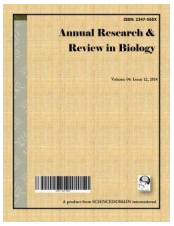

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The Relationship between Homocysteine and Fragility Fractures - A Systematic Review

Alexandru Filip[1], Nina Filip[2*], Bogdan Veliceasa[1], Cristiana Filip[2] and Ovidiu Alexa[1]

[1]Department of Orthopedics and Traumatology, University of Medicine and Pharmacy "Grigore T. Popa", Iasi, Romania.
[2]Department of Biochemistry, University of Medicine and Pharmacy "Grigore T. Popa", Iasi, Romania.

Authors' contributions

This work was carried out in collaboration between all authors. Authors AF and OA conceived the idea and wrote the first draft of the manuscript. Authors NF and BV managed the cross-opinion corrections and organized the figures. Author CF managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

It is known that increased levels of homocysteine in plasma have been associated with various diseases. Current studies show that homocysteine is a new risk factor for the development of osteoporosis. Fragility fractures are associated with increased morbidity, mortality and cause substantial financial loss to the patients and their families.
This mini-review provides a critical overview of currently available studies, examining the relationship between plasma homocysteine levels and fragility fractures. In conclusion more studies are needed to establish a clear relationship between homocysteine and fractures in elderly patients.

Keywords: Hyperhomocysteine; osteoporosis; fracture; methionine; bone fragility.

**Corresponding author: E-mail: zamosteanu_nina@yahoo.com;*

1. INTRODUCTION

Sulfur amino acid metabolism it's one of the major points of interest in biochemistry research.

Methionine and its derivatives participate in a multitude of biological processes including: protein synthesis, polyamines synthesis (spermine and spermidine essential to cell growth), synthesis of creatinine from guanidinoacetate, phosphocoline from phosphoethanolamine, methylation of DNA, etc [1].

Methionine (Met) it's one of the eight essential amino acids, being the only one containing sulfur. Cysteine (Cys), although essential in protein synthesis, is endogenously synthesized from methionine. Homocysteine (Hcy) is an amino acid that does not belong to the protein, being synthesized in the body as an intermediate in the methionine metabolism.

Both Met and Cys are taken from food proteins in a sufficient amount, unlike homocysteine that has been dosed in low amounts in various foods.

The structure of the homocysteine is shown in the Fig. 1.

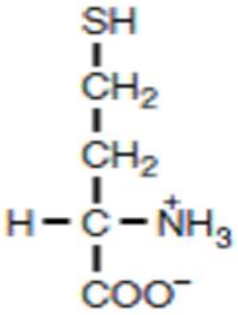

Fig. 1. The structure formula of the homocysteine

Hcy was associated with vascular diseases, for the first time in 1962 when Carson and Neil discovered metabolic abnormalities which caused mental retardation in patients with increased levels of Hcy in the urine [2]. They have published about a new disease in methionine metabolism referring to homocystinuria. Later was published a study showing on the vascular pathologies in patients with homocystinuria. It was the first time that increased Hcy level was linked to premature vascular disease [3]. Currently, it's accepted that an increased level of Hcy (higher than 15 μM) is an independent risk factor for cardiovascular diseases. Recent studies have demonstrated a strong correlation between elevated Hcy levels and chronic kidney disease, neurological disorders, osteoporosis, gastrointestinal disorders and cancer [4-7].

As a result of the growing number in homocysteine research, in the year of 2000 Mudd suggested in his work "Homocysteine and Its Disulfide Derivatives: A Suggested Consensus Terminology" a uniformity of the terminology used in these studies [8].

Homocysteine as a generic term used in scientific papers designates both the reduced thiol form of homocysteine and the compounds that will form homocysteine by cleavage of the disulfide bond.

Like, in this study from 2000, author proposes the following terms for the homocysteine serum fractions:

- fHcy – free homocystein – for free homocysteine, Hcy-H reduced or Hcy-S-R oxidized;
- bHcy – bound homocystein – for protein-bound homocysteine;
- tHcy – total homocystein – for total homocysteine.

Determining massive increases in the plasma level of homocysteine is quite easy to achieve, but the problem arises when trying to determine a level considered "normal" in the population. Several research laboratories have tried to define this normal range; however, the normal level in a population is determined by several factors, both genetic and non-genetic. On hold, this value was set at 15 μM [9].

Instead, if a population with an adequate intake of vitamins is considered, this value can be lowered to about 12 μM. Plasma homocysteine is higher in males than in females (8-12 μM in males vs. 6-10 μM in females), increases with age and decline in renal function (due to a decrease in the rate of Hcy metabolism in the kidney) and is closely related to plasma cysteine [10]. The gender difference can be partly attributed to sex hormones (estrogen, progesterone) and menstrual cycles. Men have Hcy plasma levels increased by 10%, which are supposed to be higher due to muscle mass and

increased creatine / creatinine production, a rich source of Hcy.

Currently, the range considered normal is between 5-15 μM with an average of 10 μM [11]. An increase of 2 μM homocysteine is classified as hyperhomocysteinemia (HHcy). The range of 16-30 μM was classified as moderate, 31-100 μM as an intermediate, and for higher values it was considered that HHcy was a severe one.

Hyperhomocysteinemia defines the state in which homocysteine amino acid concentrations exceed normal levels. HHcy is a consequence of enzymatic deficiencies and / or vitamin deficiencies (Fig. 2) that interfere with the normal metabolism of methionine and / or Hcy. Cofactors derived from complex B vitamins (B2, B6, B9, B12) participate in enzymatic reactions that regulate Hcy metabolism [12]. It's known that individuals with HHcy have inadequate concentrations of one or more enzyme cofactors.

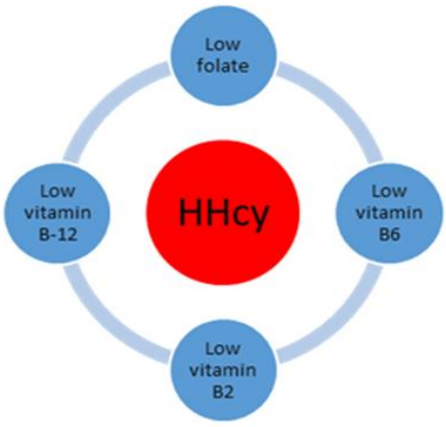

Fig. 2. Risk factors for HHcy

Genetic anomalies in Hcy metabolism enzymes: methylenetetrahydrofolate reductase (MTHFR), methionine synthase (MTR), methionine synthase reductase (MTRR), cystathionine beta-synthase (CBS) may increase the tHcy concentration and the severity of changes depends on the gene mutation site.

Life-style determinants such as smoking, sedentary, caffeine, and chronic alcohol consumption were associated with increases in tHcy levels, while exercise was associated with a decrease in tHcy [13]. Drugs have been identified that influence the plasma level of tHcy, thus opening the way for the treatment or prophylaxis of hyperhomocysteinemia-related disorders. Thus, the oral antidiabetic, metformin, produces folate depletion and B12, with an indirect impact on tHcy level; also anticonvulsant and hypolipidemic drugs have been associated with an increase in tHcy levels. As a beneficial decrease in Hcy, the penicillamine anti-rheumatic and acetylcysteine mucolytic have been identified.

Hypehomocysteinemia is today considered a severe risk factor in vascular illnesses. Many approaches envisage lowering homocysteine levels by vitamin B or oral folic acid supplementation but many recent studies show that vitamins administration fail to give a real clinical benefit and suggest that B vitamins might instead increase some cardiovascular risks in [14,15].

Like, in this study from 1997, author found a relationship between the MTHFR genotype and serum homocysteine concentration and an interaction with serum folate concentration in patients with ischemic cerebrovascular disease [16].

However not all patients with cardiovascular events or neurodegenerative diseases are enzymes deficient or poor vitamins supplied. The majority of research works report hyperhomocysteinemia associated to many diseases but the question what triggers hyperhomocysteinemia is yet to answer. An interesting hypothesis suggests that in fact hyperhomocysteinemia is more a secondary effect that amplifies in its turn the initial injury [17]. Brattström and Wilcken in [17] consider that impaired renal function due to hypertension and atherosclerosis is an important cause of the elevated plasma homocysteine found in vascular disease patients [9].

Clinical studies have shown that hyperhomocysteinemia (HHcy) is associated with bone fragility. Hcy induces apoptosis of osteoblastic cell lineage by increasing oxidative stress, which may contribute to Hcy-induced bone fragility. Like, in this study from 2016, author suggesting that statins may be beneficial for preventing Hcy-induced osteocyte apoptosis and the resulting bone fragility [18].

2. LITERATURE SEARCH METHODOLOGY

The purpose of this article is to review the literature regarding the relationship between

plasma homocysteine levels and fragility fractures. We used PubMed, Science Direct, Google Scholar to search original articles and review articles published in English language with the following key words “homocysteine”, “fragility fractures” and “osteoporosis”. The databases were searched from June 2000 to May 2017. Studies were included in the analysis of Hcy association with osteoporotic fractures if the Hcy plasma levels of cases and controls were reported. Studies were excluded if the literature was not in English or they did not have a control group. A total of 97 potentially relevant studies were retrieved from the electronic databases.

2.1 Osteoporosis, Fragility Fractures

Osteoporosis and associated fractures represent a major concern for public health due to morbidity, mortality, loss of function and decreased quality of life. Osteoporosis is a systemic skeletal disease that is characterized by low bone mass and microarchitecture deterioration of bone tissue with a consequent increase in bone fragility and fracture risk [19].

Fragility fractures are defined as a fracture that occurs as a result of a fall from standing height or less [20]. Fragility fractures are a strong indicator of underlying osteoporosis. With the risk of a new fractures being increased 1.5- to 9.5-fold following a fragility fracture, the diagnosis and treatment of osteoporosis in men and women with fragility fractures provides the opportunity to prevent future fragility fractures [21].

Fractures and their complications are the relevant clinical sequelae of osteoporosis. The most common fractures are those of the vertebrae (spine), proximal femur (hip), and distal forearm (wrist). However, most fractures in older adults are due at least in part to low bone mass, even when they result from considerable trauma. A recent fracture at any major skeletal site in an adult older than 50 years of age should be considered a significant event for the diagnosis of osteoporosis and provides a sense of urgency for further assessment and treatment. The most notable exceptions are those of the fingers, toes, face, and skull, which are primarily related to trauma rather than underlying bone strength. Fractures may be followed by full recovery or by chronic pain, disability, and death [22]. Bone disorders such as osteoporosis, Paget’s disease and cancer-related bone diseases are related to disruptions in the biochemical or cellular components of this signalling network. These disruptions lead to imbalances between bone resorption and bone formation in the Basic Multicellular Unit remodelling sequence, and/or to changes in bone turnover as expressed by the activation frequency of Basic Multicellular Units [23].

Bone diseases are often multifactorial and can exhibit high inter-individual variability. Different patients exhibit different temporal evolutions of bone mass and bone cell populations. These differences can be used to define a patient-specific “disease signature”, by the quantitative characterization of both bone resorption rate and bone formation rate (Fig. 3). Mathematical modelling in biology in the next decades is expected to develop into clinical tools to help predict the evolution of a disease in an individual and to find its optimum treatment regimes. Some authors proposed a mathematical model of bone cell interactions during bone remodelling. The model is applied to simulate a catabolic bone disease (e.g. osteoporosis) and to investigate various treatment strategies [24].

2.2 Homocysteine and Bone

Perturbation in methyl-group and Hcy balance have emerged as independent risk factors in a number of pathological conditions including neurodegenerative disease, cardiovascular dysfunction, cancer development, autoimmune disease and kidney disease [25].

HHcy may occur due to: diet rich in methionine, vitamin deficiency, kidney dysfunction, genetic abnormalities (in genes MTHFR, MTR, MTRR, CBS).

A study observed that dietary intervention with increased focus and availability of vegetables, fruits and bread, significantly reduced the concentration of tHcy. These findings suggest that the changes in the concentration of cysteine, folate and flavin mononucleotide seem to be predictors of changes in tHcy concentration [26].

Combined supplementation of calcium and Vitamin D have been proven to reduce bone loss and fracture incidence [27].

It’s possible that nutritional factors not typically linked with bone health could play a protective role for bone. Association studies have identified vitamins related to fractures or bone mineral density [28].

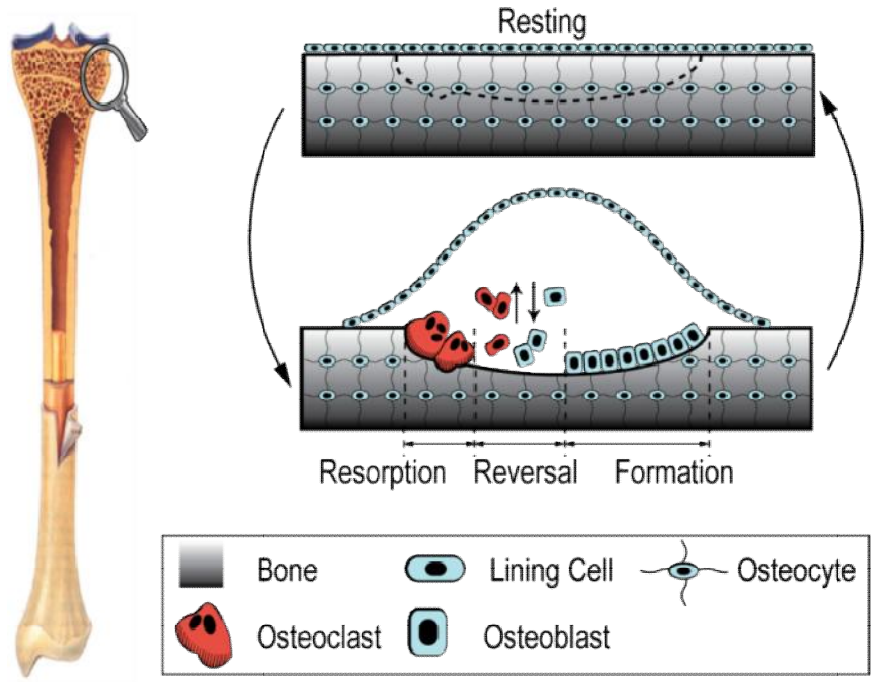

Fig. 3. Bone remodelling sequence executed by different bone cell types within Basic Multicellular Units (BMUs) (figure from [24] reproduced with permission)

Emerging evidence in groups of healthy individuals suggests a protective association of Vitamin B12 and folic acid, a detrimental effect of homocysteine and the 677C_T polymorphism in the gene encoding the folate metabolizing MTHFR enzyme. High concentrations of homocysteine and low levels of Vitamin B12 and folate, the main determinants in the metabolism of homocysteine [29] have been associated with low bone mineral density (BMD) and a higher risk of fractures in the elderly. It's known that serum homocysteine is regulated by Vitamin B12 and folic acid, and supplementation with these vitamins decreases serum homocysteine levels. It is also known that folate, Vitamin B12, Vitamin B6 and riboflavin are involved in the metabolism of an S-containing amino acid, homocysteine [30].

Recent studies have indicated a higher risk of fragility fractures among men and women with high Hcy levels [31,32]. Mudd reported for the first time that individuals with homocystinuria and very high levels of Hcy have an early onset of osteoporosis [33]. An explanation for this is that increased Hcy levels inhibit collagen cross-linking, as suggested by results from animal studies and studies on patients with homocystinuria [34]. Homocystinuria is an inborn error of amino acid metabolism caused by deficiency of cystathionine ß-synthase (CBS) activity, biochemically characterized by homocysteine (Hcy) and methionine (Met) accumulation in biological fluids and high urinary excretion of homocysteine [35].

In vitro studies indicate that high concentrations of Hcy inhibit the activity of lysyl oxidase (an enzyme involved in cross-linking of collagen) and thereby stimulate osteoclast activity in elevated concentration. Interference in cross-link formation would cause an altered bone matrix, resulting in more fragile bones [30]. Like, in this study from 2007, author indicates homocystinuria as a rare autosomal recessive disease caused by mutation of the gene for MTHFR. The enzyme MTHFR is necessary for Hcy metabolism [36]. Milder elevations of Hcy occur with a T homozygous polymorphism for MTHFR and may be linked to an increase in fracture risk.

Some authors suggest that low bone mineral density is common in both children and adults with homocystinurie and that routine assessment of bone health in this patient population is warranted [37,38]. The relationship between homocystinurie and bone mineral density is not clear.

Like, in this study from 2006, author found that Hcy-induced increases in reactive oxygen species (ROS) generation mediate the upregulation of both osteoclast formation and osteoclast activity [39].

Gerdhem et al. [37] showed a high Hcy level was associated with an increased mortality risk for elderly women included in the study. An association between Hcy, bone turnover, and Bone Mineral Density may exist. Throughout the study the association with fracture was not apparent during a fairly long follow-up in women at high risk for a fragility fracture. Data obtained contradicts previous results concerning the use of Hcy as a marker and modifiable risk factor for fracture in elderly women [33].

Ravaglia et al. [40] found that a low serum folate is responsible for the association between homocysteine and risk of osteoporotic fracture in elderly persons. Stuart et al. [41] suggest that folate and riboflavin interact to lower plasma tHcy, possibly by maximizing the catalytic activity of MTHFR. The effect may be unrelated to *MTHFR* genotype.

In 2013, Kuroda et al. [42] publishes a study according to plasma level of homocysteine was an independent risk for severe vertebral fractures. They found the homocysteine levels were also a significant risk when comparing vertebral fracture grade 0 versus grade 3, for postmenopausal Japanese women. Recent studies [43,24] report Hcy to be a newly recognized risk factor for osteoporosis.

Although contradictory opinions on the relationship between homocysteine and fragility fractures are published, yet more studies suggest that homocysteine can be a risk factor for the fractures.

3. CONCLUSION

Hyperhomocysteinemia (HHcy) is a risk factor for osteoporosis but is not fully know if HHcy affects bone mineralization or not. Osteocytes have a potential role in arbitrating bone pathogenesis during HHcy [44]. Experimental data published suggest that high Hcy levels affect both osteoclasts and osteoblasts. Homocysteine has been suggested to be a risk factor for fracture, but the causal relationship is not yet clear. There are at present only a few studies examining the association between Hcy and biochemical markers of bone turnover. Therefore, additional studies are needed to define whether HHcy is a risk factor for fracture, especially for fragility fractures.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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