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Pharmacogenomic and Metabolic Effects of Tamoxifen Treatment: The Contribution of Polymorphisms of CYP1B1 to Lipid Profile Alteration in Breast Cancer Patients

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Abstract

Background: Tamoxifen continues to be a pillar in the management of breast cancer with estrogen receptor-positive breast cancer, but there is a lack of interindividual consistency in the responses to therapy. CYP1B1 is one of the most important enzymes in estrogen metabolism; genetic polymorphisms in the enzyme can alter metabolism and drug toxicity**.**

Objectives: This study aimed to investigate the association between CYP1B1 polymorphisms (rs1056836 and rs1056827), metabolic and hormonal biomarkers, and adverse drug reactions in tamoxifen-treated breast cancer patients.

Methods: A cross-sectional study was conducted among 139 breast cancer patients receiving tamoxifen therapy. Demographic data, clinical features, lipid profile, calcium, and vitamin D3 were evaluated. PCR-based genotyping of CYP1B1 was performed at rs1056836 and rs1056827. Statistical tests were ANOVA, Kruskal-Wallis, chi-square and correlation tests.

Results: The longer the disease period, the greater the tamoxifen treatment, and the higher the BMI, the greater the increase in triglycerides and VLDL ($p < 0.05$). The vitamin D3 level was also significantly lower in obese patients ($p = 0.020$). A close relationship was also observed between the rs1056827 genotype and LDL levels, with the GT genotype associated with higher LDL levels ($p = 0.039$).

Conclusion: Polymorphisms in CYP1B1, especially at the rs1056827, have the potential to alter lipid metabolism in patients who are on tamoxifen therapy for breast cancer. Dyslipidemia is a condition associated with prolonged tamoxifen use, underscoring the need for pharmacogenomic-based monitoring and individualized treatment plans.

التأثيرات الدوائية الجينية والأيضية للعلاج بالتاموكسيفين: إسهام تعددات الأشكال الجينية في جين CYP1B1 في التغيرات التي تطرأ على دهون الدم لدى مريضات سرطان الثدي

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الملخص

الخلفية: لا يزال التاموكسيفين يُعد أحد الركائز الأساسية في علاج سرطان الثدي الإيجابي لمستقبلات الإستروجين، إلا أن الاستجابة العلاجية تختلف بصورة ملحوظة بين المرضى. ويُعد إنزيم CYP1B1من الإنزيمات الرئيسة المشاركة في أيض الإستروجين، وقد تؤثر تعددات الأشكال الجينية في هذا الإنزيم في استقلاب الدواء وسميته، مما ينعكس على فعالية العلاج وحدوث آثاره الجانبية.

الهدف: هدفت هذه الدراسة إلى تقييم العلاقة بين تعددات الأشكال الجينية CYP1B1 (rs1056836و rs1056827)والمؤشرات الأيضية والهرمونية، بالإضافة إلى التفاعلات الدوائية الضارة لدى مريضات سرطان الثدي المعالجات بالتاموكسيفين.

المواد وطرائق العمل: أُجريت دراسة مقطعية شملت 139مريضة مصابة بسرطان الثدي يتلقين العلاج بالتاموكسيفين. جُمعت البيانات الديموغرافية والسريرية، كما تم تقييم دهون الدم، والكالسيوم، ومستويات فيتامين D3.وأُجري تحديد الأنماط الجينية لتعددي الأشكال CYP1B1 rs1056836و rs1056827باستخدام تقنية تفاعل البوليميراز المتسلسل (PCR). وشملت التحليلات الإحصائية اختبار تحليل التباين(ANOVA) ، واختبار كروسكال–واليس، واختبار مربع كاي، وتحليل الارتباط.

النتائج: أظهرت النتائج أن زيادة مدة الإصابة بالمرض، وطول مدة العلاج بالتاموكسيفين، وارتفاع مؤشر كتلة الجسم (BMI) ارتبطت جميعها بارتفاع معنوي في مستويات الدهون الثلاثية (Triglycerides) والبروتينات الدهنية منخفضة الكثافة جدًا (VLDL) ($P < 0.05$). كما انخفضت مستويات فيتامين D3بصورة معنوية لدى المريضات المصابات بالسمنة ($P = 0.020$). كذلك، وُجد ارتباط معنوي بين تعدد الأشكال الجيني rs1056827ومستويات البروتين الدهني منخفض الكثافة(LDL) ، حيث ارتبط النمط الجيني GTبارتفاع مستويات LDLمقارنة بالأنماط الجينية الأخرى.($P = 0.039$)

الاستنتاج: تشير النتائج إلى أن تعددات الأشكال الجينية في CYP1B1، ولا سيما rs1056827، قد تؤثر في أيض الدهون لدى مريضات سرطان الثدي اللواتي يتلقين العلاج بالتاموكسيفين. كما يرتبط الاستخدام طويل الأمد للتاموكسيفين بحدوث اضطرابات في دهون الدم، مما يؤكد أهمية تطبيق استراتيجيات المراقبة المستندة إلى علم الصيدلة الجيني (Pharmacogenomics) ووضع خطط علاجية فردية لتحسين فعالية العلاج والحد من آثاره الجانبية.

1. Introduction

It is the most frequently diagnosed malignancy in women all over the world, and it is one of the most frequent causes of cancer-related death ((Burstein et al., 2018); (Goldhirsch et al., 2011)). ER + tumours are those that are predominant in breast cancer, and thus endocrine therapy is at the heart of managing the disease (Osborne & Schiff, 2011). Tamoxifen, another selective estrogen receptor modulator (SERM), has been in use for decades and has proved to be effective in preventing recurrence and increasing overall survival of both premenopausal and postmenopausal women who have breast cancer ((Lewis-Wambi & Craig Jordan, 2005); (Maximov et al., 2013)). Tamoxifen therapy has been linked to tremendous interindividual variations in therapeutic response and adverse drug reactions despite its already recognised clinical benefits (Goetz et al., 2008). Part of this variability can be explained by genetic variation affecting drug metabolism, estrogen biotransformation, and downstream signalling pathways(Klein et al., 2013) . CYP1B1 (cytochrome P450 1B1) plays a significant role in the metabolism of tamoxifen and in hydroxylating estrogen, hence it controls the level of estrogen in circulation and may influence treatment outcome (Li et al., 2000; (Sissung et al., 2006). Mutations in CYP1B1 have been linked to variations in enzyme activity, unlike changes in estrogen metabolite levels, and are associated with a higher risk of toxicity during CYP1B1 treatment ((Bolton & Thatcher, 2008). Tamoxifen has been reported to have, in addition to its endocrine effects, complex and contradictory effects on lipid metabolism. Although the estrogenic effect could positively influence some lipid parameters, tamoxifen has been associated with hypertriglyceridemia, disturbed very-low-density lipoprotein secretion, and increased cardiovascular risk in a predisposed patient (Sahebkar et al., 2017). Tamoxifen therapy can be accompanied by metabolic imbalances, which may also be influenced by patient factors, including body mass index (BMI) and nutritional status. Obesity is also a known risk factor of dyslipidemia and vitamin D deficiency that can worsen the adverse effects of the treatment and worsen the quality of life (X. Huang et al., 2023). In addition, vitamin D deficiency has also been linked to musculoskeletal symptoms and disease progression in breast cancer patients who are under endocrine therapy (Waltman et al., 2009). Due to the increased focus on precision medicine, the interactions among genetic polymorphisms, metabolic changes, and adverse drug reactions need to be understood to maximise tamoxifen treatment. Therefore, the present study aimed to comprehensively evaluate the pharmacogenomic and metabolic effects of tamoxifen in breast cancer patients, with a specific focus on CYP1B1 polymorphisms (rs1056836 and rs1056827), lipid profile changes, hormonal biomarkers, and adverse drug reactions.

2. Materials and Methods

2.1 Study Design and Population

It was a cross-sectional study on 139 women who had breast cancer and were undergoing tamoxifen treatment. Oncology clinics recruited patients, and they had to meet the inclusion criteria of a known breast cancer diagnosis and taking tamoxifen regularly.

2.2 Data Collection

Demographic and clinical information was obtained, including age, age at menarche, body mass index (BMI), time of disease, time of tamoxifen treatment, tumour type, receptor status, surgery, adjuvant treatment and comorbidities.

2.3 Laboratory Measurements

Blood was collected to determine serum calcium, vitamin D3, estradiol (E2), CA15-3, total cholesterol, triglycerides, HDL, LDL, and VLDL by standard biochemical analyses.

2.4 Genetic Analysis

The DNA genome was then extracted, and the CYP1B1 polymorphic loci were genotyped by polymerase chain reaction (PCR) using the genotyping loci CYP1B1: rs1056836 and CYP1B1: rs1056827.

2.5 Statistical Analysis

Data analysis was conducted using SPSS. Continuous variables were reported as mean ± SD or median (IQR). One-way ANOVA and Kruskal-Wallis were used to perform the comparisons. A p-value below 0.05 was deemed statistically significant.

3. Results

3.1 Demographic and Clinical Characteristics.

Most patients were between 32 and 50 years old (70.5%). The majority of the respondents were overweight and obese (89.2%), and were 66.2% of the respondents had estrogen receptor-positive tumors.

3.2 Biomarkers of Metabolism.

Both increased triglycerides and VLDL were significantly recorded with increased duration of disease and increased use of tamoxifen. Triglycerides and VLDL were significantly increased, and lower vitamin D3 levels were associated with obesity.

3.3. Associations Between Pharmacogenomic

A significant association was found between CYP1B1 rs1056827 genotypes and LDL levels, with GT carriers having higher LDL levels (p = 0.039), see Table1.

Table1: Description of Laboratory Biomarkers of The Studied Patients According To Rs1056827 (N=139)

***Parameter**	**GG**	**GT**	**TT**	**MC**	**P value**
Ca2	8.97±0.72	9.00±0.81	9.02±0.66	NS	0.977
Chol.	184.73±36.40	178.21±47.26	167.50±22.78	NS	0.515
LDL	93.12±30.88	107.56±47.67	86.07±7.23	**GT vs GG**	**0.039**
****Parameter**	**GG**	**GT**	**TT**	**MC**	**P value**
Vit.D3	20.00 (20.5)	18.55 (18.3)	25.50 (25.1)	NS	0.889
TG	173.00 (122.0)	171.50 (81.0)	156.50 (162.8)	NS	0.382
HDL	41.20 (12.0)	39.50 (12.8)	39.50 (20.8)	NS	0.619
VLDL	37.00 (29.5)	34.70 (17.9)	32.20 (26.3)	NS	0.601
*One-way ANOVA test was used with a significant p-value of less than 0.05. Results are presented as mean ± SD **Kruskal-Wallis test was used with a significant p-value of less than 0.05. Results are presented as median with IQR.					

Table2: Description of Laboratory Biomarkers of The Studied Patients According to Rs1056836 (N=139)

*Parameter	CC	CG	GG	MC	P value
Ca2	8.90±0.77	9.00±0.67	9.20±0.81	NS	0.620
Chol.	179.75±38.55	187.10±40.31	185.33±41.09	NS	0.582
LDL	93.48±34.68	103.44±39.98	91.61±22.87	NS	0.294
**Parameter	**CC**	**CG**	**GG**	**MC**	**P value**
Vit.D3	20.75 (24.0)	18.00 (17.7)	20.00 (21.5)	NS	0.327
TG	154.5 (103.7)	180.0 (153.3)	238.0 (287.4)	NS	0.059
HDL	42.00 (9.0)	37.35 (15.5)	41.70 (15.8)	NS	0.140
VLDL	34.70 (20.8)	38.80 (30.5)	47.60 (54.9)	NS	0.077
*A One-Way ANOVA Test gave us a significant result at a p-value less than 0.05, and we are using mean ± SD to provide a visual representation of the numbers when we looked at our data. *The Kruskal-Wallis test showed us that the difference was significant. Because we could easily calculate the median and interquartile range (IQR) of the data, we decided to present the results this way.					

4. Discussion

The present study article is an in-depth review of the pharmacogenomic and metabolic implications of tamoxifen therapy on patients with breast cancer, with specific reference to the genetic polymorphic phenotyping of CYP1B1 and lipid profiles. The piece has contributed positively to the emerging discipline of individualized endocrine therapy through offering clinical, biochemical, and genetic data of the same ((Goetz et al., 2008); (Goldhirsch et al., 2011)).

4.1 Metabolic Effects of Tamoxifen Therapy

The fact that lipid metabolism changes significantly with disease duration and the course of tamoxifen treatment is among the most noticeable outcomes of the research. The levels of triglyceride and VLDL were higher in the patients who had longer disease and treatment periods and in the patients who were obese. The results have clinical implications because tamoxifen has both estrogenic and anti-estrogenic effects on lipid metabolism (Ntukidem et al., 2008). Even though tamoxifen might lower LDL cholesterol by estrogen receptor-mediated actions, it can also enhance hepatic triglyceride production, which would predispose those with a predisposition to hypertriglyceridemia (Isobe et al., 2021).

The results of increased triglycerides and VLDL after long-term tamoxifen use confirm previous findings that it is associated with dyslipidemia and, in mild cases, severe hypertriglyceridemia and pancreatitis (Isobe et al., 2021). The mechanisms mediating these metabolic changes could be via hepatic estrogen receptor signaling, impairment of lipoprotein lipase activity, and enhancement of very-low-density lipoprotein secretion(J. K. Huang & Lee, 2022) . There was no substantial difference in total cholesterol, LDL, or HDL between the treatment periods, suggesting that triglyceride-rich lipoproteins are highly vulnerable to the tamoxifen-induced metabolic imbalance.

4.2 Impact of the Body Mass Index and Vitamin D State

The exposure to body mass index as a critical modulator of metabolic outcome in this cohort was cultivated. The levels of triglyceride and VLDL were higher in obese patients, and the levels of vitamin D3 were very low. The results are consistent with other prior findings, which show that obesity is co-morbid with dyslipidemia and decreased vitamin D bioavailability caused by adipose tissue sequestration ((Y. Huang et al., 2025).

Deficiency of vitamin D has been associated with the development of breast cancer, musculoskeletal pains, and low quality of life, especially in patients undergoing endocrine therapy (Napoli et al., 2010). The very low concentration of vitamin D3 in the obese patients could be one of the reasons why musculoskeletal adverse effects, including arthralgia, were high in this study. The results highlight the need to regularly evaluate patients on long-term tamoxifen therapy for breast cancer using metabolic and nutritional evaluation.

4.3 Pharmacogenomic Role of CYP1B1 Polymorphisms

The study's finding of a strong association between the CYP1B1 rs1056827 polymorphism and LDL levels, with carriers of the GT allele having higher LDL levels, is one of its strongest aspects. CYP1B1 is one of the enzymes involved in estrogen hydroxylation and metabolism activation of tamoxifen (Hanna et al., 2000). The CYP1B1 polymorphisms might also be used to generate variation in enzyme activity, which results in variation in the production of metabolites and, consequently, the metabolite outcome (Sissung et al., 2006). This result confirms the hypothesis that individual differences in genetic variation in estrogen-metabolising enzymes lead to interindividual differences in lipid metabolism during tamoxifen therapy. Even though there was no substantial evidence of a correlation between CYP1B1 polymorphisms and estradiol or CA15-3

concentrations, other studies suggest that CYP1B1 is likely to increase metabolic and toxic pathways rather than tumour biomarkers (Bolton & Thatcher, 2008).

4.4 Clinical and Pharmacogenomic Implications

The results of this research have significant implications for individual breast cancer treatment. Subsequently, patient identification with a higher risk of dyslipidemia due to genetic background and metabolic profile could be applied to identify monitored individuals and apply specific interventions. CYP1B1 pharmacogenomic screening (along with routine lipid and vitamin D testing) could be used to improve the safety and efficacy of long-term tamoxifen treatment ((Goetz et al., 2008); (Goldhirsch et al., 2011)).

4.5 Limitations and Future Direction of the Study.

This study has a number of limitations despite the strengths, and they include its cross-sectional study and a rather limited size of the sample, especially when it comes to rare genotypes. The environmental factors (diet and physical activity) were not measured and might have played a role in the metabolic results. It is necessary to carry out future longitudinal studies with bigger and more diverse populations that are ethnically represented to confirm these results and further explain the mechanisms between the CYP1B1 polymorphisms, estrogen metabolism, lipid changes, and adverse drug reactions.

Conclusion

CYP1B1 genetic polymorphisms, particularly RS1056827, could influence lipid metabolism among breast cancer patients receiving tamoxifen. Prolonged use of tamoxifen is connected with dyslipidemia. Individualized treatment with tamoxifen and better patient outcomes can be encouraged by introducing pharmacogenomic screening into clinical practice.

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