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Changes of diamine oxidase and D-lactate in human breast and gynecologic cancers after chemotherapy

Lixia Hu, MD[a,*], Fanliang Kong, MD[a], Qianqian Yuan, MD[a], Mengqin Huang, MD[a], Yong Huang, MD[a]

Abstract

This study investigates the changes in diamine oxidase (DAO) and D-lactate levels in cancer patients undergoing chemotherapy and their clinical significance in evaluating intestinal barrier function. Breast and gynecologic cancer patients who received chemotherapy between January 2020 and December 2023 were enrolled from our hospital. Blood samples were taken before chemotherapy, within 3 days after chemotherapy, and before the next course of chemotherapy. The level of plasma DAO and D-lactate were measured by enzyme-linked immunosorbent assay (ELISA). After chemotherapy, nutritional markers such as albumin (ALB) and prealbumin (PAB) were evaluated. Anorexia, vomiting, nausea and diarrhea were evaluated during the chemotherapy cycle. There were no notable differences in serum DAO and D-lactate levels before chemotherapy among different tumor types, tumor stage and chemotherapy type. Serum DAO and D-lactate levels after chemotherapy were significantly elevated compared to their levels before chemotherapy ($P < .05$). The plasma DAO and D-lactate levels in cancer patients before the next course of chemotherapy were higher than those observed before the initial treatment, but the difference failed to achieve statistical significance ($P > .05$). The levels of DAO before chemotherapy were higher in patients with diarrhea and anorexia after chemotherapy than those without diarrhea and anorexia ($P < .05$). The levels of D-lactate before chemotherapy were notably elevated in patients with vomiting, diarrhea and nausea after chemotherapy than those without vomiting, diarrhea and nausea ($P < .05$). Monitoring serum levels of DAO and D-lactate in cancer patients undergoing chemotherapy can serve as indicators for evaluating gastrointestinal dysfunction and nutritional status.

Abbreviations: ALB = albumin, DAO = diamine oxidase, ELISA = enzyme-linked immunosorbent assay, PAB = prealbumin, SD = standard deviation.

Keywords: cancer, chemotherapy, diamine oxidase, D-lactate

1. Introduction

Cancers of the breast and female reproductive system, such as cervical, endometrial, ovarian, and other rare gynecologic malignancies, pose a significant threat to women's health.[1] While surgical intervention is the primary treatment for early-stage cancers, chemotherapy is commonly employed for managing advanced or recurrent cases. Chemotherapy can substantially improve the prognosis of cancer patients, but it also carries the risk of serious side effects. Gastrointestinal toxicities resulting from chemotherapy can adversely impact patients' nutritional status by reducing food intake and may lead to delays or discontinuation of treatment.

The intact intestinal mucosal structure and normal intestinal barrier function are very important to improve the prognosis and prognosis of the patients with malignant tumor, this has also become an important factor affecting the process of chemotherapy. External stimuli can impair the normal intestinal structure and enhance gut barrier permeability, allowing metabolites from the gut microbiota to leak into the bloodstream.[2] Alterations in serum diamine oxidase (DAO) and D-lactate levels may represent markers of changes in gut wall permeability.

DAO is an enzyme predominantly located in the gastrointestinal tract, where it is essential for metabolizing dietary histamine. When the intestinal barrier is compromised, DAO is transferred into the bloodstream, making serum DAO activity an indirect indicator of intestinal permeability.[3] Additionally, D-lactate is frequently utilized as an indicator for clinical assessment of intestinal mucosal permeability. D-lactate is an important metabolite in the digestive system, and its presence in the blood can indicate increased intestinal mucosal permeability, serving as an early marker of intestinal mucosal damage.[4,5]

Patients with impaired intestinal barrier function had significantly decreased tolerance to chemotherapy and increased

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

[a] Department of Oncology, The Second People's Hospital of Hefei, Hefei, Anhui, China.

** Correspondence: Lixia Hu, Department of Oncology, The Second People's Hospital of Hefei, Hefei, Anhui, China (e-mail:hulixia410@163.com).*

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complications. Impairment of intestinal barrier function is linked to poor clinical outcomes and often exacerbates malnutrition. The purpose of this study was to evaluate the impact of DAO and D-lactate on the adverse reactions and nutritional status of cancer patients during chemotherapy so as to provide insights for clinical intervention.

2. Methods

2.1. Study participants

Cancer patients who received chemotherapy in our hospital between January 2020 and December 2023 were screened to be included. Inclusion criteria: Pathological diagnosis of breast cancer, cervical cancer, or ovarian cancer; complete clinical data; no surgery, radiation therapy, or other chemotherapy interventions were performed within the 4 weeks prior to this chemotherapy; the patient's informed consent form and signature on the consent form.

Exclusion criteria: the presence of major organ disease or dysfunction, the presence of other malignancies, the presence of systemic infectious disease or autoimmune disease, the presence of abnormal coagulation, the presence of neurological disorder disease, and the presence of multi-organ failure has the intestinal tract chronic inflammation and other intestinal dysfunction disease. The Ethics Committee of the Second People's Hospital of Hefei granted approval for this study.

2.2. Detection of observation indicators

Observation indicators include nutritional status and intestinal mucosal barrier integrity indicators. We assessed intestinal mucosal barrier markers such as DAO and D-lactate in peripheral blood collected 1 week before chemotherapy, within 3 days after chemotherapy, and before the next course of chemotherapy.

After chemotherapy, we evaluated nutritional markers such as albumin (ALB) and prealbumin (PAB).All blood samples were taken following an overnight fast of no <6 hours. Collected blood was immediately centrifuged at 1500 g for 15 minutes at 4°C. All serum samples were stored at −80°C until use. The serum levels of DAO and D-lactate were assessed using an enzyme-linked immunosorbent assay (ELISA) (Beijing Zhongsheng Jinyu Diagnostic Technology Co., Ltd, China). All measurement procedures were carried out following the manufacturer's instructions. The levels of ALB and PAB were detected by automatic biochemical analyzer. In addition, we evaluated the anorexia, vomiting and diarrhea during the chemotherapy cycle.

2.3. Statistical analysis

Statistical analysis was conducted using SPSS 20.0 (Chicago). Continuous data were tested for normality by the Kolmogorov–Smirnov method and all were in accordance with normal distribution, presented as mean ± standard deviation. Intergroup comparison was performed using the independent samples *t*-test, while comparison among multiple groups was conducted using 1-way analysis of variance. $P < .05$ was interpreted as statistically significant.

3. Results

3.1. Participant baseline characteristics

The patients were included 22 with breast cancer, 10 with cervical cancer and 10 with ovarian cancer. There were no notable differences in serum DAO and D-lactate levels before chemotherapy among different tumor types, tumor stage, and chemotherapy type ($P > .05$) (Table 1).

3.2. Comparison of serum DAO and D-lactate levels before chemotherapy, after chemotherapy, and before the next course of chemotherapy

The DAO and D-lactate levels after chemotherapy were significantly elevated compared with those before chemotherapy ($P < .05$), see Table 2. The plasma DAO and D-lactate levels in cancer patients before the next course of chemotherapy were higher compared with those before chemotherapy, but the difference was not statistically significant ($P > .05$).

3.3. Effects of DAO and D-lactate on the levels of ALB and PAB after chemotherapy

The levels of PAB after chemotherapy were notably reduced compared to those before chemotherapy ($P < .05$). Similarly, ALB levels also showed a decline after chemotherapy, but the difference failed to achieve statistical significance ($P > .05$), see Table 3. Subsequently, we examined the relationship between pre-chemotherapy DAO and D-lactate and post-chemotherapy PAB levels, with greater PAB reductions in patients with higher levels of DAO ($P < .05$).

3.4. Effects of DAO and D-lactate on adverse reactions after chemotherapy

We mainly evaluated the side effects such as vomiting, diarrhea, anorexia, and nausea during this chemotherapy cycle. The levels of DAO before chemotherapy were higher in patients with diarrhea and anorexia after chemotherapy than those without diarrhea and anorexia ($P < .05$), as detailed in Table 4. Additionally, the levels of D-lactate before chemotherapy were notably elevated in patients with vomiting, diarrhea and nausea after chemotherapy than those without vomiting, diarrhea and nausea ($P < .05$), see Table 4.

Table 1

Levels of DAO and D-lactate in patients with different clinical characteristics.

Characteristic	Number	DAO	*P*	D-lactate	*P*
Tumor type					
Breast cancer	22	9.58 ± 2.47	.849	14.25 ± 2.46	.880
Cervical cancer	10	9.09 ± 2.82		14.86 ± 5.42	
Ovarian cancer	10	9.02 ± 3.10		13.85 ± 3.68	
Tumor stage					
I to II	10	8.95 ± 3.04	.521	13.64 ± 4.71	.402
III to IV	32	9.56 ± 2.42		14.64 ± 3.18	
Chemotherapy type					
Adjuvant chemotherapy	20	9.15 ± 2.30	.549	14.01 ± 2.54	.598
Palliative chemotherapy	22	9.69 ± 3.02		14.68 ± 4.93	

DAO = diamine oxidase.

Table 2

Comparison of serum DAO and D-lactate levels before and after chemotherapy.

Group	Number	DAO	D-lactate
before chemotherapy	42	9.38 ± 2.60	14.29 ± 3.68
After chemotherapy	42	13.02 ± 3.82*	19.75 ± 4.41*
Before the next course of chemotherapy	42	10.29 ± 2.74†,‡	15.24 ± 2.94†,‡

DAO = diamine oxidase.
*P<.05 vs before chemotherapy.
†P<.05 vs after chemotherapy.
‡P>.05 vs before chemotherapy.

4. Discussion

The introduction of novel anticancer and molecularly targeted therapies has established chemotherapy as a standard approach for treating numerous cancers, particularly those in advanced or metastatic stages. Unfortunately, these treatments often cause gastrointestinal mucosal injury, leading to adverse effects such as anorexia, nausea, and diarrhea. Such gastrointestinal toxicity not only diminishes patients' quality of life and compromises their nutritional health but also risks treatment delays or dose reductions.[6,7] Additionally, damage to the gastrointestinal lining and associated malnutrition during chemotherapy may facilitate bacterial translocation, potentially resulting in severe, life-threatening complications.[8,9] Therefore, we monitored gut barrier function in patients with malignant tumors for early detection, diagnosis and treatment of gastrointestinal dysfunction.

Because of intestinal barrier impairment, DAO and D-lactate within the intestinal mucosal epithelium are discharged into the bloodstream.[10,11] Studies have confirmed that alterations in DAO and D-lactate levels within the peripheral blood can be gauged through noninvasive means, serving as effective indicators to mirror the condition of the intestinal mucosa.[12,13] The study by Zhang et al[14] further demonstrated that serum DAO and D-lactate are accessible and widely accepted biomarkers for evaluating intestinal barrier impairment. When the intestinal mucosal cells undergo necrosis and exfoliation, the translocation of DAO into bloodstream triggers a rise in plasma DAO levels, indicating the impairment of the intestinal mucosal barrier and alterations in intestinal permeability.[9,15,16] D-lactate is primarily synthesized by fermentation of microorganisms.[17] Under typical conditions, the intestinal epithelium serves as a barrier to keep the levels of D-lactate in the intestinal cavity in check. Nevertheless, when the structure of the intestinal mucosa suffers damage, the serum D-lactate levels will rise.[18,19] Thus, the fluctuations in the concentrations of DAO and D-lactate mirror the degree of intestinal mucosal impairment and alterations in permeability. For example, Yang et al[20] found that integrating serum DAO, D-lactate, and endotoxin levels offered a superior predictive value for gut-derived infections compared to individual markers alone, and incorporating these indicators with the diagnosis of malignant bowel obstruction further enhanced the prediction accuracy.

A previous study[21] has established that serum DAO activity significantly increases following cisplatin exposure and histopathological analysis of intestinal tissues revealed severe mucosal damage, including villous atrophy, detachment, and loss. Previous studies[22] have mostly focused on gut barrier function before and after chemotherapy for gastrointestinal tumors, and given that gastrointestinal tumors themselves may have impaired gut barrier function, this may influence the results to some extent, so we studied the levels of DAO and D-lactate during chemotherapy of breast cancer and gynecologic tumor. In our study, the levels of DAO and D-lactate in peripheral blood of patients after chemotherapy exceeded those before chemotherapy, indicating that chemotherapy has some damage to intestinal mucosa of cancer patients. Meanwhile, our study demonstrated that there were no significant differences in serum DAO and D-lactate levels before chemotherapy among different tumor types, tumor stage and chemotherapy type, which might be associated with the limited sample size. Further study is needed to expand the sample size. Our study showed that circulating DAO and D-lactate levels in cancer patients before the next course of chemotherapy exceeded those measured before the initial treatment, but the difference failed to reach statistical significance. This suggests that the use of chemotherapeutic drugs leads to a notable rise in serum DAO and D-lactate levels, which gradually return to normal during the drug-free interval.

Diarrhea and appetite loss are common gastrointestinal side effects of cancer treatments, stemming from intestinal mucosal dysfunction induced by chemotherapeutic drugs. Previous studies demonstrated that plasma DAO activities exhibited a weak relationship with appetite loss during chemotherapy in patients with gastric cancer.[22] We mainly evaluated the gastrointestinal side effects such as vomiting, diarrhea, anorexia, and nausea during this chemotherapy cycle. The results of this study revealed that pre-chemotherapy DAO levels were elevated in patients who developed diarrhea and anorexia after chemotherapy compared to those who did not. Similarly, pre-chemotherapy D-lactate levels were elevated in patients with vomiting, diarrhea and nausea after chemotherapy than those without vomiting, diarrhea and nausea. This aligns with the results of Zhang et al,[23] who assessed that serum DAO and D-lactate levels before radiotherapy were notably elevated in patients experiencing gastrointestinal dysfunction during radiotherapy for liver cancer than in the group without gastrointestinal dysfunction.

The intestinal barrier has a significant effect on nutrient absorption, and continuous damage can impair this process, ultimately leading to malnutrition.[24] Moreover, malnutrition can not only impact the completeness of the intestinal barrier but also disrupt the equilibrium of intestinal microbiota.[25,26] ALB is produced by the liver and is associated with nutritional status. PAB is rarely stored in the body and biological half-life for only 1.9 days, so its level is a sensitive indicator of recent overall nutritional status.[27] We examined the relationship between pre-chemotherapy DAO and D-lactate and post-chemotherapy PAB levels, with greater PAB reductions in patients with higher levels of DAO. This shows that DAO level may be a reliable marker of malnutrition, which is consistent with Miyoshi et al[28] findings. Geng et al[29] has demonstrated that the DAO and D-lactate levels were markedly reduced following nutritional intervention, indicating the restoration of intestinal barrier integrity. Therefore, the evaluation and intervention of nutritional status during chemotherapy should be strengthened for patients with high DAO level before chemotherapy.

There are a few limitations in this research. First, the sample number was limited, and the subject had only 3 type of

Table 3

Comparison of ALB and PAB level before and after chemotherapy (mean ± SD, g/L).

Group	Number	ALB	*P*	PAB	*P*
Before chemotherapy	42	39.01 ± 2.08	.057	2.21 ± 0.49	.046
After chemotherapy	42	38.16 ± 1.61		1.99 ± 0.41	

ALB = albumin, PAB = prealbumin, SD = standard deviation.

Table 4

Effects of DAO and D-lactate on adverse reactions after chemotherapy.

Adverse reaction	Number	DAO	*P*	D-lactate	*P*
Vomiting					
No	37	8.61 ± 3.17	.395	13.32 ± 2.72	.001
Yes	5	9.56 ± 2.46		18.31 ± 4.59	
Diarrhea					
No	35	8.77 ± 2.36	.023	13.51 ± 2.55	.038
Yes	7	10.94 ± 2.63		16.32 ± 5.31	
Anorexia					
No	29	8.63 ± 2.23	.018	14.0 ± 2.28	.538
Yes	13	10.71 ± 2.74		14.81 ± 5.43	
Nausea					
No	34	8.59 ± 2.70	.263	13.31 ± 2.87	.008
Yes	8	9.68 ± 2.54		16.82 ± 4.46	

DAO = Diamine oxidase.

cancer. Hence, it becomes essential to enlarge the sample number and tumor species to study the correlation between chemotherapy and the change of DAO and D-lactate level. Second, because serum levels of PAB and ALB are not sufficient to indicate nutritional status, additional nutritional indicators should be explored. Third, because this study only focused on single-center patients with a small sample size, the specific medications used in the treatment regimen were not classified, and the impact of different chemotherapy regimens was not considered.

5. Conclusions

In conclusion, our research centered around the impacts of DAO and D-lactate on common adverse reactions and nutritional status after chemotherapy in gastrointestinal cancer. High pre-chemotherapy DAO and D-lactate levels had a good predictive effect on vomiting, diarrhea and deterioration of nutritional indicators after chemotherapy. Monitoring serum levels of DAO and D-lactate before chemotherapy has positive reference value for the prevention and treatment of adverse reactions after chemotherapy and the whole course of nutrition management.

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Author contributions

Conceptualization: Lixia Hu, Menqin Huang.
Data curation: Lixia Hu, Fanliang Kong, Yong Huang.
Formal analysis: Lixia Hu, Fanliang Kong, Qianqian Yuan, Yong Huang.
Investigation: Lixia Hu, Menqin Huang, Yong Huang.
Methodology: Lixia Hu, Menqin Huang.
Supervision: Lixia Hu, Qianqian Yuan, Yong Huang.
Writing – original draft: Lixia Hu, Qianqian Yuan, Menqin Huang.
Writing – review & editing: Lixia Hu, Qianqian Yuan.

References

[1] Ferlay J, Colombet M, Soerjomataram I, et al. Cancer statistics for the year 2020: an overview. Int J Cancer. 2021;149:778–89.
[2] Turner JR. Intestinal mucosal barrier function in health and disease. Nat Rev Immunol. 2009;9:799–809.
[3] Bischoff SC, Barbara G, Buurman W, et al. Intestinal permeability: a new target for disease prevention and therapy. BMC Gastroenterol. 2014;14:189.
[4] Sun XQ, Fu XB, Zhang R, et al. Relationship between plasma D(-)-lactate and intestinal damage after severe injuries in rats. World J Gastroenterol. 2001;7:555–8.
[5] Sheedy JR, Wettenhall RE, Scanlon D, et al. Increased d-lactic acid intestinal bacteria in patients with chronic fatigue syndrome. In Vivo. 2009;23:621–8.
[6] Aapro M, Arends J, Bozzetti F, et al; ESMO (European School of Medical Oncology). Early recognition of malnutrition and cachexia in the cancer patient: a position paper of a European School of Oncology Task Force. Ann Oncol. 2014;25:1492–9.
[7] Vandebroek AJ, Schrijvers D. Nutritional issues in anti-cancer treatment. Ann Oncol. 2008;19(Suppl 5):v52–5.
[8] Berg RD. Bacterial translocation from the gastrointestinal tract. J Med. 1992;23:217–44.
[9] Swank GM, Deitch EA. Role of the gut in multiple organ failure: bacterial translocation and permeability changes. World J Surg. 1996;20:411–7.
[10] Mantis NJ, Rol N, Corthesy B. Secretory IgA's complex roles in immunity and mucosal homeostasis in the gut. Mucosal Immunol. 2011;4:603–11.
[11] Zhang H, Chen Y, Chen Y, et al. Dietary pterostilbene supplementation attenuates intestinal damage and immunological stress of broiler chickens challenged with lipopolysaccharide. J Anim Sci. 2020;98:skz373.
[12] Luo Y, Yang Q, Li B, Yao Y. Establishment of a quality control circle to reduce biofilm formation in flexible endoscopes by improvement of qualified cleaning rate. J Int Med Res. 2020;48:300060520952983.
[13] Mahlknecht A, Abuzahra ME, Piccoliori G, Enthaler N, Engl A, Sonnichsen A. Improving quality of care in general practices by self-audit, benchmarking and quality circles. Wien Klin Wochenschr. 2016;128:706–18.
[14] Zhang R, Chen YN, Zhang J, Liu J. Elevated serum levels of diamine oxidase, D-lactate and lipopolysaccharides are associated with metabolic-associated fatty liver disease. Eur J Gastroenterol Hepatol. 2023;35:94–101.
[15] Zhang JB, Du XG, Zhang H, et al. Breakdown of the gut barrier in patients with multiple organ dysfunction syndrome is attenuated by continuous blood purification: effects on tight junction structural proteins. Int J Artif Organs. 2010;33:5–14.
[16] Zhao Y, Qin G, Sun Z, Che D, Bao N, Zhang X. Effects of soybean agglutinin on intestinal barrier permeability and tight junction protein expression in weaned piglets. Int J Mol Sci. 2011;12:8502–12.
[17] Garrote GL, Abraham AG, Rumbo M. Is lactate an undervalued functional component of fermented food products? Front Microbiol. 2015;6:629.
[18] Upadhyay N, Jaiswal P, Jha SN. Detection of goat body fat adulteration in pure ghee using ATR-FTIR spectroscopy coupled with chemometric strategy. J Food Sci Technol. 2016;53:3752–60.
[19] Chavan SS, Mahajan A, Talbar SN, Desai S, Thakur M, D'Cruz A. Nonsubsampled rotated complex wavelet transform (NSRCxWT) for medical image fusion related to clinical aspects in neurocysticercosis. Comput Biol Med. 2017;81:64–78.
[20] Yang S, Zhang X, Ma H, et al. Value of combining the serum d-lactate, diamine oxidase, and endotoxin levels to predict gut-derived infections in cancer patients. J Nutr Oncol. 2023;8:101–6.
[21] Liu W, Zhang H, Hou YY, et al. Arginyl-fructosyl-glucose, a major Maillard reaction product of red ginseng mitigates cisplatin-evoked intestinal toxicity in vivo and in vitro. Food Funct. 2022;13:11283–97.
[22] Namikawa T, Fukudome I, Kitagawa H, Okabayashi T, Kobayashi M, Hanazaki K. Plasma diamine oxidase activity is a useful biomarker for evaluating gastrointestinal tract toxicities during chemotherapy with oral fluorouracil anti-cancer drugs in patients with gastric cancer. Oncology (Huntingt). 2012;82:147–52.
[23] Zhang L, Guo Y, Xu H. Clinical study on serum D-lactate, diamine oxidase, and bacterial endotoxin in radiotherapy-treated patients with primary liver cancer. Hebei Med. 2023;16:2431–2434+2439.
[24] Clark WA, Cress EM. Nutritional issues and positive living in human immunodeficiency virus/AIDS. Nurs Clin North Am. 2018;53:13–24.
[25] McKenzie C, Tan J, Macia L, Mackay CR. The nutrition-gut microbiome-physiology axis and allergic diseases. Immunol Rev. 2017;278:277–95.
[26] Mills S, Stanton C, Lane JA, Smith GJ, Ross RP. Precision nutrition and the microbiome, part I: current state of the science. Nutrients. 2019;11:923.
[27] Wang QR, Long J, Wang CC, Hu JL, Lin N, Tang SH. Case report of atypical undernutrition of hypoproteinemia type. Open Life Sci. 2023;18:20220766.
[28] Miyoshi J, Miyamoto H, Goji T, et al. Serum diamine oxidase activity as a predictor of gastrointestinal toxicity and malnutrition due to anticancer drugs. J Gastroenterol Hepatol. 2015;30:1582–90.
[29] Geng ST, Zhang JB, Wang YX, et al. Pre-digested protein enteral nutritional supplementation enhances recovery of CD4(+) T cells and repair of intestinal barrier in HIV-infected immunological non-responders. Front Immunol. 2021;12:757935.