longitudinal section and endometrial thickness ≥ 5 mm required re-examination at our hospital;.[3] Hysteroscopy and endometrial biopsy performed at our hospital with available histological endometrial results.[4] Complete blood test results retained at our hospital.

Exclusion Criteria

Patients were excluded if they1. had malignant diseases or tumors other than malignant endometrial conditions2. were receiving anticoagulant or antiplatelet therapy3. had severe cardiopulmonary dysfunction, and4. had acute or subacute lower reproductive tract infections.

The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and approved by the ethics committees of Beijing Obstetrics and Gynecology Hospital, Capital Medical University (2022-KY-051-01).

Data

We collected data on age, height, weight, age at menarche and menopause, number of pregnancies, parity, and the presence of cancer in immediate family members. Self-reported histories of hypertension, diabetes or the use of antihypertensive drugs or hypoglycemic medications were recorded.

All patients chose their diet according to their habits. All blood samples were collected in the morning after the patient had fasted for at least 8 hours. Fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C) levels were measured and standardized in units of (mg/dL).

Patients were classified as having endometrial hyperplasia or polyps, uterine fibroids, endometrium, atypical adenomatous polyps, atypical endometrial hyperplasia, or endometrial cancer, based on postoperative pathological section analysis. In the first analysis, endometrial hyperplasia or polyps, uterine fibroids, and endometrial polyps were included in the group of patients who did not require further treatment, whereas the other three categories were included in the group that required additional surgery. In the second analysis, patients with endometrial cancer were listed separately, whereas the remaining patients were grouped together.

The proxy indicators for insulin resistance were TyG, METS-IR, and TG/HDL-C ratio. The calculation formula is: METS-IR: ln [(2 x FBG (mg/dL)+serum TG level (mg/dL)] x BMI (kg/m2)/ln [serum HDL-C level (mg/dL)]; TyG:ln [TG (mg/dL) × FBG (mg/dL)/2]; TG/HDL-C ratio: TG (mg/dL)/HDL-C (mg/dL).

Statistical Analysis

All statistical analyses were performed using SPSS version 26.0, sigmastat 3.5, and Excel. We analyzed grade data through analysis of variance, measured data of patients between different groups through one-way ANOVA, and established relevant models through binary logistic regression to verify the influence of the dependent variable on the outcome. Statistical significance was set at $p < 0.05$.

Results

A total of 356 patients were included in this study. In the first analysis, 108 patients were classified into the cancer and precancerous lesion groups, while 248 patients were included in the normal or benign disease group. The results showed that in both groups of patients, the proportion of patients with precancerous lesions and endometrial cancer with hypertension was significantly higher than that in the normal or benign disease groups (P=0.000), and fasting blood glucose levels were also significantly elevated (P=0.009). No significant differences were observed in other variables (Table 1).

Table 1 General Information of Patients with Endometrial Cancer and Precancerous Lesions Compared to Normal or Benign Disease Groups

	Endometrial Cancer And Precancerous Lesions Group (N=108)	**Normal or benign disease group (n =248)**	**P**
Age	60(56–64)	59(54.5–64)	0.057
BMI	25.52(23.373–28.144)	24.444(22.39–27.125)	0.021
Menarche age	14(13–16)	14(13–16)	0.884
Menopausal age	51(50–53)	51(49–53)	0.762
Pregnancy times	3(1.25–3)	3(2–4)	0.245
Production times	1(1–2)	1(1–2)	0.928
Hypertension			0.000
No	44	145	
Yes	64	103	
Diabetes			0.275
No	83	203	
Yes	25	45	
Family history of cancer			0.945
No	87	199	
Yes	21	49	
FBG (mg/dl)	107.46 (98.37–121.86)	103.14 (96.03–112.59)	0.009
TG (mg/dl)	116.952 (85.499–148.848)	105.877(75.31–147.519	0.170
TC (mg/dl)	199.627(174.118–234.606)	199.241(176.631–227.262)	0.759
HDL (mg/dl)	72.644(63.492–88.66)	73.216(63.206–87.516)	0.757
LDL (mg/dl)	121.701±36.304	122.64±38.381	0.829

Table 2 Relevant Data on Insulin Resistance in Patients with Endometrial Cancer and Precancerous Lesions Compared to Normal or Benign Disease Groups

	Endometrial cancer and precancerous lesions group (n=108)	Normal or benign disease group (n =248)	P
METS-IR	34.772 (31.319–39.155)	32.829 (29.53–37.507)	0.017
TyG	8.725 (8.403–9.068)	8.581 (8.273–8.994)	0.071
TG/HDL-C	1.061 (0.719–1.429)	1.035(0.724–1.389)	0.646

The comparison results of insulin resistance-related indicators between the two groups were inconsistent (Table 2). METS-IR in the precancerous lesion and cancer groups was significantly higher than that in the normal or benign disease groups (P=0.017), and TyG was slightly elevated, but not significantly (P=0.071), indicating the presence of insulin resistance in patients with precancerous lesions and love. However, there was no significant difference in the TG/HDL-C ratio between the groups (P=0.646).

The clinical characteristics of the participants were analyzed based on METS-IR quartiles (Table 3). The different quartiles were defined as follows: Q1 (18.353–29.710), Q2 (29.812–33.312), Q3 (33.316–38.018), Q4 (38.039–54.042). Compared to the low METS-IR group, age, BMI, FBG, TG, HDL, and the prevalence of hypertension and diabetes changed significantly (P<0.05). Age, BMI, FBG, TG, hypertension, and diabetes increased with an increase in METS-IR,

Table 3 The Baseline Data of Participants Grouped According to the Quartiles of METS-IR

	Q1 (n=89)	Q2 (n=89)	Q3 (n=89)	Q4 (n=89)	P
Age	58(54–61.25)	59(55–64.25)	60(55–64.25)	60(57–65)	0.029
BMI	21.338 (19.922–22.507)	23.833 (23.029–24.609)	25.806 (24.765–27.344)	29.516 (27.627–31.246)	<0.001
Menarche age	51(50–53)	51(49–53)	51(49–53)	51(49–53)	0.890
Menopausal age	14(13–16)	14(13–16)	15(13–16)	14(13–16)	0.372
Pregnancy times	2(2–3)	3(2–3)	3(2–4)	2(1–4)	0.473
Production times	1(1–2)	1(1–2)	1(1–2)	1(1–2)	0.440
Hypertension					0.000
No	59	54	45	31	
Yes	30	35	44	58	
Diabetes					0.043
No	76	76	72	62	
Yes	13	13	17	27	
Family history of cancer					0.395
No	72	71	77	76	
Yes	17	18	12	23	
FBG (mg/dl)	100.8 (92.475–108.45)	100.62 (95.49–109.575)	105.3 (98.415–116.1)	112.32 (102.24–129.015)	<0.001
TG (mg/dl)	75.31 (54.046–104.991)	106.32 (85.942–129.577)	113.408 (83.063–147.962)	147.076 (116.952–198.464)	<0.001
TC (mg/dl)	206.391 (182.235–237.891)	199.434 (175.278–230.741)	203.685 (169.48–227.359)	192.477 (172.572–225.33)	0.360
HDL (mg/dl)	89.804 (75.647–103.961)	76.076 (67.782–87.516)	70.356 (62.348–77.935)	63.492 (55.484–70.928)	<0.001
LDL (mg/dl)	120.874±36.761	123.991±41.838	124.379±34.394	120.174±37.94	0.837
Pathological results					0.125
Endometrial cancer or precancerous lesions	20	24	32	32	
Normal or benign diseases	6	65	57	57	

Table 4 The Baseline Data of Participants Grouped According to the Quartiles of TyG

	Q1 (n=89)	Q2 (n=89)	Q3 (n=89)	Q4 (n=89)	P
Age	58 (54–63.25)	60 (55–65)	59 (54–62)	61 (57–65)	0.008
BMI	23.712 (21.83–25.788)	24.342 (22.583–26.81)	25.1 (23.405–27.535)	25.865 (23.505–28.685)	<0.001
Menarche age	14 (13–16)	14 (13–16)	14 (13–16)	14 (13–16)	0.338
Menopausal age	51 (49–53)	51(50–53)	50(49–52)	52(49–54)	0.219
Pregnancy times	2(1–3)	3(2–3)	3(2–4)	3(2–4)	0.261
Production times	1(1–2)	1(1–2)	1(1–2)	1(1–2)	0.172
Hypertension					0.016
No	55	54	43	37	
Yes	34	35	46	52	
Diabetes					0.000
No	76	80	74	56	
Yes	13	9	15	33	
Family history of cancer					0.751
No	73	72	68	73	
Yes	16	17	21	16	
FBG (mg/dl)	98.82(91.395–108.18)	100.98 (95.13–109.17)	104.94(98.46–111.6)	115.92 (101.7–135.81)	<0.001
TG (mg/dl)	60.248 (46.736–71.766)	95.688 (86.606–104.548)	128.47 (118.281–141.981)	190.49 (158.594–238.113)	<0.001
TC (mg/dl)	189.385 (162.813–218.276)	200.98 (184.844–233.736)	207.551 (175.761–232.963)	207.937 (177.21–233.06)	0.006
HDL (mg/dl)	84.656 (68.068–91.806)	76.076 (69.784–91.091)	72.072 (63.349–88.946)	64.064 (57.772–74.932)	<0.001
LDL (mg/dl)	112.078±35.965	125.418±38.773	129.183±35.056	124.192±37.281	0.014
Pathological results					0.108
Endometrial cancer or precancerous lesions	19	26	32	32	
Normal or benign diseases	70	63	57	57	

whereas HDL negatively correlated with them. As the proportion of pathological results in Q3 and Q4 was the same, we combined Q1 and Q2 and compared them with the Q3/4 group. The results showed that the higher the level of METS-IR, the higher the incidence of endometrial cancer or precancerous lesions (P=0.021).

Similarly, we displayed the clinical characteristics of the participants based on the TyG quartiles (Table 4). The different quartiles were as follows: Q1 (3.723–8.336), Q2 (8.338–8.649), Q3 (8.651–9.020), Q4 (9.023–10.732). The proportion of patients with age, BMI, FBG, TG, HDL-C, LDL-C, hypertension, and diabetes was considered to be significantly different among the different TyG groups. Among them, the proportion of age, BMI, FBG, TG, HDL-C, hypertension, and patients with diabetes had the same effect on TyG as on METS-IR, but the changed trend of LDL was not stable When grouped according to quartiles, there was no significant difference in the pathological results among patients in the different TyG groups; however, there was a significant difference between the two groups (P=0.029).

Furthermore, we screened for age, BMI, hypertension, diabetes, FBG, METS-IR, and TyG with higher specificity in the two groups for binary logistic regression analysis. The results showed that only hypertension was significantly associated with the presence of precancerous lesions or cancer (P=0.031). Patients with a history of hypertension had a 1.729-fold increased risk of developing endometrial cancer or precancerous lesions. Other factors were not significantly associated with these outcomes (Table 5).

Table 5 Logistics Regression Results of Patients with Endometrial Cancer and Precancerous Lesions Compared to Normal or Benign Disease Groups

Variables	b	SE	Waldχ2	P
Age	0.019	0.019	1.02	0.312
BMI	0.141	0.096	2.135	0.144
Hypertension	0.548	0.254	4.668	0.031
Diabetes	−0.131	0.357	0.135	0.714
FPG	0.008	0.007	1.019	0.313
METS-IR	−0.065	0.064	1.008	0.315
TyG	0.231	0.288	0.64	0.424

Discussion

In recent years, the incidence of endometrial cancer has increased, with patients with menopause comprising the majority of new cases.[11] A history of metabolic syndrome or its persistent presence is believed to increase the risk of endometrial cancer in women.[12] Insulin resistance is an important metabolic indicator of various pathological and physiological disorders, including abnormal glucose and lipid metabolism, elevated blood pressure, and hyperuricemia. They can also indirectly lead to diseases related to metabolic disorders.[13] The effects of glucose and lipid metabolism on the pathogenesis and prognosis of endometrial cancer have been well established. In many previous studies, diabetes has been considered as an important factor in the pathogenesis of endometrial cancer.[14–16] Recently, novel non-insulin scores based on conventional clinical indicators such as FBG, TG, HDL-C, and BMI have been developed and applied in large retrospective studies or statistical analyses.[17] Owing to its related indicators being considered for routine examinations before surgery or during physical examinations in clinical practice, assessing insulin resistance has become more convenient.

This study focused on patients with postmenopausal status undergoing hysteroscopic screening for endometrial cancer, exploring whether TyG and METS-IR have a predictive effect on screening patients with endometrial cancer. The TyG index is a parameter derived from fasting blood glucose and TG levels, and TyG-related indicators have been recognized for their value in the diagnosis of metabolic syndrome.[18,19] Luo et al[20] found in a study of the Chinese population that the area under the ROC curve (AUC) of the TyG index (0.785, 0.691–0.879) was higher than that of HOMA-IR (0.73, 0.588–0.873) in patients with type 2 diabetes with BMID < 35 kg/m2, suggesting that the ability of the TyG index to recognize insulin resistance is better than that of HOMA-IR in non-overweight Chinese patients.

In recent years, various indicators related to TyG have been used to diagnose and predict metabolic syndrome, especially hypertension and early hypertension.[21,22] In our study, the incidence of hypertension significantly increased in the endometrial cancer and precancerous lesion groups, and the number of patients increased with an increase in the TyG index. However, in logistic regression analysis, only hypertension was associated with the incidence of endometrial cancer and precancerous lesions, indicating the need to separately analyze the prevalence of hypertension and TyG. In the prevalence analysis, these two influencing factors showed significant differences.

In 2018, Chavolla et al[23] developed the METS-IR to evaluate insulin sensitivity and predict the incidence of visceral fat and type 2 diabetes. Studies have found that METS-IR can be used as a detection tool in primary healthcare to identify high-risk populations for diseases or as an indicator of insulin resistance occurrence.[24–26] It can also discriminate subjects of normal weight.[27,28] In our study, participants with higher METS-IR values were grouped according to METS-IR quartiles, indicating a higher probability of developing endometrial cancer and precancerous lesions. However, according to logistics statistics, METS-IR is not one of the influencing factors of endometrial cancer and precancerous lesions, suggesting that METS-IR can provide information for patients who already have indications for hysteroscopy but cannot be used as a criterion for hysteroscopy examination. In the comparative analysis with the TyG index, the factors that changed with the increase in the two indices were roughly the same, indicating that the two indices have roughly the

same effect on patient stratification, but both have no significant impact on the outcome of endometrial cancer and precancerous lesions.

Screening and management of endometrial cancer are important, especially in patients first diagnosed after menopause.[29,30] Although many database studies have shown that obesity and diabetes are factors affecting the poor prognosis of endometrial cancer[31] and that weight reduction surgery can also reduce the incidence rate of endometrial cancer,[32] the effects of correcting obesity and treating diabetes in endometrial patients are different. Raffone et al[33] reported that diabetes did not affect the efficacy of conservative treatment in simple endometrial hyperplasia, atypical endometrial hyperplasia, and early endometrioid carcinoma. Furthermore, in a Korean big data study,[34] weight loss may improve the oncological findings of women with obesity-related endometrial tumor abnormalities who received progesterone treatment, suggesting that obesity and diabetes cannot be generalized to patients with endometrial cancer. In our study, the weight and METS-IR of patients with endometriosis were significantly higher than those of patients without endometriosis; however, there was no significant difference in the rate of diabetes between the two groups, suggesting that the level of insulin resistance indicators was more important for the pathogenesis of endometriosis, even if diabetes could not be diagnosed. Further research is needed to confirm whether insulin resistance can be detected through weight loss or early physical examination and whether medication can be used to treat insulin resistance and reduce the occurrence of endometrial lesions. Similarly, it has been confirmed that insulin resistance leads to hypertension.[35] Although hypertension and endometrial cancer have been identified in many observational studies, the underlying mechanisms remain unclear.[36] Early intervention in a population with hyperinsulinemia or insulin resistance is helpful in identifying high-risk groups for hypertension;[37] however, whether it can reduce the incidence rate of endometrial lesions also requires further research.

Currently, most studies calculate and group insulin replacement indicators in patients who have already been diagnosed with the disease. Unlike other studies, we selected patients who underwent endometrial cancer screening, meaning that patients with endometrial cancer and precancerous lesions were in the early stages of disease progression. This provided data on the role of METS-IR and TyG indices in disease identification. However, due to the small sample size, we were unable to calculate the optimal cutoff values, and further research with a larger dataset is needed.

Ethical Approval

The study was carried out in accordance with the ethical standards laid down in the Declaration of Helsinki, and was approved by the ethics committees of Beijing Obstetrics and Gynecology Hospital, Capital Medical University (2022-KY-051-01). Informed consent was waived due to the retrospective nature of this study, in line with Article 39 of the "Measures for the Ethical Review of Biomedical Research Involving Humans" issued by the National Health Commission of the People's Republic of China (Order No. 11), which states that informed consent may be waived for "retrospective studies that do not affect the rights and interests of the subjects". This waiver is also consistent with international guidelines, including: The Council for International Organizations of Medical Sciences (CIOMS) Guidelines, specifically Guideline 10 on modifications and waivers of informed consent. The World Health Organization (WHO) Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants. As the type of study in this trial is a retrospective analysis of the original data, the above Ethics Committee has approved the waiver of patient consent. Each patient was recorded for data security. The ethics committee felt that this study could exempt patients from informed consent.

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No contributors not mentioned in the text.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors have no conflicts of interests to declare.

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