Plasma Total Homocysteine Is Influenced by Prandial Status in Humans: The Hordaland Homocysteine Study[1]

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ABSTRACT Plasma total homocysteine (tHcy) is a risk factor for cardiovascular disease, adverse pregnancy outcomes and impaired cognitive function. No population-based studies on the possible influence of prandial status on tHcy have been published. The aim of this study was to investigate the variation in plasma tHcy levels in relation to time since last meal. A cross-sectional, population-based study including 18,044 individuals in Western Norway was conducted. Most subjects were in the age groups 40–42 and 65–67 y. Participants who had not eaten during the past 6 h before the blood sampling had significantly higher mean tHcy levels compared with those who had eaten; 11.7 [95% confidence interval (CI): 11.4–12.1] vs. 11.2 (95% CI: 11.1–11.3) μmol/L among men ($P = 0.03$) and 10.2 (95% CI: 9.9–10.6) vs. 9.7 (95% CI: 9.6–9.7) μmol/L among women ($P = 0.003$). In all groups except older women, tHcy concentrations were generally higher with increasing time after a meal (P-trend <0.01 in all 3 groups). These findings suggest that fasting status and time since last meal may influence levels of tHcy and should be considered in studies of tHcy as a risk factor for cardiovascular and other diseases, and when comparing tHcy values among studies. J. Nutr. 131: 1214–1216, 2001.

KEY WORDS: • homocysteine • prandial status • humans

Plasma total homocysteine (tHcy)[3] is a risk factor for cardiovascular disease (1,2), pregnancy complications (2,3) and impaired cognitive function (2). Homocysteine metabolism is dependent on B-vitamins, including folate, B-12, B-6 (2) and riboflavin (4), and several studies have demonstrated inverse associations between fasting tHcy levels and dietary intake and blood levels of folate and vitamin B-12 (5–9). Another important factor in homocysteine metabolism is methionine, an essential amino acid found in foods rich in animal protein. Earlier studies have shown that methionine from protein causes marginal changes in tHcy level (9–11). In addition to B-vitamins and protein, it has been shown that a semivegetarian very-low-fat, folate-rich diet may reduce fasting tHcy concentration, whereas a high fat diet may increase it (12).

Only a few studies have examined postprandial changes of tHcy (10–12). In a study of 15 persons, Ubbink et al. (11) showed that tHcy concentrations decreased significantly after breakfast, with the lowest level after 4 h, followed by a gradual increase to prebreakfast level 8 h later. Guttormsen et al. (10), in a study of 13 subjects, found a nonsignificant decrease in tHcy-levels after breakfast, after which the levels rose slowly and reached maximum levels 8 h after dinner. In the latter study, the daily variation of tHcy was ± 1 μmol/L relative to the mean. The low fat, folate-rich diet fed in the study by Duell et al. (12) resulted in 5-h postprandial tHcy levels significantly lower than before the meal, compared with significantly higher postprandial levels after the high fat meal.

The purpose of these analyses was to examine the relation of tHcy levels to prandial status (time since last meal) in a large population. The Hordaland Homocysteine Study (13) afforded the opportunity to examine these issues among >18,000 adult and elderly men and women.

SUBJECTS AND METHODS

The Hordaland Homocysteine Study was conducted initially in 1992–1993 as a collaboration between The National Health Screening Service and the University of Bergen. The study population and data collection were described previously (13). Briefly, a total of 24,815 subjects aged 40–67 y from Hordaland County in Western Norway were invited to attend. The overall attendance rate was 72.7%. The study protocol was approved by the Data Inspectorate and the Regional Committee for Medical Research Ethics of Western Norway.

Information on diet and other variables was collected through self-administered questionnaires. The clinical examinations and blood sampling were performed between 0800 and 1800 h. A general question "Have you eaten during the last 6 h before the examination?" was asked. In addition, time since last meal was reported in 10 categories, i.e., from <1 h to ≥9 h. Because the number of participants in the last groups (from 6 to 9 h or more) was small, these groups were combined. Type of meal (breakfast, lunch, dinner or other) was also recorded.

Plasma tHcy was measured by HPLC and fluorescence detection (14,15). The tHcy distribution was markedly skewed, and geometric means with 95% confidence intervals are therefore presented. Linear regression analyses were used to examine the relationship between tHcy and time since last meal with adjustment for age, smoking habits and coffee consumption. Time since last meal was used as a continuous variable and P-values for linear trend are given. All statistical analyses were performed using the Statistical Package for the Social Sciences 9.0 for Windows (SPSS, Chicago, IL). Tests of significance were two-tailed, and P-values < 0.05 were considered significant.

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[3] Abbreviations used: tHcy, plasma total homocysteine.

TABLE 1

The Hordaland Homocysteine Study population 1992–1993, plasma total homocysteine (tHcy) concentrations by prandial status

		All participants		Participants who had eaten during the past 6 h[1]		Participants who had not eaten during the past 6 h		
Gender	Age group	*n*	Plasma tHcy[2]	*n*	Plasma tHcy[2]	*n*	Plasma tHcy[2]	*P*-value[3]
	y		*μmol/L*		*μmol/L*		*μmol/L*	
Men	40–42	6110	10.8 (10.8–10.9)	5769	10.8 (10.7–10.9)	323	11.4 (11.0–11.8)	0.002
	43–64	336	11.3 (10.9–11.6)	309	11.2 (10.9–11.6)	26	11.4 (10.4–12.6)	0.78
	65–67	2127	12.4 (12.3–12.6)	2036	12.4 (12.2–12.5)	90	13.1 (12.3–13.9)	0.08
	All age groups	8573	11.2 (11.2–11.3)	8114	11.2 (11.1–11.3)	439	11.7 (11.4–12.1)	0.030
Women	40–42	6485	9.2 (9.0–9.2)	6231	9.1 (9.1–9.2)	245	10.0 (9.6–10.4)	<0.001
	43–64	347	9.9 (9.6–10.2)	330	9.8 (9.5–10.2)	16	11.0 (9.2–13.1)	0.15
	65–67	2639	11.1 (11.0–11.2)	2555	11.1 (11.0–11.2)	81	10.9 (10.2–11.6)	0.56
	All age groups	9471	9.7 (9.6–9.7)	9116	9.7 (9.6–9.7)	342	10.2 (9.9–10.6)	0.003

[1] May include breakfast, lunch, dinner or other meal with nonspecified food.
[2] Values are geometric means (95% confidence interval).
[3] *P*-values for comparisons between those who had and those who had not eaten during the past 6 h.

RESULTS

Participants' age, gender and tHcy levels according to fasting status are listed in **Table 1**. Mean tHcy levels increased with age and were higher in men than in women ($P < 0.0001$). Of all participants, 10.5% had eaten within 1 h of the blood draw, 32.2% within 2 h, 53.6% within 3 h and 4.3% had not eaten during the past 6 h. Participants who had not eaten during the past 6 h before the blood sampling had significantly higher mean tHcy levels compared with those who had eaten; 11.7 vs. 11.2 μmol/L ($P = 0.03$) among men and 10.2 vs. 9.7 μmol/L ($P = 0.003$) among women. The differences were most pronounced in the youngest age groups. Age- and gender-specific tHcy levels by time since last meal are presented in the **Figure 1** for the youngest (40–42 y) and oldest (65–67 y) age groups. In men, plasma tHcy levels were almost constant during the first 2 h after the meal. Among the oldest men, tHcy levels increased after 2 h, whereas among the youngest men, the increase started later. In the youngest female group, tHcy increased slowly for up to 6–7 h and then increased more sharply. No significant differences with time since last meal were seen among the oldest women. Trend tests, adjusted for age, smoking habits and coffee consumption, were significant for all groups except the oldest women.

Similar tHcy-patterns after a meal were also present in stratified subgroups of the study population, e.g., smokers and nonsmokers, as well as vitamin supplement users and nonusers.

When the same analyses were confined to subjects who had eaten breakfast as their last meal (2877 men and 4359 women), tHcy levels were lowest during the h 1 after the meal, followed by increasing levels during the next 6–7 h (*P*-trend, adjusted for age, smoking habits and coffee consumption, were <0.0001 for men and 0.009 for women, data not shown). After lunch, tHcy concentrations increased slightly for the first 3 h among men only ($P = 0.029$). No significant increase was seen after dinner.

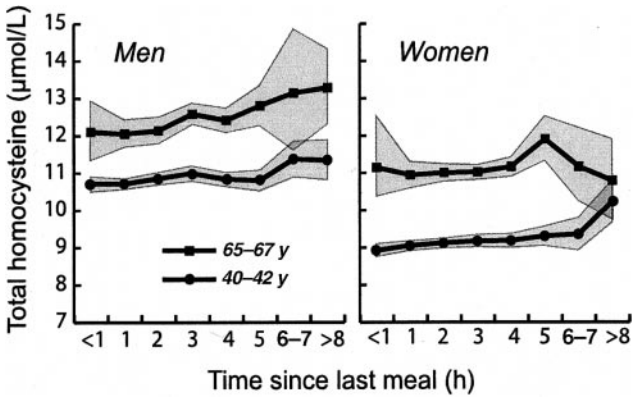

FIGURE 1 Plasma total homocysteine (tHcy) concentration in men and women according to time since last meal by age group. The data are given as geometric mean values with 95% confidence bands. The last meal may include breakfast, lunch, dinner or other meal with nonspecified food. The youngest men (40–42 y): $n = 6035$, *P*-trend (adjusted for age, smoking habits and coffee consumption) = 0.003; the oldest men (65–67 y): $n = 2071$, *P*-trend = 0.001; the youngest women (40–42 y): $n = 6456$, *P*-trend < 0.0001; the oldest women (65–67 y): $n = 2615$, *P*-trend = 0.2.

DISCUSSION

Our results are generally in agreement with previous reports from smaller studies (10–11,16) that demonstrated an association among tHcy levels, fasting status and time since last meal. Guttormsen et al. (10) studied 10 women and 3 men, all healthy with a mean age of 24 y, Ubbink et al. (11) 3 men and 12 women (mean age 32 y) who were members of the laboratory staff, and Chambers et al. (16) 10 men and 7 women, all healthy volunteers from the hospital staff (mean age 33 y). In all 3 studies, as in this study, tHcy levels decreased during the first few hours after breakfast (10–11) or methionine-free juice after (presumably) an overnight fast (16) and then began to increase. After dinner, tHcy increased with increasing time, reaching the maximum value 8 h later (10).

The magnitude of differences in tHcy concentrations related to prandial status varies among the studies. Consistent with the present study, tHcy levels decreased 3–8% during the first few hours after breakfast (10–11) or methionine-free juice (16). Changes in tHcy after h 2 differ among the studies. After a heavy breakfast containing ~30 g of protein (11), tHcy continued to decrease slightly beyond h 2 (8% from fasting); from h 4, a slight increase was seen, but the tHcy levels remained lower than prebreakfast fasting levels even for 8 h. The study by Guttormsen et al. (10) found slight increases

from h 2 after a breakfast containing 15–18 g of protein, and by h 6, the tHcy levels were still lower than before breakfast. In the study in which only juice was given (16), tHcy increased 18% (from fasting) by h 4. In the present study (nonspecified food), tHcy started to increase from h 2, and by h 6, the tHcy level was ~7% higher than the fasting level.

Guttormsen et al. (10) and the present study demonstrated no decrease in tHcy after dinner. In both studies, tHcy increased for several hours after dinner, although not significantly in the present study. In the former study (10), tHcy increased slowly and was 13.5% higher after 8 h. The different pattern seen after dinner vs. breakfast could perhaps be related to a longer fasting period preceding breakfast than dinner, resulting in a higher premeal tHcy level before breakfast than before dinner. Our finding of significantly lower tHcy levels in participants who had eaten vs. not eaten for the past 6 h may support this explanation.

Although the present study measured tHcy values in different subjects at different time points after a meal, the other studies referred to here were longitudinal with repeated measurements in the same subjects. The latter study design is more optimal for following the time course of a meal effect, whereas the large sample size of the present study may outbalance the noise created by possible interindividual variability in meal effects.

The fat content of the meal may also be important with regard to postprandial changes in tHcy. Twenty subjects were fed 2 meals containing either 10 or 37% of energy in the form of fat (both meals covered 50% of the daily energy intake) and tHcy was measured 5 h later (12). After the meal containing 10% fat, the tHcy decreased 7.6%, whereas after the meal with 37% fat, tHcy increased 12.1%.

Earlier studies (1,2) showed that tHcy is a continuous and graded risk factor for cardiovascular disease and mortality, with no apparent threshold effect. Nygård et al. (17) demonstrated that the relation between tHcy and cardiovascular mortality is nearly linear, and individuals with preexisting cardiovascular disease or different cardiovascular symptoms had 0.4–1.2 μmol/L higher tHcy values than those without such clinical history or symptoms. In support of the potential importance of even small differences in tHcy is the recent report that small physiologic increments in tHcy, 2–3 μmol/L, may have detrimental effects on vascular endothelial function (18). Although the observed difference between fasting and nonfasting tHcy levels in the present study was significant, it was nevertheless relatively modest (~0.5 μmol/L, or 5%). It is unclear whether these differences may be clinically relevant or induce attenuation of effect measures due to misclassification.

In conclusion, the present study shows that tHcy concentrations vary significantly by fasting status, and levels were generally higher with increasing time since last meal. This implies that in addition to major lifestyle determinants of tHcy such as smoking, vitamin supplement use and coffee consumption, prandial status or time since last meal should be considered in studies of plasma tHcy as a risk factor for common diseases.

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