Serum Homocysteine in breast cancer patients receiving chemotherapy with or without thrombosis

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دراسة مستوى الهوموسيستايين لدى مرضى اورام الثدى الذين يتلقون علاج كيمائى مع وجود او عدم وجود تجلط بالدم

رسالة

توطئة للحصول على درجة الماجستير فى الباطنه العامة

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الملخص العربى

ان الهوموسيستايين حامض امينى غير اساسى يحتوى على الكبريت وينتج من الميثايونين(حامض امينى اساسى) .

وفى عمليه الايض الطبيعى يتحول مباشره الى سيستايين أو تعاد عمليه المثيله فيتحول الى ميثايونين. وهو يوجد فى البلازما مرتبطاً بالبروتين(غالباً بالالبومين) أو حراً. ومن العادى ان توجد نسبه ضئيله جداً فى دم وبول الناس الاصحاء .وتصل معدلاته الطبيعيه فى البلازما حوالى٦-١٤ميكرومول / لتر.

وتعتمد نسبته فى البلازما على خطوتين أيضيتين هما عمليه عدم المثيله للهوموسيستايين وعمليه اعاده المثيل ثانيه الى الميثايونين .والانزيمات الهامه فى هذه الخطوات هى سيستايين بيتا سينثتاز والميثيلين تتراهيدروفولات ريدكتاز بالتتابع .ويعمل فيتامين ب٦ كعامل مساعد فى عمليه عدم المثيله للهوموسيستايين بينما يعمل كلاًمن فيتامين ب١٢ والفولات كعاملين مساعدين فى عمليه اعاده المثيله ثانيه الى الميثايونين. وهناك طريق أخر هو المثيله المعتمده على البيتان للهوموسيستايين .

وقد أثبتت العديد من الدراسات ان زياده نسبه الهوموسيستايين فى الدم تؤدى الى زياده نسبه الاصابه بامراض الاوعيه الدمويه للقلب، كما ان المرضى المصابين بفقدان الهوموسيستايين فى البول (هو مرض وراثى ناتج عن خلل فى ايض الهوموسيستايين) يصابون بامراض الاوعيه الدويه للقلب بنسبه عاليه فى فتره المراهقه وحتى اثناء الطفوله . وثبت من البيانات المتاحه ان الهوموسيستايين هو عامل خطوره مستقل فى الاصابه بتصلب الشرايين .

وقد اجريت الدراسة على ثلاثين حالة(٢٠ حالة مرضية و١٠ ضوابط) جميع الحالات كانت اناث .وقد تم قياس معدل

الهوموسيستايين بالدم فى المجموعة الظابطه وكذلك فى الحالات المرضية قبل وبعد العلاج الكيمائى

وقد أسفرت الدراسة عن النتائج التالية :

١.ارتفاع مستوى الهوموسيستايين فى البلازما فى مجموعة المرضى عن المجموعة الظابطة وإن لم تكن ذات دلاله احصائية عالية فقد كانت عالية بنسبة يزيد معها عامل خطورة تجلط الدم .

٢. انخفاض مستوى الهوموسيستايين فى البلازما فى مجموعة المرضى بعد العلاج الكيمائى مقارنة بنفس المجموعة قبل العلاج الكيمائى .

الاستنتاجات:

ارتفاع مستوى الهوموسيستايين فى البلازما يمكن أن يكون عامل خطورة مستقل فى الاصابة لتصلب الشرايين . الترابط بين الهوموسيستايين وعوامل الخطوره الرئيسية فى امراض مثل ارتفاع الضغط ، التدخين ، ارتفاع مستوى الكولسترول الكلى .. الخ . يحتاج لمزيد من الدراسات .

يحتاج تاثير الانواع المختلفة للعلاج الكيمائى المعطى لمرضى اورام الثدى على مستوى الهوموسيستايين بالدم الى مزيد من الدراسات .

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List of abbreviations

-tHcy	Total Homocysteine.
-ELISA	Enzyme-Linked Immunosorbent Assay.
- MHC	Major Histocomptability Complex.
- PCA	Procoagulant Activity.
- IL-1	Interleukin-1.
-TNF	Tumour Necrosis Factor.
-vWF	Von Willebrand Factor.
-DVT	Deep venous thrombosis.
-MPD	Myeloproliferative Disease.
-NBTE	Nonbacterial Thrombotic Endocarditis.
- DIC	Disseminated Intravascular Coagulation.
- PT	Prothrombin Time.
-PTT	Partial Thromboplastin Time.
-APL	Acute Promyelocytic Leukemia.
-IgG	Immunoglobulin G.
-IgA	Immunoglobulin A.
-AML	Acute Myeloid Leukemia.
-CML	Chronic Myeloid Leukemia.
-ALL	Acute Lymphocytic Leukemia
-CEA	Carcinoembryonic Antigen.
-AT III	Anti-Thrombin III

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Introduction:

In normal individual , haemostasis is controlled and inappropriate thrombosis doesn't occur . However in malignant diseases , haemostatic mechanisms are significantly altered . This alteration may result in thrombosis or to lesser extent haemorrhage **(Almot and Smith ,1996)**

The second most common cause of death (after infection) in - Patients with malignant diseases are thrombosis and thromboembolic complications . Thrombotic episodes may also precede the diagnosis of cancer by months or years , thus representing a potential marker for occultmalignancy **(Donati , 2004)** .

Thrombosis can be defined as the pathologic process resulting from the inappropriate initiation and propagation of the haemostatic response .Thrombi are solid masses or plugs formed in the circulation from blood constituents .They result in ischaemia from local vascular obstruction or from embolization and obstruction of a distal part of the circulation **(Loscalzo , 2005) .** Arterial thrombi show structural differences from venous thrombi. In arteries , thrombi develop in relation to platelet reaction and accumulation in response to vessel wall damage while in veins , thrombus formation usually follow the generation of coagulated blood in areas of retarded blood flow **(Loscalzo , 2005) .**

Aim of work :

Detection of serum homocysteine level in breast cancer patients receiving chemotherapy for early detection of thrombosis and if there is a relationship between chemotherapy , breast cancer and thrombosis

HYPERCOAGULABLE STATES IN MALIGNANCY

-In normal individual , haemostasis is controlled and inappropriate thrombosis doesn't occur . However in malignant diseases , haemostatic mechanisms are significantly altered . This alteration may result in thrombosis or to lesser extent

haemorrhage **(Almot and Smith ,1996) .**

-One of the most frequent hematological complications encountered by the practicing oncologist is disordered coagulation. Thromboembolic disease affects approximately 15% of all cancer patients**(Green KB,2005)** . This includes superficial and deep venous thrombosis, pulmonary emboli, thrombosis of venous access devices, as well as arterial thrombosis and embolism. It is the second leading cause of death for cancer patients **(Donati ,2004)** . although obviously in many of these patients, thromboembolic disease represents only one of many complications of the end-stage patient.

-Thrombotic events represent one of the most common complications, and a frequent cause of mortality, in patients with malignancy **(Donati MB ,2004)** . Postmortem studies have revealed an incidence of thrombosis of nearly 50% in cancer patients **(Donati MB ,2004)** .

Indeed, it seems that venous thromboembolism may indicate a

poor prognosisfor patients with malignancy insofar as, in many instances, it signifies advanced disease **(Sorensen HT 2006)** .
A greater appreciation of the impact of venous thromboembolism in cancer patients in recent years has led to several trials in which prophylactic anticoagulation was shown to be efficacious in select cancer groups **(Bern MM ,2007)** , and perhaps even to confer some survival benefit. However, such trials have yielded no clear consensus as to the merits of routine anticoagulation in the general cancer population. Furthermore, although the association

of a prothrombotic state with malignancy has been the subject of medical inquiry for more than a century (dating back to its recognition in 1865 by Trousseau), the etiological mechanisms underlying this association are not well-understood.

-A hypercoagulable or prothrombotic state of malignancy occurs due to the ability of tumor cells to activate the coagulation

system. It has been estimated that hypercoagulation accounts for a significant percentage of mortality and morbidity in cancer patients. Prothrombotic factors in cancer include the ability of tumor cells to produce and secrete procoagulant/fibrinolytic substances and inflammatory cytokines, and the physical interaction between tumor cell and blood (monocytes, platelets, neutrophils) or vascular cells. Other mechanisms of thrombus promotion in malignancy include nonspecific factors such as the generation of acute phase reactants and necrosis (i.e., inflammation), abnormal protein metabolism (i.e., paraproteinemia), and hemodynamic compromise (i.e., stasis). In addition, anticancer therapy (i.e., surgery/chemotherapy/hormone therapy) may significantly increase the risk of thromboembolic events by similar mechanisms, e.g., procoagulant release, endothelial damage, or stimulation of tissue factor production by host cells. However, not all of the mechanisms for the production of a hypercoagulable state of cancer are entirely understood. In

this review, we attempt to describe what is currently accepted about the pathophysiology of the hypercoagulable state of cancer.

- Cancer and its treatment can affect all three arms of Virchow's classical triad of causation of thromboembolic disease: alteration in blood flow, damage of endothelial cells, and elaboration of procoagulants. Cancer can affect blood flow by mechanical effects on blood vessels near a tumor. Also, the angiogenesis induced by many tumors causes the creation of complexes of blood vessels that are aberrant in appearance and have very disordered flow. In fact, flow in these vessels can vary not only in magnitude, but also in direction. Endothelial cells can also be damaged directly by tumors or chemotherapy.

Procoagulants can be increased on the surface of cancer cells, and may also be secreted into the blood stream by cancer cells **(Donati MB 2004) .**

-Examples of molecules elaborated by cancer cells that can

predispose to disordered coagulation include tissue factor, a Vitamin K-dependent cysteine protease that activates factor X, and a mucin procoagulant that activates prothrombin. Furthermore, chemotherapy treatment can cause a reduction in levels of the anticoagulant proteins C and S. Indwelling venous access devices may also predispose to thrombosis by altering blood flow, damaging endothelial cells, and serving as a surface upon which procoagulants can promote thrombosis. In addition, other factors can cause dysregulation of the normal mechanisms of thrombosis and hemostasis. Certain tumors cause thromboembolism by direct extension and blockage of neighboring vessels. The best-known example is probably renal cell carcinoma, which can be associated with inferior vena cava (IVC) thrombus by direct extension of tumor into this vessel. Long-term survival of patients with this disorder has been reported after complete resections of the tumor and thrombosed vessel. Other tumors are associated with a secondary thrombocytosis **(Constanti V, 2005)** .