Assessment of a Possible Link Between Hyperhomocysteinemia and Hyperuricemia

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Background/Aim: Hyperhomocysteinemia and hyperuricemia are both considered risk factors for coronary artery disease. However, the relationship between the 2 has not yet been thoroughly investigated. This study aimed to evaluate this relationship more closely.

Material and Methods: This study is a retrospective cross-sectional analysis of data from a screening center in Israel assessing 16,477 subjects, within an age range of 20 to 80 years.

Results: The mean age of the study sample was 46 years, and 68% were males. Hyperuricemia was found in 24.9% and 14.6% of subjects with elevated and normal homocysteine serum levels, respectively ($P < 0.001$). A positive association was found between homocysteine serum levels and uric acid serum levels. Compared with subjects with normal homocysteine serum levels, those with hyperhomocysteinemia had an odds ratio (OR) for hyperuricemia of 1.7 (95% confidence interval [CI], 1.5–1.9) and 1.6 (95% CI, 1.1–2.5) for males and females, respectively. After multivariate adjustment for age, hypertension, body mass index, estimated glomerular filtration rate, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and thiazide use, the association remained significant in males (OR, 1.5; 95% CI, 1.3–1.7; $P < 0.001$) but not in females (OR, 0.9; 95% CI, 0.6–1.6; $P = 0.82$).

Conclusions: This large cohort showed a significant association between hyperhomocysteinemia and hyperuricemia. Sex differences were observed. This study suggests that accelerated atherosclerosis may be a consequence of the combined effect of these 2 factors.

Key Words: homocysteine, uric acid, atherosclerosis, adenosine, vitamin B12, folic acid

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Elevated homocysteine levels were first shown to be related to the risk of atherosclerosis 40 years ago.[1,2] Since then, numerous studies have suggested a link between hyperhomocysteinemia and coronary syndromes.[3–6] Possible mechanisms for the association between homocysteine and atherosclerosis include stimulation of smooth muscle cell growth, reduction in endothelial cell growth and endothelial cell relaxation, and decreased synthesis of high-density lipoprotein (HDL).[7] Increased uric acid levels have also been shown to play a key role in cardiovascular diseases.[8–11] Uric acid causes endothelial dysfunction and thereby increases oxidative stress, causing microvascular disease. This induces vascular smooth muscle cell proliferation and reduces endothelial nitric oxide (NO) bioavailability.[12]

Several studies have indicated a possible association between hyperhomocysteinemia and hyperuricemia.[13–18] This association has been found both in patients with coronary artery disease and in healthy subjects. However, these studies included relatively small numbers of subjects, and some were restricted to the male population.[15,17]

We conducted a cross-sectional study in a large group of subjects attending a screening center in Israel to assess the possible relationship between hyperhomocysteinemia and hyperuricemia in both males and females.

METHODS

Data from a screening center at the Rabin Medical Center in Israel were analyzed. This referral center provides regular health assessments for employees of different companies. The center's main goals are to screen for occult ischemic heart disease and occult malignancy. Here we use the most recent data. Approximately 24,000 people were assessed from 2000 to 2013. The population attending the center for screening includes males and nonpregnant female subjects with an age range between 20 and 80 years. At every visit, each individual undergoes a thorough medical history and a complete physical examination along with a series of blood and urine tests. Hyperuricemia is defined as greater than 7.0 mg/dL for men and greater than 5.6 mg/dL for women.[19] We assessed the prevalence of hyperuricemia in 2 homocysteine categories: less than or equal to 15 μmol/L (normal levels) and greater than 15 μmol/L (high levels).[20]

Serum uric acid levels were performed on a Beckman Coulter AU 2700, using an enzymatic color test. In the test, uric acid is converted by uricase to allantoin and hydrogen peroxide (H_2O_2). H_2O_2 reacts with 4-aminoantipyrine in the presence of N,N-bis (4-sulfobutyl)-3,5-dimethylaniline to produce a chromophore, which is read bichromatically at 660/800 nm. The amount of dye performed is proportional to the uric acid concentration in the sample.

Serum homocysteine levels were performed on an Abbott AxSYM system. The assay is based on the fluorescence polarization immunoassay technology.

Bound homocysteine (oxidized form) is reduced to free homocysteine that is enzymatically converted to S-adenosyl-L-Homocysteine (SAH). SAH and labeled fluorescein tracer compete for the sites on the monoclonal antibody molecules. The intensity of polarized fluorescent measured by fluorescence polarization immunoassay optical assembly is proportional to the homocysteine concentration in the sample.

The Helsinki Ethics Committee of the Rabin Medical Center approved the study.

Statistical Analysis

Categorical variables were compared using the Fisher exact test. Continuous variables are presented as mean (SD) or as median (interquartile range [IQR]) when appropriate. These were

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TABLE 1. Baseline Characteristics of the Study Population (16,477 Subjects)

	Males, n = 11,295 (68%)	Females, n = 5182 (32%)	*P*
Age, mean (SD), y	46.3 (9.9)	46.3 (9.9)	0.7
Hypertension, %	11.3	5.8	<0.001
Diabetes mellitus, %	4.1	2.5	<0.001
Smoker, %	15.8	16.8	0.08
Alcohol consumption, %	19.3	11.3	<0.001
BMI, mean (SD)	27.0 (4.0)	25.0 (5.0)	<0.001
eGFR (CKD-EPI), mean (SD), mL/min per 1.73 m^2	96.3 (13.9)	98.6 (13.7)	<0.001
HDL cholesterol, mean (SD), mg/dL	47.3 (10.3)	60.3 (13.8)	<0.001
LDL cholesterol, mean (SD), mg/dL	121.3 (30.6)	116.9 (30.9)	<0.001
Triglycerides, median (IQR), mg/dL	117 (85–166)	92 (68–127)	<0.001
Uric acid, mean (SD), mg/dL	6.1 (1.1)	4.3 (1.0)	<0.001
Homocysteine, median (IQR), μmol/L	12 (10–14)	9 (8–11)	<0.001

CKD-EPI indicates Chronic Kidney Disease Epidemiology Collaboration.

compared with the use of Student *t* test and Mann-Whitney *U* test, respectively. Kolmogorov-Smirnov test was used to assess the distribution pattern of the data. Median and IQR range was used for data that did not show a normal distribution pattern. As for our cohort, this was relevant for the triglycerides, homocysteine, B12, and folic acid serum levels. For all other data, which showed a normal distribution pattern, the mean (SD) was used. Pearson correlation test was used to assess the association between homocysteine serum levels and uric acid serum levels.

Logistic regression analysis was used to assess the odds ratio (OR) of hyperuricemia in the elevated homocysteine category compared with the normal category (the reference category). Model 1 presents the crude association. Model 2 shows results adjusted for age. Model 3 shows results adjusted for age, hypertension, body mass index (BMI), estimated glomerular filtration rate (eGFR), low-density lipoprotein (LDL) cholesterol, HDL cholesterol, and thiazide use. All analyses were conducted using R—a language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Data from 16,477 subjects with all the data components relevant for the assessment were recorded from 2000 to 2013. The clinical characteristics of the subjects are presented in Table 1. These data comprised our study sample. The mean (SD) age of the study sample was 46.0 (10) years, and 32% were females. No statistically significant age difference was found between males and females. The smoking patterns of male and female subjects were similar ($P = 0.7$ and $P = 0.08$, respectively). However, males were found to have significantly higher rates of hypertension, diabetes mellitus, alcohol consumption, BMI, uric acid, LDL cholesterol, triglycerides, and homocysteine levels ($P < 0.001$ for all). The eGFR in males and the levels of HDL

TABLE 2. Characteristics of Subjects With High and Normal Homocysteine Levels

	High Homocysteine, n = 2033 (12.3%)	Normal Homocysteine, n = 14,444 (87.7%)	*P*
Age, mean (SD), y	46.9 (10.1)	46.2 (9.8)	0.004
Males, %	90.3	65.5	<0.001
Hypertension, %	12.9	9.1	<0.001
Diabetes mellitus, %	3.7	3.5	0.73
Smoker, %	17.7	15.9	0.003
Alcohol consumption, %	16.3	16.8	0.572
BMI, mean (SD)	26.6 (4.3)	27.0 (4.0)	0.001
eGFR (CKD-EPI), mean (SD), mL/min PER 1.73 m^2	92.2 (16.2)	97.7 (13.4)	<0.001
HDL cholesterol, mean (SD), mg/dL	47.8 (10.8)	51.9 (13.2)	<0.001
LDL cholesterol, mean (SD), mg/dL	122.6 (31.3)	119.5 (30.7)	<0.001
Triglycerides, median (IQR), mg/dL	119 (87–166)	107 (78–152)	<0.001
Uric acid, mean (SD), mg/dL	6.2 (1.4)	5.4 (1.4)	<0.001
Homocysteine, median (IQR), μmol/L	18 (16–22)	10 (9–12)	<0.001
Vitamin B12, median (IQR), pmol/L	214 (169–280)	283 (220–371)	<0.001
Folic acid, median (IQR), nmol/L	13 (10–17)	20 (15–27)	<0.001

CKD-EPI indicates Chronic Kidney Disease Epidemiology Collaboration.

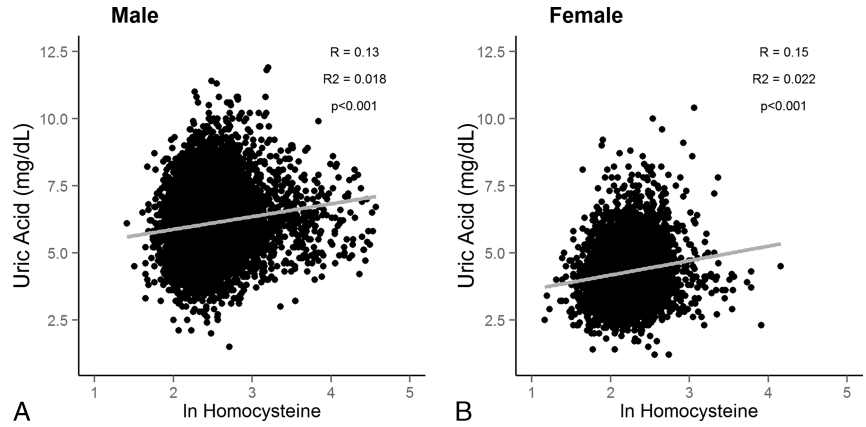

FIGURE 1. Correlation between uric acid serum levels and homocysteine serum levels. A, Male sex. B, Female sex.

cholesterol were found to be significantly lower ($P < 0.001$). Among the 16,477 subjects studied, 87.7% were found to have had normal homocysteine serum levels, whereas 12.3% had elevated homocysteine serum levels. The characteristics of subjects with high and normal homocysteine levels are presented in Table 2.

Overall, hyperuricemia was found in 24.9% and 14.6% of subjects with elevated and normal homocysteine serum levels, respectively ($P < 0.001$). A positive association was found between homocysteine serum levels and uric acid serum levels. This was true for both males and females (Fig. 1, A and B).

As a group, subjects with elevated homocysteine serum levels compared with subjects with normal homocysteine serum levels had an OR for hyperuricemia of 1.7 (95% confidence interval [CI], 1.5–1.9) and 1.6 (95% CI, 1.1–2.5) for males and females, respectively. Both results were found to be significant ($P < 0.001$ and $P = 0.025$, respectively). After multivariate regression analysis adjusting for age, hypertension, BMI, eGFR, LDL cholesterol, HDL cholesterol, and thiazide use, the association remained significant in males (OR, 1.5; 95% CI, 1.3–1.7; $P < 0.001$) but not in females (OR, 0.9; 95% CI, 0.6–1.6; $P = 0.82$; Table 3).

DISCUSSION

In this large cross-sectional study, we evaluated the association between hyperhomocysteinemia and hyperuricemia for both males and females. For both males and females, a significant association was found, but it was substantially attenuated in females after multivariate adjustment for age, hypertension, BMI, eGFR, LDL cholesterol, HDL cholesterol, and thiazide use. A few previous studies have assessed the relationship between these 2 variables; however, these studies included relatively small numbers of subjects[13–17] or were conducted only in males.[15,17] In contrast, our study included more than 14,000 subjects with normal homocysteine levels and more than 2000 subjects with hyperhomocysteinemia and included both males and females.

TABLE 3. Association Between Elevated Homocysteine Serum Levels and Hyperuricemia (>7.0 mg/dL for Men and >5.6 mg/dL for Women)*

	Males		Females	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Model 1	1.7 (1.5–1.9)	<0.001	1.6 (1.1–2.5)	0.025
Model 2	1.7 (1.5–1.9)	<0.001	1.8 (0.9–2.1)	0.17
Model 3	1.5 (1.3–1.7)	<0.001	0.9 (0.6–1.6)	0.82

Model 1, crude; model 2, adjustment for age; model 3, adjustment for age, hypertension, BMI, eGFR, LDL cholesterol, HDL cholesterol, and thiazide use.

*The reference category relates to subjects with normal homocysteine serum levels.

Our study nevertheless has its limitations. It is cross-sectional in nature, and data were collected from a selected population attending an examination center.

It should also be noted that hyperhomocysteinemia may be the result of either a genetic variability of the MTHFR enzymatic activity or the result of vitamin deficiencies including vitamin B12, vitamin B6, and folic acid. This study did not assess the genetic status of the subjects or their vitamin B6 levels. As expected, subjects with hyperhomocysteinemia also had lower levels of vitamin B12 and folic acid compared with subjects with normal levels of homocysteine.

Numerous studies have shown that both hyperhomocysteinemia[1–6] and hyperuricemia[8–11] pose an increased risk for accelerated atherosclerosis.

Various suggestions have been made regarding the mechanism whereby hyperhomocysteinemia might induce vascular injury. These include an increase in smooth muscle cell proliferation and enhancement of collagen production,[21] prothrombotic effects and decreased endothelial antithrombotic activity,[22–26] oxidative stress inducing injury to endothelial cells by free radicals,[27] platelet accumulation secondary to direct proaggregatory effects of homocysteine,[28,29] and inhibition of NO synthase leading to a decrease in the production of NO.[28,30]

Uric acid may also affect the vascular system in various ways including induced endothelial dysfunction and reduction of NO bioavailability and NO-dependent vascular dilatation.[31,32] Although uric acid is considered a major antioxidant in the serum, in the cell, it exerts a pro-oxidant effect. This reflects the oxidant-antioxidant paradox of uric acid.[33] In adipocytes, the oxidative stress is associated with activation of nicotinamide adenine dinucleotide phosphate oxidase.[34] Another important deleterious effect of uric acid is the stimulation of angiotensin II production in vascular endothelial cells.[35]

Our study clearly shows that hyperhomocysteinemia and hyperuricemia are related to each other in men. Therefore one could speculate that accelerated atherosclerosis might be a consequence of the combined effect of these 2 factors.

Male/female differences may be partly explained by sex differences in homocysteine metabolism. Homocysteine is normally metabolized by 1 of 2 divergent pathways: transsulfuration and

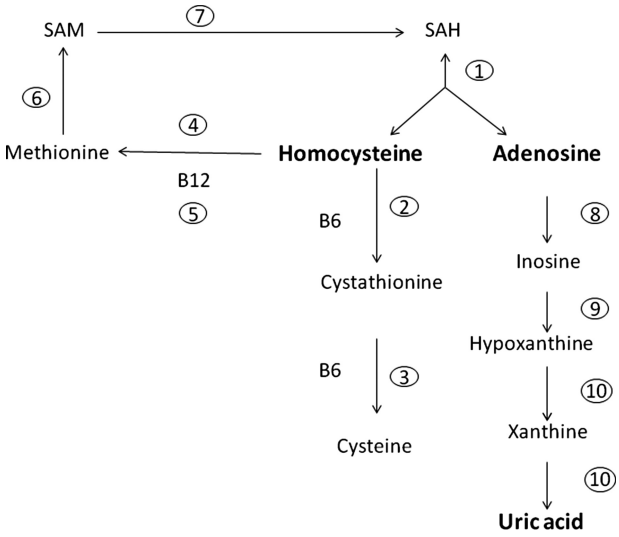

FIGURE 2. Homocysteine and uric acid metabolism. The circled numbers refer to the following enzymes: 1, SAH hydrolase; 2, cystathionine-β-synthase; 3, cystathionine-γ- lyase; 4, BHMT; 5, methionine synthase; 6, methionine adenosyltransferase; 7, methyltransferases; 8, adenosine deaminase; 9, phosphorylase; 10, xanthine oxidase. SAM indicates S adenosylmethionine.

remethylation (Fig. 2). In the former, homocysteine is converted to cysteine by cystathionine-β-synthase and by cystathionine-γ- lyase where vitamin B6 is a cofactor. In the latter, homocysteine is converted to methionine by either methionine synthase, where B12 is a cofactor, or by betaine-homocysteine methlytransferase (BHMT). Studies in mice have shown sex differences in these metabolic pathways. In addition, although BHMT activity has been shown to be 60% higher in males than in females, females have been shown to have a higher flux of homocysteine through the transsulfuration pathways.[36] Thus, it is anticipated that males lacking betaine will have higher homocysteine levels than females; this can be explained by their inability to recycle it via BHMT to methionine coupled with reduced flux through the transsulfuration pathway.[36]

A possible theoretical link between hyperhomocysteinemia and hyperuricemia is the adenosine molecule. In the methionine-homocysteine cycle, methionine is converted to SAH, which is split into homocysteine and adenosine.[37] In addition, adenosine is metabolized to uric acid (Fig. 2).[38]

It is possible that SAH hydrolase would normally recycle homocysteine and adenosine back to SAH.[39] However, to recycle homocysteine and adenosine back to SAH, a stoichiometric ratio of homocysteine to adenosine of 1:1 is needed. Thus, if one is lacking, the recycling kinetics will be affected, leading to an excess of the other substance. Under conditions of hypoxia and tissue ischemia, vascular adenosine synthesis and release is upregulated, causing significantly increased circulating concentrations. Thus, under any one or more of these conditions, adenosine is quickly degraded to uric acid, such that homocysteine accumulates.

In addition, it should be noted that adenosine might be formed from fructose, particularly from high dietary intakes of this substance.[40] Many sweet beverages are made using high fructose corn syrup, particularly carbonated beverages such as soft drinks containing caffeine, lemonade, and orangeade. The consumption of these beverages has skyrocketed over the last 4 decades, alongside a sharp rise in obesity and the metabolic syndrome. Lastly, adenosine and uric acid are also formed from alcohol.[41,42] None of the aforementioned pathways of adenosine synthesis have a direct connection to homocysteine. However, if these processes push the body to remove the excess adenosine rapidly, homocysteine will be left without a matching adenosine and will thus accumulate. Moreover, if one of the enzyme cofactors (vitamin B12, betaine, zinc, vitamin B6) that activate the recycling pathways is lacking, homocysteine and adenosine will accumulate. In these circumstances, adenosine will probably be metabolized to uric acid and homocysteine may accumulate.

We suggest that there may be cumulative or synergistic deleterious effects as a result of dietary and alcohol consumption habits, vitamin deficiencies, and genetic variability of the MTHFR enzymatic activity, leading to high levels of both homocysteine and uric acid. It would appear that females are better adapted to "escape" high homocysteine via the transsulfuration pathway than males. Further studies are needed to establish whether treatment of hyperhomocysteinemia patients decreases their uric acid levels.

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