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Review

Excel Diet for Homocystinuria: How Can We Use?

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Abstract

Background: Methionine restricted diet prevents homocystinuria complications, seems like *Marfan* syndrome. Homocystinuria is a metabolism disease but *Marfan* syndrome is a genetic disorder have similar symptoms. But only homocystinuria have neuropsycologic abnormalities and high methionine levels. Homocystein is an intermediate oxidized product, transform both of methionine or cystein. High methionine levels lead to neuropsycologic features, may be also premature ageing, in marfanoid persons with homocystinuria, because of creates over-methylating status in whole organism and also DNA. These high methylating status have found in cancer patients.

Introduction

Diet plays an important role on the body molecular composition. Gout, diabetes, hypertension, coeliac and phenylketonuria are known as the diseases that needs a strongly and traditional diet control. Purine control; sugar control; salt control; gluten-free diet and phenylalanin free diet are recommended for above diseases, respectively.

The clues from the patients have these diseases, leads to dermatologists to search the pathways of skin diseases and modern approaches to excel diet modifying, from DNA nucleotide sequence and aminoacids to protein synthesis, enzyme and catalysts belongs dermatologic diseases. For example DNA nucleotide methylation differs DNA melting point and autoflourescence of extracted DNA from cancer patients [1]. The clues from homocystinuria support cancer, diabetes, aging research as a methylating status [2].

Marfan Syndrome and Marfanoid Persons with Homocystinuria

Marfan syndrome is an autosomal dominant, elastic fibril disease have an unique phenotyping feature. Marfanoid patients have a dolikocephale and thin body structure and accompying defects pectus excavatus or pectus carinatus, scolyosis, arachnodactyly [3], joint hypermobility, muscle contractions [4, 5], aorta and hearth diseases, ocular finding as lens subluxation [5, 6], intracranial hypertension, respiratory function disorders because of fibrillin-1 genetic defect [7, 8, 9, 10, 11]. Homozygotic persons have several features of the syndrome, besides heterozygotic persons have only few features [12]. The most of the marfanoid persons shows homocystinuria or homocystinuria with

methylmalonic aciduria and needs excell diet modifications [**7, 9, 13, 14**] .

Biochemistry of Homocystein Metabolism

Blood homocystein and methionine levels are increased and cystein level is decreased in homocystinuria generally. Homocystin, composed of two homocystein molecule by the way of reduction, is an oxydized intermediate product. The source of homocystein is generally methionine. Homocystein transforms to cystein or methionine by the two-way. Whether homocystein and serin are composed of cystein, or partly is also shows remetylation of homocystein to methionine by the catalyse of B_{12} (cyanocobalamin) and folate in healthy persons [**15, 16, 17**]. But the patients with homocystinuria blood homocysteine levels are found high as a intermediate oxydizing status.

Harmful effects of homocystein appears in the result of the production of oxydants and accumulation of disulphydes in the blood. The production of oxydants occurs while reduction of homocystein to homocystin and the accumulation of disulphydes while the reaction of homocystein with protein thiol groups. The most reactive product is thiolacton along this pathway [**15**].

Cystationin-beta synthase deficiency or catalyse deficiency by B6 (pyridoxin) shows homocysteinemia and methioninemia, and mental retardation and seizures appears in homocystinuria Type 1. Eye damage also occurs in the result of deficiency in glutathion synthesis as a antioxydant agent, because of low cystein levels [**18**].

Homocysteinemia but low methionin levels occurs in type 2, 3, 4 homocystinuria and these patiens do not have mental retardation nor seizures [**19, 20**].

Type1 homocystinuria is a rare disease and treated with vitamin B6 and cystein [**18**]. Other types of homocystinuria seems more frequently, and improve with vitamin B12 and folate or sometimes diet with methionin because of methionin synthetase deficiency [**19**]. Another treatment choice is betain= trimethylgliserid (Cystadone 4g/180 ml]) also a methylating agent [**20, 21, 22**] .

Enzyme Defects

Until today, some enzyme defects are defined on homocystinuria patients.

1. ***Methylene tetrahydrofolate reductase deficiency (type 2):*** Methionin level is decreased in this autosomal recessive enzyme defect. And low cholin levels are defined in brain tissue. Methionin level is increased by giving betain [remethylizating agent] in diet or as a drug. Other enzyme defects lead to low methionin levels are methionin synthase and methionin synthase reductase deficiency [**19, 23, 24, 25, 26**].
2. ***Cystathionin beta synthase deficiency (type 1):*** Homocysteinemia and methioninemia are defined in this autosomal recessive disorder with the symptoms malar rash, thin hair and cutis marmorata [**21, 24, 25, 26, 27, 28**].
3. ***Transcobalamin deficiency:*** In this autosomal recessive disorder, vitamin B12 can not transport in the cell, with the symptoms microcephaly, megaloblastic anemia, mental retardation, seizures, cerebral atrophy, muscular dystonia (cbIE type), and other type (cbIC) is also autosomal recessive disorder with homocystinuria and methylmalonic asiduria [**1, 6, 29, 30, 31, 32**].
4. ***Adenosyl methionin transferase deficiency:*** S-adenosylmethionine (AdoMet) lies at an intersection of nucleotide and amino acid metabolism and performs a multitude of metabolic functions. The bioenergetic systems convert environmental calories into ATP, acetyl-Coenzyme A (acetyl-CoA), s-adenosyl-methionine (SAM) and reduced NAD(+) Folate-deficient, iron-rich diet, transgenic mice lacking in apolipoprotein E (ApoE-/- mice) demonstrate impaired activity of glutathione S-transferase (GST), resulting in increased oxidative species within brain tissue despite abnormally high levels of glutathione. These mice also exhibit reduced levels of S-adenosyl methionine ([SAM) and increased levels of its hydrolysis product S-adenosyl homocysteine, which inhibits SAM usage. The mechanism by which Vitamin B12 prevents

demyelination of nerve tissue is still not known. The evidence indicates that the critical site of B12 function in nerve tissue is in the enzyme, methionine synthase, in a system which requires S-adenosylmethionine. In recent years it has been recognized that S-adenosylmethionine gives rise to the deoxyadenosyl radical which catalyzes many reactions including the rearrangement of lysine to beta-lysine [**33**].

Other diseases with homocystinuria

Homocystinuria was found in several disease and syndrome as Behçet's disease, diabetes, metabolic syndrome, cardiovascular diseases, thrombosis [**34, 35, 36, 37, 38**] mental illnes, nephropathia but still in discussion. Although, marfanoid persons have exactly related homocystinuria and the treatment of homocystinuria is also changed phenotype [**2, 39**]. Because of these reasons, homocystinuriatest is involved in newborn screening panel, recently [**40, 41, 42, 43**].

Excel Diet for Homocystinuria

Methionine restricted diet is need to avoid these foods, contain methionine: meat, fish, yogurt, beans, eggs, onion, garlic, lentils, sesame seeds, wheatgerm, soy protein concentrate, oat, peanuts, corn yellow, rice brown. Methionine resticted diet have supported longer life span in experimental animal studies.

Patients can consume these foods contain cysteine: poultry, wheat, broccoli, red pepper [**44**].

Onion, garlic, eggs are also contain both of cysteine and methionine.

Cystathionin is composed of methionine and serin by cystathionin beta synthase [**27**] and transform to cysteine by cystathionin gamma lysase. Cysteine is nonessential aminoacid but may be essential in newborn, olders, malabsorption and metabolic syndromes [**15**].

The respectable antioxydant gluthation is composed of cysteine, glycine and glutamic acid and prevents lens dislocation in this syndrome [**5, 15**].

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