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Hyperhomocysteinemia in Asian Indians Living in the United States

MANISHA CHANDALIA, NICOLA ABATE, ALBERTO V. CABO-CHAN, JR., SRIDEVI DEVARAJ, ISHWARLAL JIALAL, AND SCOTT M. GRUNDY

Center for Human Nutrition (M.C., A.V.C.-C., S.M.G., N.A.), the Department of Internal Medicine (M.C., A.V.C.-C., S.M.G., N.A.), and Division of Endocrinology and Metabolism (M.C., A.V.C.-C., N.A.), University of Texas Southwestern Medical Center at Dallas, Dallas, Texas 75390-9169; and Laboratory for Atherosclerosis and Metabolic Research (S.D., I.J.); University of California Davis Medical Center, Davis, California 95616

Hyperhomocysteinemia has been reported in Asian Indians (people from Indian subcontinent) to be related to relatively low plasma levels of folate and vitamin B-12. However, a true ethnic-related characteristic has not been excluded. This study was done to determine whether Asian Indians have high plasma homocysteine compared with Caucasians in the United States in the era of folate fortification, and whether low vitamin B-12 or insulin resistance may account for possible interethnic differences in plasma homocysteine. A total of 227 Asian Indians (131 males and 96 females) and 155 Caucasians (66 males and 89 females) completed a questionnaire for medical, family, and personal history. They had height, weight, and blood pressure measured and fasting blood drawn for routine chemistry, TSH, plasma homocysteine, vitamin B-12, and folate. Oral glucose tolerance test and vitamin B-6 was measured in a subgroup of 66 Asian Indians (47 males and 19 females) and 63 Caucasians (33 males and 30 females). Asian Indians were found to have significantly higher plasma homocysteine than Caucasians (median of 12.6 and 8.0 μmol/liter, $P < 0.0001$, respectively) and lower plasma concentrations of B-6 (median 49 *vs.* 70 nmol/liter; $P = 0.05$, respectively). Plasma folate was relatively high and similar in both ethnic groups. Plasma vitamin B-12 was significantly lower in Asian Indians than Caucasians (median of 204 *vs.* 320 pmol/liter, $P < 0.0001$, respectively). Vitamin B-12 correlated significantly with plasma homocysteine. When vitamin B-12 was between 150 and 379 pmol/liter, the regression curve between vitamin B-12 and homocysteine had significantly different slope in the two ethnic groups (P value < 0.05) and Asian Indians had significantly higher homocysteine for any level of vitamin B-12. Although insulin resistance, measured as insulin area under the curve by oral glucose tolerance test was higher in Asian Indians and correlated significantly with homocysteine, it did not explain inter-ethnic differences in plasma homocysteine in a multivariate analysis. We conclude that Asian Indians living in the United States have significant elevation of plasma homocysteine concentrations despite normal plasma folate. Lower plasma concentrations of vitamin B-12 and lower insulin sensitivity may contribute to this finding but only partially explained the ethnic-related hyperhomocysteinemia of the Asian Indians. (*J Clin Endocrinol Metab* 88: 1089–1095, 2003)

SEVERAL EPIDEMIOLOGICAL OBSERVATIONS have linked hyperhomocysteinemia to increased risk for cardiovascular disease (CVD) (1–10), and clinical trials are ongoing to elucidate whether intervention to reduce plasma homocysteine will reduce CVD risk. One factor that could affect plasma homocysteine concentrations in populations is food fortification with folate. Although related to a different rationale, this intervention has been in place in the United States since 1998 and has been accompanied by a trend toward decreased plasma homocysteine concentrations (11–15). Whether this trend will translate into decreased CVD morbidity and mortality remains to be assessed. An important question is whether the impact of food fortification with folate on CVD risk is different in individuals or ethnic groups whose excessive CVD risk is not explained by traditional risk factors. For example, Asian Indians, an ethnic group originating from the Indian subcontinent (including India, Pakistan, and Bangladesh), which is increasingly represented within the United States multiethnic population has a 2-fold to a 4-fold higher risk for CVD than do persons of European descent (Caucasians) (16–21). We and other investigators have previously reported that Asian Indians are more insulin resistant than Caucasians (21–24). They further have lower plasma high-density lipoprotein-cholesterol concentrations (20–24) and higher prevalence of type 2 diabetes (24). This clustering of CVD risk factors, commonly found in the metabolic syndrome, does not entirely explain the excessive risk of this population. Consequently, it must be asked whether emerging risk factors, such as hyporhomocysteinemia, contribute independently to CVD risk. Because elevated homocysteine may be prothrombotic, it is conceivable that the homeostatic balance that should reduce the propensity to form large thrombi and stabilize existing atherosclerotic plaques can be tipped over to the opposite by hyperhomocysteinemia. Higher plasma homocysteine concentrations compared with Europeans have been reported in Asian Indians living in various geographical areas (18, 25–30). Because homocysteine concentrations are affected by dietary intake of folate, vitamin B-12 and B-6, and dietary availability of these substances vary in different areas of the world; the question arises whether an ethnic predisposition to hyperhomocysteinemia exists within the Asian Indian population irrespective of their geographical location. If so, insight on the mechanisms involved in ethnic differences in plasma homocysteine may shed some light on the pathogenesis of

Abbreviations: AUC, Area under the curve; BMI, body mass index; CVD, cardiovascular disease; OGTT, oral glucose tolerance test.

this condition and on its impact on cardiovascular disease in various populations. One mechanism of ethnic-related hyperhomocysteinemia in Asian Indians has been suggested to be insufficient dietary folate intake and low plasma folate (26–29). This may be a case in South Asia or certain other parts of the world, but may not be applicable in the United States This study was performed to test the hypothesis that folate fortification currently in place in the United States does not eliminate ethnic differences in plasma homocysteine between Asian Indians and Caucasians. Because vegetarianism and excessive insulin resistance are other important characteristics of Asian Indians that may impact plasma homocysteine, we also evaluated the relative role of low vitamin B-12 and insulin resistance on ethnic-related differences in plasma homocysteine among Asian Indians and Caucasians living in the United States.

Materials and Methods

Subjects

Two groups of subjects participated in this study: 155 were Caucasians (66 males and 89 females), and 227 were Asian Indians (131 males and 96 females) living in the United States. They were recruited for this study by public advertisement. The study was approved by the Institutional Review Board of the University Texas Southwestern Medical Center at Dallas (Dallas, TX). All subjects signed a written informed consent. All subjects were interviewed and provided with questionnaires for detailed medical, personal, social, and family history. The height, weight, and blood pressure measurements were performed in all the subjects. Fasting blood sample was collected in all the subjects.

Biochemical analyses

Plasma glucose concentration was assayed using a glucose oxidase method. Plasma insulin was determined by immunoassay (Linco Research Inc., St. Louis, MO). The homocysteine assay is based on the fluorescence polarization immunoassay technology and was performed on the Abbott Laboratories Imx (Abbott Park, IL) as described previously (31). Vitamin B-6 was measured by HPLC, and vitamin B-12 and folate were measured by chemiluminescence assay on the Centaur (Bayer Diagnostics, Tarrytown, NY). These as well as measures of glucose, TSH, creatinine are standard routine techniques in the clinical biochemistry laboratory.

Oral glucose tolerance test (OGTT)

Sixty-six Asian Indians (47 males and 19 females) and 63 Caucasians (33 males and 30 females) volunteered to also participate in OGTT and anthropometric evaluation. These volunteers were recruited by public advertisement and screened for hematological and blood chemistry abnormalities. Subjects with diabetes mellitus and other endocrine disorders, coronary heart disease, liver function test abnormalities, and those receiving any form of therapies were excluded from OGTT study. At the time of enrollment, each volunteer was administered a health history questionnaire that included the number of days of the week planned physical exercise was performed. After 12 h fasting, subjects had an iv catheter placed in a forearm vein to collect blood. A solution containing 75 g of glucose was administered orally to the subjects (Tru-Glu 100, Fisher Scientific, Pittsburgh, PA). Blood was collected at time −30; −15; 0; 30; 60; 90; 120; 150; and 180 min for measurement of glucose and insulin concentrations.

Anthropometry

Anthropometric measurements were done in all subjects participating in OGTT study. Height and weight were measured by standard procedures. Waist circumference was measured at the umbilical level. The average of two measurements was used for analysis. Body composition was determined using underwater weighing, as previously reported (32). Body composition was studied by determination of body density in a Whitmore volumeter (Whitmore Enterprise, San Antonio, TX). Each subject was submerged in water up to the chin in a seated position. Then each subject was given 3000 ml gas to rebreath (45% oxygen, 10% helium, and 45% nitrogen) and went completely underwater. Total volume displacement was measured to the nearest 50 ml. After resurfacing, the helium concentration was measured in the exhaled gas by mass spectrometry (model 1100, Perkin-Elmer, Shelton, CT). Total submerged gas volume was calculated by the formula: total gas volume (ml) = 300 ml He/final He conc. + 100 ml (for abdominal gas). Total gas volume was subtracted from total displacement volume to give total body volume. Total body mass (kilograms) measured to the nearest 0.1 kg, was divided by body volume to obtain body density. Siri's equation (32) was used to estimate the percentage of total body fat, lean body mass, and total fat mass.

Statistical analysis

Area under the curve (AUC) during OGTT was calculated using the trapezoidal rule. For skewed variables (homocysteine, vitamin B-12, and triglycerides), the data were log transformed before analysis. Two-sample *t* tests were used to compare the Asian Indian and Caucasian groups. Analysis of covariance models were employed to adjust for potential confounding factors such as vitamin B-12 and insulin AUC. Chi-square test was performed to evaluate ethnic differences in percentage of subjects who underwent physical activity each week. A code from 0 to 3 was assigned to the number of days of the week each subject engaged in planned physical activity (0 d; 1–2 d; 3–5 d; 6–7 d/wk). Pearson correlation coefficients and linear regression models were used to assess the relationship between continuous variables. The Potthoff extension of the Johnson-Neyman technique (33) was used to calculate simultaneous regions of significance for comparing groups while adjusting for covariates. Statistical analysis was performed using SAS version 8.2 (SAS Institute, Cary, NC).

TABLE 1. General characteristics of subjects

	Asian Indian	Caucasians	*P*
n (males/females)	227 (131/96)	155 (66/89)	
Age (yr)	40 ± 9	40 ± 14	0.5
BMI (kg/m^2)	24.5 ± 3	25.8 ± 5	<0.007
Systolic BP (mm Hg)	124 ± 17	122 ± 16	0.29
Diastolic BP (mm Hg)	79 ± 12	75 ± 11	0.002
Total cholesterol (mmol/liter)	4.64 ± 0.9	4.48 ± 1.0	0.11
LDL cholesterol (mmol/liter)	2.8 ± 0.8	2.6 ± 0.9	0.007
HDL cholesterol (mmol/liter)	1.2 ± 0.3	1.3 ± 0.4	0.004
Triglycerides (mmol/liter)	1.6 ± 1.2	1.5 ± 1.5	0.05[a]
TSH (μU/ml)	2.0 ± 1.2	2.4 ± 1.6	0.31
Creatinine (μmol/liter)	77 ± 15	78 ± 16	0.6

Data are expressed as mean ± SD. *P* values are from two-sample *t* test.
[a] Log transformed.

Results

In Table 1, the general characteristics of Asian Indian subjects are compared with those of the Caucasian subjects. The age range and mean was similar between groups. The average body mass index (BMI) was higher in Caucasians than Asian Indians. Plasma total cholesterol and triglycerides were similar, but plasma high-density lipoprotein cholesterol was significantly lower and low-density lipoprotein cholesterol was significantly higher in Asian Indians. Asian Indians had higher diastolic blood pressure than Caucasians. However, plasma TSH and serum creatinine, factors that can influence plasma homocysteine, were similar in both the groups. None of the subjects in both the groups had diabetes, CVD, or other significant illness. The level of exercise reported (number of days during the week each subject engaged in any form of physical activity) was found significantly lower in the Asian Indians compared with the Caucasians (χ^2, $P < 0.05$).

Plasma concentrations of homocysteine, B-12, and folate are shown in Fig. 1. Plasma homocysteine was significantly higher in Asian Indians than in Caucasians [mean ± SD; 14 ± 6.5 *Vs.* 8.7 ± 3.6 μmol/liter (median: 12.6 *vs.* 8 μmol/liter); $P < 0.0001$; respectively]. Plasma folate was similar in both the groups and in both was in high normal range. The Asian Indian group had mean plasma B-12 concentration significantly lower compared with the Caucasian group [mean ± SD; 258 ± 200 *vs.* 342 ± 133 pmol/liter (median: 204 *vs.* 320 pmol/liter); $P < 0.0001$, respectively]. Figure 2 depicts association of plasma homocysteine with plasma B-12 both in Asian Indians and Caucasians. Both the groups showed a strong correlation between plasma homocysteine and plasma B-12. However, the regression lines for the two ethnic groups were different for lower plasma vitamin B-12 concentrations. When we further analyzed the differences between the regression lines in the two ethnic groups, we found that both the slopes and the intercepts were significantly different for the plasma concentrations of vitamin B-12 less than 379 pmol/liter (P values < 0.05 for both the intercept and slope). Therefore, for any level of vitamin B-12 less than 379 pmol/liter, the Asian Indian had higher plasma concentrations of homocysteine than the Caucasians. This difference in the two ethnic groups was lost when plasma B-12 was higher than 379 pmol/liter.

Table 2 shows comparison of significant characteristics of Asian Indians and Caucasians participating in OGTT. Both the groups were matched for age, BMI, and total body fat, factors that are known to affect plasma homocysteine. Both the groups also had similar plasma TSH and serum creatinine. These were healthy young volunteers without any acute or chronic illness. Despite similar plasma glucose during OGTT, plasma insulin AUC was significantly higher in Asian Indians, implying more insulin resistance compared with Caucasians (Fig. 3). Plasma folate was similar in both groups. However, Asian Indians continued to show significantly higher homocysteine and low B-12 than Caucasians.

Increasing insulin AUC during OGTT was significantly correlated with increasing plasma concentration of homocysteine for the whole study group (Fig. 4). Therefore, because elevated OGTT insulin AUC reflects insulin resistance and may contribute to the inter-ethnic difference in plasma homocysteine, we analyzed contribution of vitamin B-12 and insulin AUC for the difference in plasma homocysteine in both the ethnic groups. As shown in Table 3, after adjusting for both B-12 and insulin AUC, the difference in plasma homocysteine remained significant between the two ethnic groups.

Plasma concentrations of B-6 were measured in 31 Asian Indians and 45 Caucasians who had OGTT and were significantly lower in Asian Indians compared with Caucasians

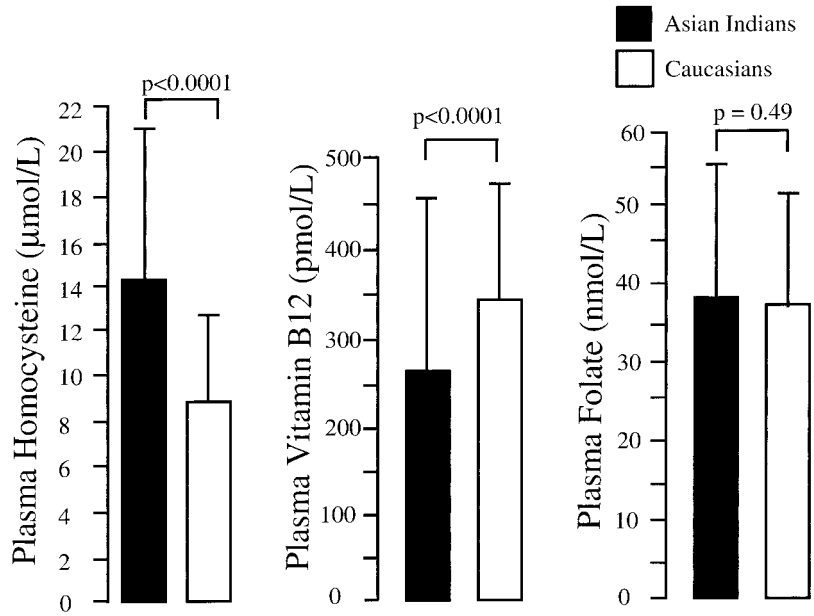

FIG. 1. Plasma homocysteine (A), plasma vitamin B-12 (B), and plasma folate (C) in Asian Indian (*dark bars*) and Caucasians (*open bars*). The *error bars* represent SD. Two sample *t* test on log transformed data were used for computing the *P* value.

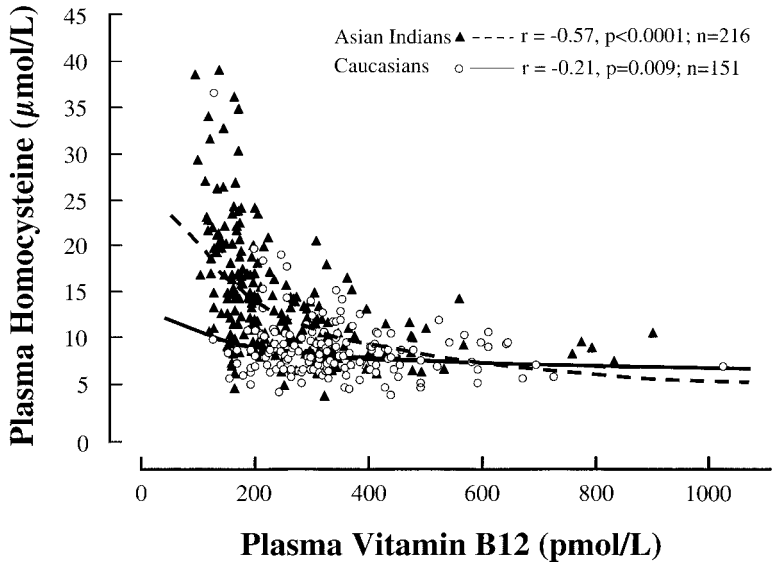

FIG. 2. The relationship of plasma homocysteine and plasma vitamin B-12 in Asian Indians (▲) and Caucasians (○). Pearson correlation was used for computing the correlation coefficient (r). The best-fit regression curves for Asian Indians and Caucasians are represented by *interrupted* and *solid lines*, respectively.

TABLE 2. Characteristics of subjects undergoing OGTT

	Asian Indian	Caucasians	*P*
n (males/females)	66 (47/19)	63 (33/30)	
Age (yr)	31 ± 10	30 ± 8	0.43
BMI (kg/m^2)	23.9 ± 3.5	23.7 ± 4.15	0.81
Total body fat (%)	25.8 ± 6.3	24.0 ± 8.6	0.23
Waist circumference (cm)	81 ± 10	81 ± 11	0.74
Folate (nmol/liter)	34.4 ± 16.3	36.5 ± 14.5	0.47
B12 (pmol/liter)	231.7 ± 87 (236)	332.8 ± 129.9 (301)	0.0001[a]
Homocysteine (μmol/liter)	11 ± 6 (9)	7 ± 2 (6.7)	<0.0001[a]

Data are expressed as mean ± SD. Median is reported in *parentheses* for data with skewed distribution. *P* values are from two-sample *t* test.
[a] Log transformed.

TABLE 3. Ethnic comparison of plasma homocysteine after adjustment for differences in B12 and insulin area under the curve during OGTT

	Asian Indians	Caucasians	P^a
Homocysteine (μmol/liter)	9.8 (9.0–10.7)	6.8 (6.1–7.3)	<0.0001
Homocysteine (after adjustment for B12) (μmol/liter)	8.9 (8.1–9.8)	7.0 (6.4–7.7)	0.0006
Homocysteine (after adjustment for B12 and insulin AUC) (μmol/liter)	8.8 (8.0–9.7)	7.1 (6.5–7.8)	0.003

Data are reported as geometric mean, with 95% confidence interval in *parentheses.*
[a] ANCOVA.

[mean ± SD; 70.5 ± 78 *vs.* 100 ± 97 nmol/liter (median: 49 *vs.* 70 nmol/liter); $P = 0.05$, respectively]. There was no correlation between plasma B-6 and homocysteine concentrations.

Discussion

The primary finding of this study was that Asian Indians have higher plasma concentrations of homocysteine than Caucasians, when both are living in the same geographical area in the United States. This relative hyperhomocysteinemia in Asian Indians is independent of plasma folate level. The fortification of cereals and grains since January 1998 in the United States has significantly improved plasma folate levels in the population (11, 13, 14). Our study supports the benefits of food fortification with folate with resulting high-normal levels of plasma folate eliminating folate deficiency as a possible pathogenetic factor for the hyperhomocysteinemia in Asian Indians in the United States. Because low plasma vitamin B-12 is related to high plasma homocysteine (10, 11, 30), the observation that the Asian Indians in this study had lower vitamin B-12 would support its role in hyperhomocysteinemia of Asian Indians living in US. However, the data presented in Fig. 2 of this study show that, whereas in subjects with high plasma concentrations of vitamin B-12 there are no ethnic differences in plasma homocysteine, low plasma vitamin B-12 concentrations are associated with ethnic differences. In this study, high plasma homocysteine concentrations in the Asian Indians were ob-

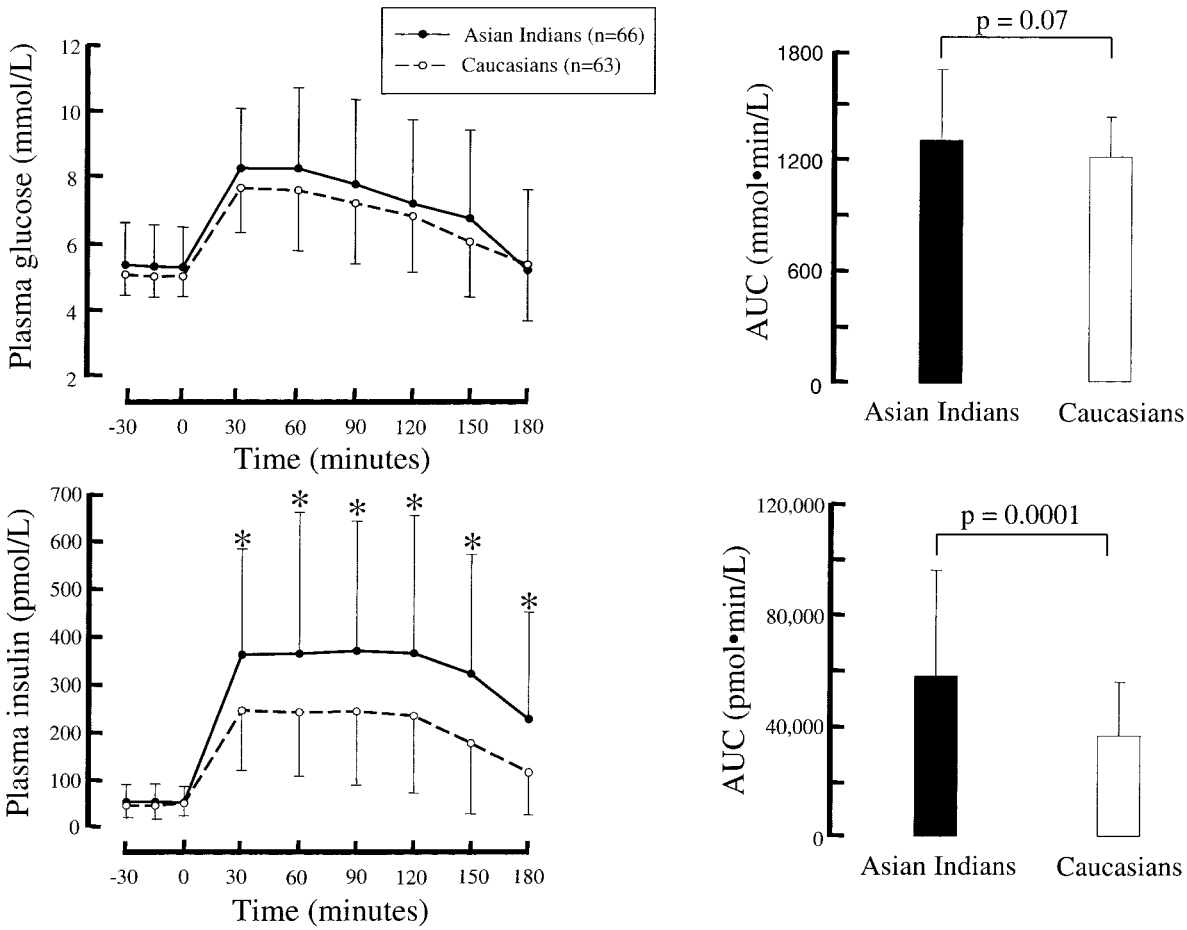

FIG. 3. Plasma glucose and insulin concentration during OGTT in Asian Indians (●) and Cuacasians (○). Insulin AUC is represented in Asian Indians with *dark bar* and in Caucasians with *open bar*. *, $P < 0.05$ for that time point.

served even within levels of vitamin B-12 considered normal for the general population (between 150 and 379 pmol/liter). The Asian Indians in this study did not have frank vitamin B-12 deficiency as reported from the study done in India (27–30). However, because the majority of the Asian Indians are either vegetarian or infrequent meat/dairy products consumer, it is possible that dietary intake in Asian Indians is not similar to that of the Caucasians in our area. Therefore, the question is whether higher dietary vitamin B-12 intake is necessary to assure plasma vitamin B-12 concentrations, which would reduce ethnic differences in plasma homocysteine. Certainly, the fact that Asian Indian subjects with vitamin B-12 higher than 379 pmol/liter have similar homocysteine as Caucasians raises the possibility of fortification with B-12 as a means to achieve higher plasma B-12 and lower homocysteine. However, further studies are needed with supplementation before such recommendation can be made. Another observation supported by our analysis of correlations is that for any level of vitamin B-12, within the clinically normal range, Asian Indians had higher homocysteine than Caucasians, suggesting factors other than B-12 involved in causing high homocysteine. Therefore, it appears that an interaction between factors related to vitamin B-12 intake and/or absorption and other yet unknown factors determines the ethnic-related hyperhomocysteinemia of Asian Indians.

If factors other than vitamin B-12 are involved in the pathogenesis of the hyperhomocysteinemia in Asian Indians, one should consider conditions that are known to be typically present in this ethnic group and are also involved in homocysteine metabolism. Along this line, several reports linking insulin resistance to plasma homocysteine level are of interest (34–36). As previously reported by us (22) and others (23), Asian Indians have more insulin resistance compared with Caucasians even after matching for age, BMI, and total body fat. Although the findings of increased insulin resistance in Asian Indians are associated with reduced level of physical activity in the Asian Indians, the role of exercise in the pathogenesis of the excessive insulin resistance of Asian Indians is still unclear (37). Nevertheless, this study confirmed that Asian Indians have increased insulin AUC during OGTT, indicative of insulin resistance. Although not all investigations have confirmed an association between insulin resistance and plasma levels of homocysteine (38, 39), our study support a relationship between insulin resistance and hyperhomocysteinemia reported in some previous studies (34–36). Thus, insulin resistance could contribute to the higher plasma levels of homocysteine of Asian Indians. Within the

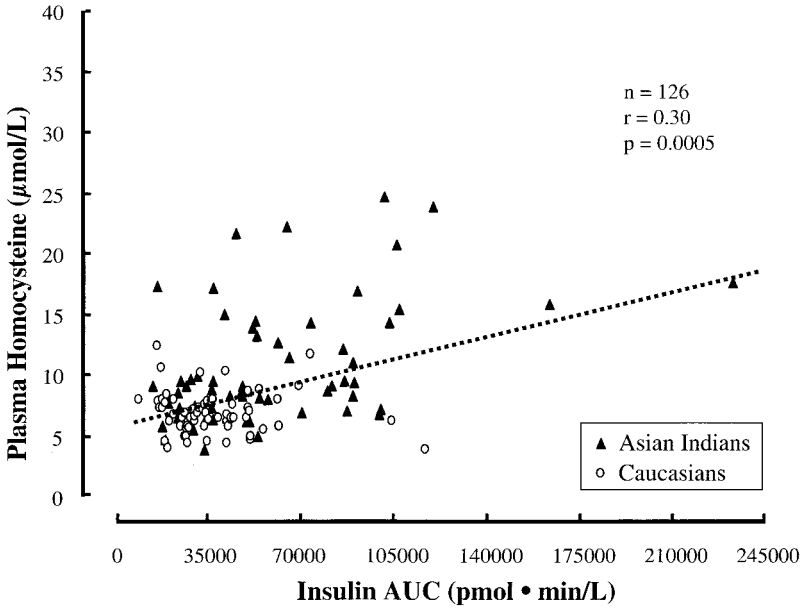

FIG. 4. The relationship of plasma homocysteine and AUC for insulin during OGTT in Asian Indians (▲) and Caucasians (○). Pearson correlation was used for computing the correlation coefficient (r). The best-fit regression curve is represented by *interrupted line*.

subgroups that had OGTT evaluation, Asian Indians still had higher plasma homocysteine and lower plasma vitamin B-12, compared with the Caucasians. However, in a multivariate model analysis, ethnicity was significantly associated with plasma homocysteine, independently of the insulin AUC.

Other factors known to affect plasma homocysteine, such as hypothyroidism or renal insufficiency, were also ruled out as causes of ethnic differences in this study. Our data therefore suggest ethnic-related hyperhomocysteinemia, which is not entirely explained by plasma folate, vitamin B-12, and insulin resistance or other common acquired factors playing a role in homocysteine metabolism. We suggest that genetic factors play a potentially important role in the hyperhomocysteinemia of Asian Indians. Genetic factors may directly affect homocysteine metabolism. Genetic factors may also affect vitamin B-12 intake and/or absorption, leading to excessive plasma concentrations of homocysteine in the presence of even mild reduction of plasma vitamin B-12 concentrations.

Vitamin B-6 levels were found to be lower in Asian Indians. We did not measure homocysteine following a methionine load. Therefore, another potential mechanism for ethnic-related hyperhomocysteinemia could be found in the homocysteine metabolism pathways that involve vitamin B-6 not explored in this study. Another limitation of our study is that plasma methylmalonic acid concentration was not measured. Methylmalonic acid has been reported to be a better predictor of subclinical vitamin B-12 deficiency and tissue B-12 levels. However, our study did not aim at evaluating the role of subclinical B-12 deficiency. We compared B-12 levels in two ethnic populations and found that Asian Indians have lower, albeit normal levels of B-12.

It is of interest that plasma B-6 concentrations were found to be lower in the Asian Indians than in the Caucasians. However, no correlation was found between B-6 and homocysteine. Because B-6 could play a role in cardiovascular risk factors, independent of homocysteine (40–42), lower plasma concentrations of this vitamin in Asian Indians could explain part of the excessive cardiovascular risk of this ethnic group. Larger and more targeted investigations on this issue are needed to explore this hypothesis.

In conclusion, our study on Asian Indians living in the United States shows an ethnic-related excess of plasma homocysteine concentrations compared with Caucasians. Although insulin resistance and plasma levels of vitamin B-12 and B-6, but not folate, may contribute to the ethnic-related hyperhomocysteinemia of Asian Indians living in the United States, our study suggests that other ethnic-related factors, such as genetic, may play a more significant role. It is possible that evaluation of the genetic bases of hyperhomocysteinemia may shed some lights into the observed ethnic differences in plasma homocysteine concentrations. Intervention with vitamin B-6 and B-12 supplementation and lifestyle changes to reduce insulin resistance may be necessary in susceptible ethnic groups like the Asian Indians. The implications for CVD risk reduction in this and other susceptible ethnic groups are still poorly understood but certainly deserve future investigations.

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Address all correspondence and requests for reprints to: Manisha Chandalia, M.D., 6011 Harry Hines Boulevard, Dallas, Texas 75350-9169. E-mail: Manisha.Chandalia@UTSouthwestern.edu.

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