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Original research article

Correlation between BMI and plasma homocysteine levels in pre and postmenopausal women

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Abstract

Homocysteine occupies a branch point in methionine, cysteine and S-adenosylmethionine (SAM) metabolism. About half of the homocysteine formed is conserved by remethylation to methionine in the "methionine cycle". The other half is irreversibly converted by cystathionine-β-synthase (CBS) and cystathionine γ-lyase to cysteine. After getting the informed consents from the subjects, 2.5ml of fasting blood samples were collected for lipid profile in a plain vacutainer tube and 2.5 ml of blood sample were collected in EDTA tubes for homocysteine estimation. This however, was done after the 7th day of the last menstrual period for premenopausal group. Samples were centrifuged at 3000 rpm to separate serum and plasma for the analysis of lipid profile and homocysteine estimation. The positive correlation between BMI and homocysteine which clearly indicates the increase in BMI results in increase in plasma homocysteine levels with Pearson correlation co-efficient of 0.232 and p value of 0.11.

Keywords: BMI, Plasma homocysteine, pre and postmenopausal women

Introduction

Homocysteine is a sulphur-containing amino acid, which was first described by Butz and du Vigneaud in 1932 at the University of Illinois. A compound was isolated and crystallized by heating methionine in sulfuric acid that had chemical properties similar to those of cysteine and cysteine and suggested that it be called homocysteine since it had the structure of the next higher symmetrical homolog of cysteine. There is no specific codon for the amino acid homocysteine and is therefore not present in naturally occurring proteins [1, 2].
In 1964, Mudd and his colleagues identified the enzyme defect in homocysteine metabolism and established that homocystinuria was due to deficiency of cystathionine β synthase [3]. In 1968, while attending conference in human genetics at the Massachusetts General Hospital in Boston, Kilmer S McCully, MD, encountered two children with a genetic disorder called homocystinuria. Autopsy done on an 8 year old homocystinuric child who died of a stroke 35 years earlier, the arteries looked exactly like those of elderly men with arteriosclerosis. It

ISSN 2515-8260 Volume 09, Issue 02, 2022

It stroked McCully that the primary pathology is fibrotic changes in the inner arterial lining, which thickens and hardens the artery there by causing arteriosclerosis [4]. This could be a direct result of exposure to an elevated level of homocysteine in the circulating blood.
Homocysteine occupies a branch point in methionine, cysteine and S-adenosylmethionine (SAM) metabolism. About half of the homocysteine formed is conserved by remethylation to methionine in the "methionine cycle". The other half is irreversibly converted by cystathionine-β-synthase (CBS) and cystathionine γ-lyase to cysteine. Thus, CBS is involved directly in the removal of homocysteine from the cycle and in the biosynthesis of cysteine, a precursor of glutathione, which is a major redox regulating metabolite of the cell [5].
The liver and kidney are supposed to be the most important organs for uptake and metabolism of homocysteine. Renal excretion of homocysteine does not seem to be an important route of elimination. Only about 1% of the tHcy filtered by the glomeruli is normally found in urine.
Very often, one or more of the homocysteine metabolism pathways are inhibited by enzymes deficiencies or because of vitamin deficiencies and the result is an accumulation of homocysteine and an increase of its levels in the blood [6].
Deficiency of enzymes due to genetic causes or vitamin deficiency results in a condition known as Homocystinuria.

Methodology

The ethical clearance was obtained from the institutional ethical committee. An informed consent was taken from all the study subjects before the collection of sample.
The study subjects were selected based on following inclusion and exclusion criteria.

Inclusion criteria

Confirmed post-menopausal women who are attending the Gynecology outpatient department were included in the study as cases.
Regular menstruating pre-menopausal women were included in the study as controls.

Exclusion criteria

- Known case of hypertension.
- Obesity.
- Known case of diabetes mellitus.
- Known case of cardiovascular disease.
- Known case of hepatic, metabolic and renal disease.
- Any neoplasia.
- Arthritis or any other inflammatory disease.
- And those who are on hormone replacement therapy or lipid lowering drugs.
- Subjects with history of surgical menopause.

Collection of blood samples

After getting the informed consents from the subjects, 2.5ml of fasting blood samples were collected for lipid profile in a plain vacutainer tube and 2.5 ml of blood sample were collected in EDTA tubes for homocysteine estimation. This however, was done after the 7^{th} day of the last menstrual period for premenopausal group.
Samples were centrifuged at 3000 rpm to separate serum and plasma for the analysis of lipid profile and homocysteine estimation.

ISSN 2515-8260 Volume 09, Issue 02, 2022

The following methods were used for the analysis of lipid profile parameters and homocysteine estimation.

1. Total cholesterol by enzymatic CHOD-PAP method.
2. Triglycerides by enzymatic GPO-PAP method.
3. HDL cholesterol by direct method.
4. LDL cholesterol by Friedwald's formula.
5. VLDL cholesterol by using formula = Triglycerides/5.
6. Total plasma homocysteine levels by enzymatic method.

Results

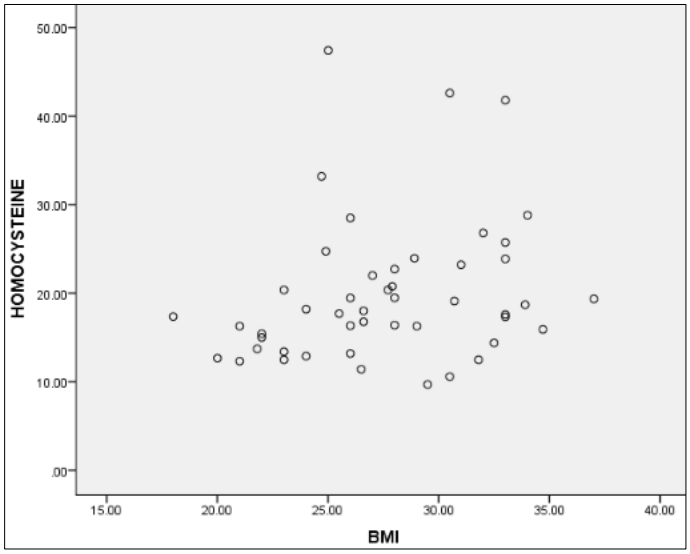

Fig 1: Correlation between BMI and plasma homocysteine levels in postmenopausal women

Figure 1 revealed the correlation of BMI with plasma homocysteine level in post-menopausal women. This figure depicts the positive correlation between BMI and homocysteine which clearly indicates the increase in BMI results in increase in plasma homocysteine levels with Pearson correlation co-efficient of 0.232 and p value of 0.11.

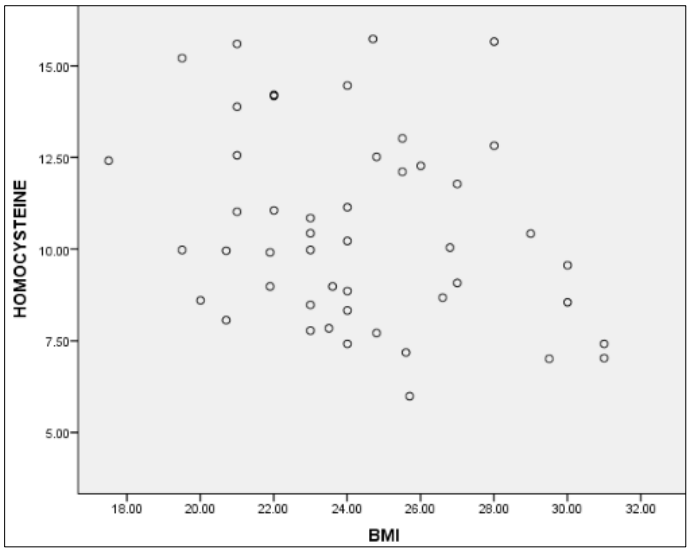

Fig 2: Correlation between BMI and homocysteine in premenopausal women

ISSN 2515-8260 Volume 09, Issue 02, 2022

Figure-2 showed the weak correlation between BMI and plasma homocysteine level in premenopausal women with Pearsons correlation coefficient = 0.28, p value= 0.05.

Discussion

Homocysteine is an intermediate product, which occupies a vital role in the metabolism of the essential amino acid, methionine. In the methionine cycle, homocysteine is a key branch point intermediate, which functions to generate one carbon methyl groups for transmethylation reactions essential to all life forms. It can be diverted from methionine cycle into the two step transsulfuration pathway to generate the non-essential amino acid cysteine [7].

The general structure of methionine containing sulfide-sulfur can be designated as R-S-R'. Homocysteine and cysteine are sulfhydryl compounds designated as R-SH or reduced form.

Premenopausal women are relatively protected from coronary artery disease and atherosclerosis as compared to post-menopausal women and this is attributed to the effects of the female sex hormone estrogen. Estrogen impact on methionine/homocysteine metabolism may be a key aspect in elucidating its effects. Homocysteine is metabolized by two pathways: remethylation and transsulfuration. In remethylation, homocysteine is salvaged by acquisition of a methyl group from N5-methyl tetrahydrofolate in a vitamin B12 dependent pathway or from betaine pathway occurring primarily in the liver. When excess methionine is formed or cysteine synthesis is required, homocysteine enters the transsulfuration pathway, in which it condenses with serine to form cystathionine. This further hydrolyze to form cysteine which in turn can be incorporated into glutathione [8].

Atherosclerotic vascular disease remains the leading cause of death in the Western countries despite the dietary changes, exercise regimens and lipid lowering drugs that have decreased the myocardial infarction rate in recent years. Hypercholesterolemia is a renowned risk factor for atherosclerosis [9].

Homocysteine which is formed during methionine metabolism exists either as reduced (homocysteine, a thiol RSH) or oxidized (homocysteine, a disulfide RSSR) form. Its redox chemistry is dominated by its thiol group (SH).

In biological system, homocysteine is present as the disulfide homocysteine (RSSR), as a mixed disulfide with other low-molecular weight thiols (homocysteine-cysteine and homocysteine-glutathione mixed disulfide and as a homocysteine disulfide cross-linked to proteins [10].

In normal individuals, the free form (reduced) represents less than 2% of plasma homocysteine, whereas low-molecular weight disulfides and mixed disulfides account for 30% and protein bound homocysteine accounts for 70%. The free homocysteine increases exponentially as the plasma homocysteine levels increases in patients with genetic disorders of homocysteine metabolism [11].

Glutathione is the major intracellular thiol and is present as mmol/L concentrations. As the main function of glutathione is to scavenge reactive intermediates, it plays a vital role in protecting cell from oxidative stress.

However thiols such as glutathione and homocysteine have a dark side that makes them potentially harmful to the cells. In the presence of metal ions and oxygen, they auto-oxidize, generating highly reactive partially reduced oxygen species.

These thiols initiate peroxidation by producing hydroxyl radicals and oxidatively cleave proteins in a reaction that requires iron. Copper oxidizes glutathione more efficiently than iron. Thus regulating the oxidation state of sulfur containing amino acids is an important strategy for curbing cellular damage [12].

One important risk factor for atherosclerosis is an elevated level of low-density lipoprotein, which is a major carrier of cholesterol. Oxidation of lipid moieties renders low-density lipoprotein atherogenic and promotes vascular disease.

ISSN 2515-8260 Volume 09, Issue 02, 2022

Conclusion

Depicts the positive correlation between BMI and homocysteine which clearly indicates the increase in BMI results in increase in plasma homocysteine levels with Pearson correlation co-efficient of 0.232 and p value of 0.11.

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