STUDY OF THE RELATIONSHIP BETWEEN HOMOCYSTEINE LEVEL AND BONE MINERAL DENSITY AMONG EGYPTIAN ELDERLY

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LIST OF ABBREVIATIONS

ADL : Activity of Daily Living
Ado : Adenosine
AIDS : Acquired Immune Deficiency Syndrome
BMD : Bone Mineral Density
CRF : Chronic renal faluiure
CVD : Cardiovascular disease
DEXA : Dual energy x-ray absorptiometry
DM : Diabetes mellitus
DTT : Dithiolthrito
EDTA : Ethylene diamine tetra hydro acetic acid
FDA : Food and drug administration
GDS : Geriatric Depression Scale
HBP : Homocysteine binding protein
Hcy : Homocysteine
HIF : Hog intrinsic factor
H-Pylori : Helicobacter Pylori
HRT : Hormonal replacement therapy
HTN : Hypertension
IADL : Instrumental Activity of Daily Living
MMSE : Mini Mental Stata Examination.
MTHFR : Methylenetetrahydrofolate reductase
PTH : Para thyroid hormone
SAH : S- adenosyl -L-homocysteine
SAH hydrolyase: S- adenosyl -L-homocysteine hydrolyase
SD : Standard deviation
TECP : tris 2-carboxylethyl phosphine hydrochloride

Vit B12 : Vitamin B12

WHO : World Health Organization

Aim of the work and hypothesis

To detect the relationship between level of homocysteine and BMD among elderly.

Hypothesis:

There is a relationship between hyperhomocysteinaemia and hypovitaminosis B12 and BMD.

INTRODUCTION

Osteoporosis is a major health problem that is characterized by low bone mineral density (BMD), deterioration of bone microarchitecture, and an increased risk of fracture ***(Melton, 2003).***

Osteoporotic fractures are associated with increased morbidity and mortality and with substantial economic costs ***(Vander et l., 2001)***.

It has been hypothesized that the metabolism of homocysteine is involved in osteoporosis ***(Caliskan et al., 2001).***

Homocysteine is an amino acid intermediate formed during the metabolism of methionine. Elevated plasma homocysteine concentrations may be associated with osteoporosis and may increase the risk of fracture, which can lead to substantial disability high medical costs, and death ***(de Leeuw et al.,*** **2001)**

Some studies suggested that the total homocysteine concentration is strongly associated with the risk of fracture in elderly (***Clark et al., 1998)*** and ***(Hak et al., 2000).***

In the general population, a mildly elevated plasma level of homocysteine, termed hyperhomocysteinemia, is a common condition. Hyperhomocysteinemia is recognized as a major risk factor for

atherosclerotic and thromboembolic disease as well as for cognitive impairment, including that seen in Alzheimer's disease ***(Schnyder et al., 2001).***

Vitamin B12 is important for DNA synthesis and may affect bone formation. It has been linked to osteoblastic activity in clinical studies and cell culture ***(Carmel et al., 1999).***

This vitamin has been associated with osteoblast activity and bone formation, and patients with pernicious anemia have been shown to have greater risk of fracture ***(Clarke, 2001).***

Although vitamin B12 deficiency is rare in young healthy people; the prevalence of vitamin B12 deficiency is more common in the elderly ***(Pluijm et al., 2001).***

Possible causes of vitamin B-12 deficiency are several, including absorptive disorders such as inability to manufacture intrinsic factor or absorptive problems resulting from gastric surgery ***(Tucker et al., 2000).***

Several studies have also shown that dietary deficiency may also be a significant contributor to low serum levels ***(Howard et al., 1998).***

Because subclinical vitamin B12 deficiency is common in elderly people, it may play role in bone health ***(Kim et al., 1996).***

If vitamin B12 is related to bone health, so supplementation of vitamin B12 may help to prevent osteoporosis in elderly people (***Tucker et al., 2002).***

Review

Homocysteine and vitamin B12.

Metabolism of homocysteine:-

Homocysteine (Hcy) is a sulfur-containing amino acid formed during the metabolism of methionine. Homocysteine is metabolized by one of two pathways: remethylation and transsulfuration ***(Kuo et al., 2005).***

In the remethylation cycle, homocysteine is salvaged by the acquisition of a methyl group in a reaction catalyzed by methionine synthase ***(Lentz et al., 2002).***

Vitamin B12 (cobalamin) is an essential cofactor for methionine synthase, N5-methyl-tetrahydrofolate is the methyl donor in this reaction, and N5, N10-methylenetetrahydrofolate reductase functions as a catalyst in the remethylation process ***(Sachdev et al., 2002).***

Under conditions in which an excess of methionine is present or cysteine synthesis is required, Hcy enters the transsulfuration pathway. In this pathway, Hcy condenses with serine to form cystathionine in a reaction catalyzed by the vitamin B6 dependent enzyme cystathionine synthase ***(Seshadri et al., 2002).***

Cystathionine is subsequently hydrolyzed to form cysteine, which may in turn be incorporated into glutathione or further metabolized to sulfate and excreted in the urine ***(Kuo et al., 2005).***

Nutritional deficiencies in the vitamin cofactors (folate, vitamin B12, and vitamin B6) required for homocysteine metabolism may promote hyperhomocystinemia ***(Diaz, 2000).***

Homocysteine and vitamins:-

Markedly elevated Hcy concentrations have been observed in patients with nutritional deficiencies of the essential cofactor vitamin B12 and the cosubstrate folate ***(Pastore et al., 2006).***

Negative correlations between serum vitaminB12, folate, and vitamin B6 concentrations and plasma Hcy concentrations have been observed in normal subjects ***(Ravaglia et al., 2005).***

Some author have suggested that inadequate plasma concentrations of one or more B vitamins are contributing factors in approximately two thirds of all cases of hyperhomocystinemia (***Ravaglia et al., 2005).***

Vitamin supplementation can normalize high Hcy concentrations however; it remains to be determined whether normalizing Hcy concentrations will improve cardiovascular morbidity and mortality ***(Reimann et al., 2006).***

Relation between homocysteine with, coffee and smoking:-

Some authors suggest there is a relation between Hcy and some factors such as coffee, tea alcohol and smoking ***(Kenket et al., 2001).***

Coffee consumption is positively associated with the Hcy concentration in both men and women in most but not all observational studies ***(Koehler et al., 2001).***

Recent intervention trials have shown that this effect of coffee is causal ***(Urgert et al., 2000).***

Caffeine might be the factor that elevates the Hcy concentration because it may inhibit the conversion of homocysteine to cysteine by acting as a vitamin B_6 antagonist ***(Jacques et al., 2001)*** and ***(Grubben et al., 2000).***

Additionally, recent evidence showed that chlorogenic acid, a polyphenol that is present in coffee in the same amount as caffeine, may also partly be responsible for the increase in the Hcy concentration. When polyphenols are metabolized, methyl groups from methionine are necessary, which results in a higher production of homocysteine ***(Olthof et al., 2001).***

Both caffeine and chlorogenic acid are also present in tea, although in smaller doses, which explains the absence of a clear association between the Hcy and tea consumption ***(Christensen et al., 2001).***

Smoking is positively associated with the homocysteine concentration ***(Rasmussen et al., 2000)*** and ***(de Bree et al., 2001d).***

The fact that the smoking effect remains after correction for coffee consumption and folate intake excludes important confounding ***(Koehler et al., 2001)*** and ***(de Bree et al., 2001b).***

However, smokers generally consume a less healthy diet, thus residual confounding of, for example, B vitamin intake cannot fully be excluded, in one study the effect of smoking disappeared after correction for plasma folate ***(Saw et al., 2001).***

The exact mechanism behind the increase in the Hcy concentration is unidentified, but smoking may induce local effects in cells exposed to cigarette smoke, influence the Hcy concentration by changing the plasma thiol redox status, or inhibit enzymes such as methionine synthase ***(Blom and Verhoef .,2000).***

Relation between Hcy and alcohol:-

Alcohol consumption is probably associated with the Hcy concentration in a J-shaped fashion, moderate alcohol consumers have a lower Hcy concentration compared with nondrinkers, whereas alcoholics have elevated Hcy concentrations ***(Halsted, 2001).***

An inverse relationship between alcohol consumption in the moderate consumption range was observed in men only, and in men and women combined ***(de Bree et al., 2001b)*** and ***(Koehler et al., 2001).***