Role of ATP-citrate lyase and Glycosyltransferases Enzymes in Ovarian Cancer Patients

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Received: 18/8/2024
Accepted: 5/11/2024
Online: 2/6/2026

ABSTRACT

Background: Ovarian cancer (OC) remains the deadliest of all gynecological tumors. Because there are no obvious clinical symptoms, OC is difficult to diagnose early, which makes it an aggressive disease, highlighting the vital need for reliable biomarkers. This research aimed to investigate the role of ATP-citrate lyase and glycosyltransferase levels in ovarian cancer patients. **Methodology:** 140 women with ovarian cancer and control women aged 35- 65 years were categorized into three groups upon enrollment in this case-control study: 40 women as controls, 50 as group I(untreated), and 50 as group II (treated) were collected from Al-Amal Hospital for Radiation and Nuclear Medicine and Oncology Teaching Hospital at Baghdad Medical City. **Results:** The results showed elevated levels of ACLY and GTs enzymes in group I patients compared with the mean value recorded in the control group (P-value <0.0001). Whereas, the result showed no significant difference between group II and control (P-value =0.2149). A receiver operating characteristic curve analysis showed high sensitivity, as indicated by the area under the curve. **Conclusions:** The current study concluded that ACLY and GTs could be used as tools to help diagnose and predict ovarian cancer in the future.

Keywords: Ovarian cancer, ATP citrate lyase, Glycosyltransferases.
https://doi.org/10.24126/jobrc.2026.20.1.885

INTRODUCTION

A particular kind of cancer called ovarian cancer starts in the ovaries, which are a component of the female reproductive system (1). Effective treatment is difficult since it may go unnoticed until it has spread throughout the abdomen and pelvis (2). Some symptoms may not be immediately apparent, including abdominal or pelvic pain, bloating, trouble eating, and frequent urination (3). Age, certain reproductive circumstances, and genetic predisposition are risk factors (4). Ovarian cancer is too frequently detected at an advanced stage, even though early detection is essential for better results (5). Chemotherapy and surgery are usually part of the treatment (6,7).

Lipids are a family of chemicals that are insoluble in water and are essential nutrients for the body, including glycerol and triacylglycerol sterols, phosphates, and sphingolipids (8). Furthermore, lipids are widely distributed as active molecules in cellular organelles and provide a substantial amount of energy that is essential to life in a range of signaling channels to take part in the processes of differentiation, inflammation, immunity, and cell division (9). The four main routes show the distribution of lipids: uptake, lipogenesis, storage, and utilization by the cell. The synthesis of fatty acids is referred to as lipogenesis, and the mevalonate pathway is the one that primarily leads to the synthesis of isoprenoids and cholesterol (10,11)

The liver and white adipose tissue are where ATP-citrate lyase (ACLY) is most frequently expressed (12,13), whereas the brain, heart, small intestine, and muscles are where it is least expressed (12). Additionally, pancreatic beta cells express and function ACLY (14). Additionally, certain clinical diseases are linked to the overexpression of ACLY (15).

Several cancers are characterized by altered lipid metabolism, including increased de novo synthesis and fatty acid degradation (16,17,18). This dysregulation may support cancer cells in invasion, proliferation, and metastasis. Numerous studies have found that a variety of malignancies have noticeably elevated levels of the expression and

activity of several enzymes involved in the production and catabolism pathways of fatty acids (phospholipids and cholesterol) (19).

One indicator of cancer is the aberrant expression of glycosyltransferases (GTs), resulting in aberrant glycosylation patterns. Moreover, the production of these glycoconjugates has been linked to tumor growth, invasion, and metastasis (20). In particular, ceramide glycosyltransferases catalyze the production of the glycosphingolipid (GSL) skeleton and ceramide glycosylation, which are crucial for controlling tumor growth and are significantly associated with a bad prognosis for cancer patients (21).

Research has shown that alterations in glycosylation, controlled by specific glycosyltransferases, are associated with cancer development and prognosis (22). Additionally, studies highlight the significance of lipid metabolism in ovarian cancer, in which fatty acid synthase and other enzymes regulate lipid production and uptake, impacting tumor growth, migration, and drug resistance (23,24). The dysregulation of fatty acid metabolism, coupled with glycosylation changes mediated by glycosyltransferases, contributes to the aggressive nature of ovarian cancer and its resistance to therapies, emphasizing the interconnectedness of these processes in driving tumorigenesis and poor patient outcomes (20).

Because fatty acids are essential for the malignant growth of cancer, rate-limiting enzymes may be able to modulate lipid metabolism and hence serve as therapeutic targets by preventing the synthesis of fatty acids, speeding up their oxidation-based breakdown, directing them into storage, delaying their release from storage, and preventing their intake (25,26). Therefore, one of the most common and important characteristics of tumor cells is metabolic reprogramming (27). In numerous tumor tissues, ACLY and GTs are overexpressed and are essential to the first rate-limiting step of de novo lipogenesis (28). Therefore, histone acetylation, fatty acid synthesis (FAS), and cholesterol metabolism all depend on ACLY levels and activity, and these processes can all be involved in tumor signaling (26,29).

METHODOLOGY

2.1 Study design

This case-control study was conducted between 1 January 2023 and 1 June 2023 at Al-Amal Hospital for Radiation and Nuclear Medicine and Oncology Teaching Hospital at Baghdad Medical City. There were two groups of 100 ovarian cancer patients in the research population, group I (untreated) and group II (treated) with chemotherapy, and 40 control cases. The study excluded patients with congenital adrenal hyperplasia, diabetes, hyperprolactinemia, renal impairment, thyroid disorders, hypertension, and chronic smoking.

2.2 Sample Selection Procedures

Blood samples have been collected from the subjects and processed based on established protocols. The patient's written assent was recorded in the questionnaire, along with verbal consent from the Chemistry Department at Al-Nahrain University in Baghdad. In brief, using a disposable syringe, 5mL of blood has been collected by venipuncture in tubes having a clot activator. The tubes were centrifuged for 10 minutes at 4000 rpm, and the resulting serum was transferred to Eppendorf tubes. For sample integrity, all tubes have been stored at -20°C until analysis. The concentrations of ACLY and GTs in the sera were determined using the Human ATP-citrate lyase ELISA® Kit (Abcam (UK)) and Glycosyltransferases ELISA® Kit (Abcam (UK)).

2.3 Statistical Analysis

Data analysis was done by SPSS version 20. A one-way analysis of variance (ANOVA) was used to compare the mean values among the three groups. The data have been considered significant at $p \leq 0.05$(30). To ascertain whether the marker could accurately predict a disease, the receiver operating characteristic (ROC) curve was examined.

Ethical approval

The research was approved by the Research Ethics Committee of the college of science/ university of Al-Nahrain (No.2/3/441, dated 07/02/2023). The committee confirmed compliance with approved scientific and ethical standards.

RESULTS

The mean ± standard deviation (SD) values of serum ACLY and GTs enzyme in ovarian cancer patients and the control group are shown in Table 1. After applying the ANOVA test, the results show highly significant differences (*P-value* <0.0001) in the concentrations of both ACLY and GTs in ovarian cancer group I (untreated) in comparison to the control group.

Table 1: Assessment of serum levels of ATP citrate lyase and glycosyltransferase enzyme in ovarian cancer patients and the control group

Variable	mean value ±SD			P-value (ANOVA)
	Control	Group I	Group II	
ACLY(IU\mL)	B47.83±13.52	A77.73 ±20.40	B53.62 ±10.43	<0.0001
GTs(ng\mL)	C1.763±0.143	A4.269±1.22	B2.44±1.05	<0.0001

Different capital letters mean significant at the 0.05 level (P ≤ 0.05).

Additionally, the mean ± SD of ACLY in patients with ovarian cancer group I was found to be significantly high (77.73 ±20.40 IU\mL) compared to the mean value observed in the control group (47.83±13.52 IU\mL), as illustrated in Figure 1-A.

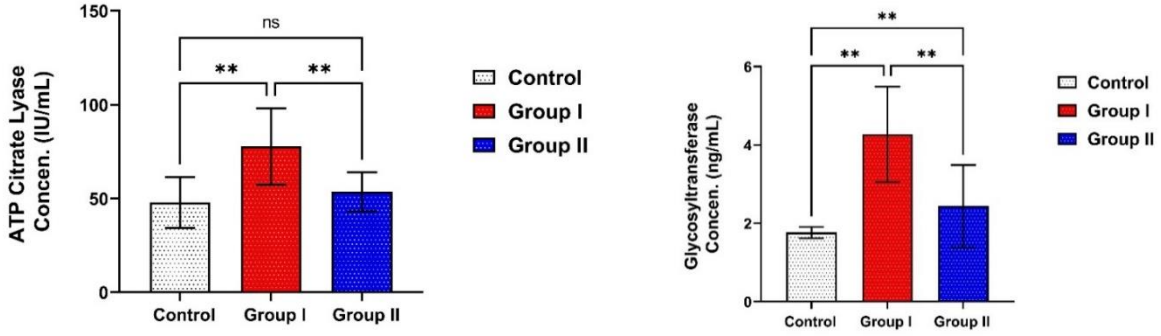

Figure 1: (A) Serum ACLY concentration (IU\mL) in a control group, patients of group I(untreated), and patients of group II (treated), (B) Serum GTs concentration (ng\mL) in a control group, patients of group I(untreated), and patients of group II (treated).

Furthermore, there is a significant difference between group I (untreated) and group II (treated) (P-value <0.0001), and the mean ± SD of ACLY in patients of ovarian cancer group II (treated) was found to be significantly lower (53.62±10.43 IU\mL) compared to the mean value observed in the group I(untreated) (77.73 ±20.40 IU\mL), whereas, the result showed no significance between control and group II (treated) (P-value = 0.2149), as shown in Figure 1.

Additionally, the mean ± SD of glycosyltransferases in patients of ovarian cancer group I and group II were found to be significantly high, respectively (4.269±1.22 ng\l) (2.44±1.05ng\l) compared to the mean value observed in the control group (1.763±0.143 ng\l), as illustrated in Figure 1-B, and there is a significant difference between group I and group II (P-value <0.0001).

ROC analysis was performed to assess the diagnostic significance of ATP citrate lyase and glycosyltransferase enzymes. The AUC in ROC analysis indicates the test's advantage. The results are tabulated in Table 2 and in Figures 2 and 3, respectively.

Table 2: Diagnostic criterion values and coordinates of ROC curve analysis for ACLY and GTs in the differentiation of study groups.

Parameter	Type of correlation	AUC	Sensitivity	Specificity	Cut-off value
ACLY	Control vs group I	1.0	100%	96.97%	>58.5
	Control vs group II	1.0	100%	96.67%	>62.7
	Group I vs group II	0.9839	96.67%	87%	55.23
GT	Control vs group I	0.9967	100%	96.97%	>3.48
	Control vs group II	1.0	100%	97 %	>2.61
	Group I vs group II	0.9876	93.33%	93.33%	>4.04

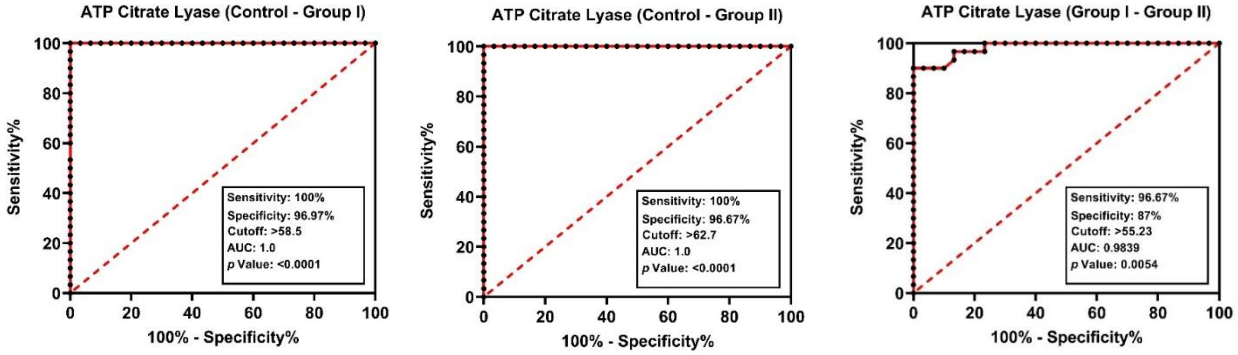

Figure 2: The ROC analysis for A-control vs group I B- control vs group II C- group I vs group II, showed the AUC, sensitivity, specificity, cutoff, and P-Value.

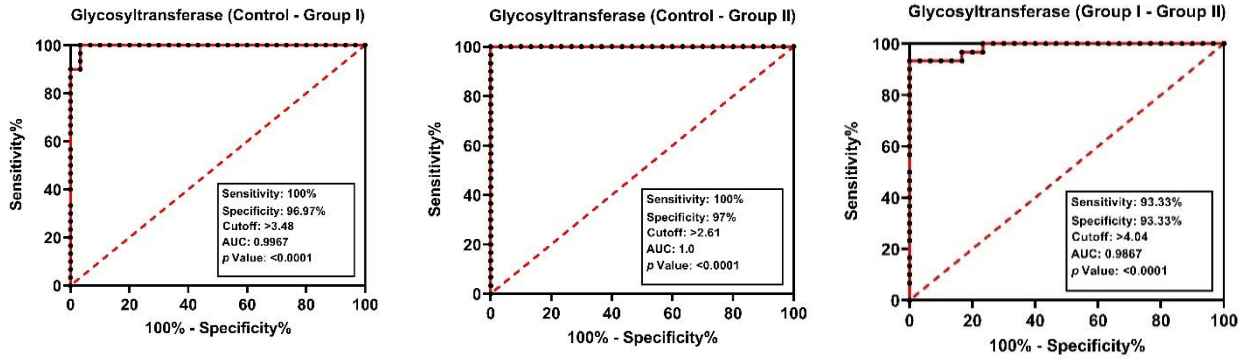

Figure 3: The ROC analysis for A-control vs group I B- control vs group II C- group I vs group II, showed the area under the curve (AUC), sensitivity, specificity, cutoff, and P-Value.

DISSCUSION

An important factor influencing the aggressiveness and progression of ovarian cancer is the dysregulation of lipid metabolism. Research demonstrates that abnormal lipid metabolism, such as elevated fatty acid production and cholesterol metabolism, stimulates tumor cell growth, migration, and chemoresistance, resulting in a bad prognosis (31,32).

According to the results of this study, patients in group I had higher levels of ACLY enzyme in comparison with the control group. These results align with the research conducted by Nousheen Zaidi, which showed that elevated levels of ACLY are crucial for tumor cell growth and progression, and that inhibition of ACLY halts cancer cell proliferation *in vitro* and *in vivo*(33). In addition, Evelyn Orsó reported that inhibition of ACLY reduces endogenous cholesterol production and inhibition of ACLY alters gene expression in macrophages (34). Furthermore, recent studies have suggested that ACLY inhibitors have the potential to treat hyperlipidemia and cancer, and new effective ACLY inhibitors are needed for better treatment outcomes (35). Hence, ACLY is a possible cancer treatment target.

Glycosylation, a fundamental post-translational modification of proteins, plays an important role in various cellular activities such as cell proliferation, differentiation, transformation, adhesion, and tumor immune surveillance (36). Additionally, glycosyltransferases are dysregulated in various types of cancer, leading to changes in the glycosylation patterns of cancer cells.

Furthermore, the dysregulation of glycosyltransferases in cancer cells presents an opportunity for the development of novel cancer therapies. Targeting these enzymes could potentially lead to more effective, targeted treatments for various types of cancer.

The findings of this study demonstrated a significant increase in glycosyltransferase serum levels in group I (untreated) compared with the control group and a substantial decrease in group II (treated) compared with group I. This finding is consistent with the research conducted by Xuyao Xu and colleagues, who found that glycosyltransferase genes may be a promising biomarker for the progression of ovarian cancer and a potential target for treatment (22).

CONCLUSION

The results showed that OC patients had significantly higher serum levels of ACLY and GTs. Hence, it may also serve as a predictor of ovarian carcinogenesis. It should be included in the OC screening profile to aid in early identification and the planning of suitable intervention strategies.

ACKNOWLEDGMENT

We are sincerely grateful to the staff, healthcare professionals, and administration at the Al-Amal Hospital for Radiation and Nuclear Medicine and Oncology Teaching Hospital at Baghdad Medical City for their unwavering dedication and exceptional care provided to patients, as well as for their assistance in providing and collecting the necessary samples for our research. Overview and scheduling of relevant intervention measures.

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دور انزيم ATP-citrate lyase and Glycosyltransferases في مريضات سرطان المبايض

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الخلاصة

خلفية عن الموضوع: يبقى سرطان المبيض هو الأكثر فتكاً بين جميع الأورام النسائية. ونظرًا لعدم وجود أعراض سريرية واضحة، يصعب تشخيصها مبكرًا، مما يجعله مرضًا عدوانيًا وبهذ يسلط الضوء على الحاجة الحيوية إلى مؤشرات حيوية موثوقة. يهدف هذا البحث إلى دراسة دور مستويات أدينوسين ثلاثي الفوسفات لياز سترات وناقلة الغليكوزيل في مرضى سرطان المبيض. **طرق العمل:** تم جمع140 عينة دم من نساء مصابات بسرطان المبيض ونساء كمجموعة ضابطة تتراوح أعمارها بين 35 و65 عامًا وتم تقسيمهم إلى ثلاث مجموعات عند التسجيل في دراسة الحالات والشواهد ، حيث تم جمع 40 امرأة كمجموعة ضابطة، و50 امرأة مصابة لم تتلقى العلاج الكيميائي و50 امرأة تلقت العلاج وتم جمع العينات المصابة من مستشفى الأمل للطب الإشعاعي والطب النووي ومستشفى الأورام التعليمي في مدينة الطب ببغداد. **النتائج:** أظهرت النتائج فروقا معنوية في ارتفاع مستويات إنزيم ACLY في مرضى المجموعة الأولى مقارنة بالقيمة المتوسطة المسجلة في مجموعة التحكم P-value (<0.0001). في حين لم تظهر النتيجة أي أهمية بين المجموعة الثانية والمجموعة الضابطة (قيمة P = 0.2149). وأظهر تحليل منحنى طابع التشغيل المستقبلي حساسية عالية وفقاً للمساحة الواقعة تحت المنحنى. **الاستنتاج:** تلخص الدراسة الحالية إلى أنه يمكن استخدام انزيم ATP-citrate lyase and Glycosyltransferases كأدوات تساعد مستقبلا في تشخيص سرطان المبيض والتنبؤ به.

الكلمات المفتاحية: سرطان المبيض، أدينوسين ثلاثي الفوسفات لياز سترات، ناقلة الغليكوزيل.