日本人男性におけるシトクロムP450 1A2遺伝子多型、コーヒー摂取と糖代謝異常

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Cytochrome P450 1A2 Polymorphisms, Coffee Consumption and Impaired Glucose Metabolism in Japanese Men

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Abstract

Objective: Coffee consumption has been related to decreased risk of type 2 diabetes, but it is unclear whether this relation is affected by cytochrome P450 1A2 (CYP1A2), a primary enzyme of caffeine metabolism. We examined the associations of two functional genetic polymorphisms of CYP1A2 with glucose tolerance status and the effect modification of the *CYP1A2* polymorphisms on the association between coffee and impaired glucose metabolism.

Methods: The subjects were 2263 male officials aged 46-59 years in the Self-Defense Forces in Japan. Individual glucose tolerance status was classified into normal glucose tolerance, Impaired Fasting Glycemia (IFG), Impaired Glucose Tolerance (IGT) or type 2 diabetes by a 75 g oral glucose tolerance test. IFG and IGT were combined as a single entity (IFG/IGT). Coffee consumption was assessed by a self-administered questionnaire. The *CYP1A2* polymorphisms (*CYP1A2*1C* and *CYP1A2*1F*) were genotyped by the PCR-RFLP method.

Results: Neither *CYP1A2*1C* nor *CYP1A2*1F* showed a measurable association with IFG/IGT or type 2 diabetes. Coffee consumption was inversely associated with IFG/IGT and type 2 diabetes. The inverse association between coffee and type 2 diabetes was significant in the GG genotype of *CYP1A2*1C*, but not in the GA and AA genotypes combined (interaction P=0.07). This effect modification was more evident among smokers (interaction P=0.03). Neither of the two polymorphisms modified the association between coffee and IFG/IGT.

Conclusions: The *CYP1A2*1C* polymorphism modified the association between coffee and type 2 diabetes, especially among current smokers, suggesting that caffeine may not be negligible in the coffee-diabetes association.

Keywords: Caffeine; Coffee; Cytochrome P450 1A2; Impaired glucose metabolism; Single nucleotide polymorphism: Type 2 diabetes

Introduction

Coffee consumption has been related to decreased risk of type 2 diabetes in different populations [1,2]. It has also been reported that coffee consumption is protectively associated with impaired glucose tolerence, as measured by the standard Oral Glucose Tolerance Test (OGTT) [3,4]. Coffee contains a wide variety of bioactive compounds, including caffeine, chlorogenic acid, magnesium and trigonelline [5]. Despite the consistent observation between coffee and type 2 diabetes [1-6], it is unclear what ingredients in coffee infusion exert a protective effect on glucose metabolism. Since decaffeinated coffee has also been associated with a decreased risk of type 2 diabetes in several studies [7,8], it is suggested that non-caffeine coffee compounds may be more important as protective component. For a potent antioxidant property and some beneficial effects on glucose absorption and metabolism, phenolic compounds such as chlorogenic acid rather than caffeine have drawn much attention [5,6]. However, caffeine intake itself was shown to be associated with a decreased risk of type 2 diabetes in large prospective studies of men and women [9]. In this study, the inverse association with type 2 diabetes risk was much weaker for decaffeinated coffee as compared with caffeinated coffee. Caffeine is a glycogen phosphorylase inhibitor that may lower plasma glucose [10]. Moreover, caffeine has thermogenic, anti-inflammatory and lipolytic effects, which may be mechanistic explanations for a protective association between coffee and type 2 diabetes [11,12]. In addition, caffeine metabolites have been shown to possess an antioxidant property [13,14], suggesting a protective role of caffeine in glucose metabolism.

Caffeine is metabolized primarily by cytochrome P450 1A2 (CYP1A2) in the liver [5]. Of a number of *CYP1A2* Single Nucleotide Polymorphisms (SNPs), two functional SNPs have been known. One is *CYP1A2* -3860G>A (*CYP1A2*1C*, rs2069514), which is more common in Asians than in Caucasians. The GG genotype of the *CYP1A2*1C* is associated with increased enzyme activity in smokers [15]. Another functional SNP is *CYP1A2* -163C>A (*CYP1A2*1F*, rs762551), which is common in various populations [16]. Smokers with the AA genotype of the *CYP1A2*1F* polymorphism have higher activity of the enzyme than those with the CA or CC genotype [17].

We hypothesize that *CYP1A2* genotype may modify the association between coffee consumption and glucose tolerance status if caffeine has a primary effect on glucose metabolism. The present study aims to investigate the association of *CYP1A2*1C* and *CYP1A2*1F* polymorphisms with glucose tolerance status as determined by OGTT and the effect modification of the *CYP1A2* polymorphisms on the association between coffee and impaired glucose metabolism in middle-aged Japanese men. Furthermore, because the induction of CYP1A2 by smoking varies with the *CYP1A2*1C* and *CYP1A2*1F* polymorphisms [15,17], we also examined the effect modifications of these polymorphisms among smokers and nonsmokers separately.

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Materials and Methods

Study population

The present study was a cross-sectional study of middle-aged Japanese men. Subjects were male officials in the Self-Defense Forces who underwent a pre-retirement health examination between January 1997 and March 2001 at the Self-Defense Forces Fukuoka and Kumamoto Hospitals. All officials retiring from the Self-Defense Forces received a pre-retirement health examination as part of a nationwide program which offered a comprehensive medical examination. Details of the health examination have been described elsewhere [18]. In addition to blood samples for routine use in the health examination, a sample of 7 mL fasting venous blood was obtained for the purpose of medical research. The study was approved by Ethics Committee of the Kyushu University Faculty of Medical Sciences. All study subjects gave written informed consent prior to their participation in the study.

In a consecutive series of 2459 men aged 46-59 years, five men refused to participate in the survey. We excluded 169 men for the following reasons: past history of gastrectomy (n=38), chronic hepatitis or liver cirrhosis (n=49), use of steroids (n=6), use of antidiabetic drugs (n=43) and undetermined glucose tolerance status (n=36). Some of these men had two or more of the exclusion criteria. Furthermore, we excluded 22 men because DNA samples were not available, leaving 2263 men in the present study analysis.

Glucose tolerance status

A 75g OGTT and other clinical examinations were carried out during a 5-day admission period. After an overnight fast, venous blood was drawn for measurement of plasma glucose before and 2 hours after the oral glucose load. Plasma glucose levels were determined by the glucose oxidase method using commercial reagents (Shino Test, Tokyo, Japan). Subjects were classified as having normal glucose tolerance, Impaired Fasting Glycemia (IFG), Impaired Glucose Tolerance (IGT) or type 2 diabetes in accordance with the World Health Organization (WHO) diagnostic criteria [19].

Coffee consumption and other lifestyle characteristics

Lifestyle factors including coffee consumption were ascertained by using a self-administered questionnaire [3,20]. The subjects reported weekly frequency of coffee drinking, and those drinking coffee daily reported the number of cups consumed per day. Types of coffee and the way of drinking coffee were not specifically assessed. Green tea consumption was ascertained likewise. Coffee and green tea intakes estimated from the questionnaire were shown to be fairly valid; Spearman rank correlation coefficients for coffee and green tea were 0.75 and 0.64, respectively in comparison with the 28-diet record [20].

Coffee consumption was categorized into null, weekly and daily consumption. Green tea consumption was categorized into 4 groups (0, 1-2, 3-4 and ≥5 cups per day). Smoking habit was classified into lifelong nonsmoking, past smoking, current light (<25 cigarettes per day) and heavy (≥25 cigarettes per day) smoking. Ever-alcohol drinking was defined as having drunk alcoholic beverages at least once per week for one year or longer. The subjects reported whether they were lifelong nondrinkers, past drinkers or current drinkers, and current alcohol drinkers reported consumption frequencies and amounts of five different alcoholic beverages (sake, shochu, beer, whisky/brandy and wine) on average in the past year. Beverage-specific alcohol consumption was classified into two or three categories. Leisure-time physical activity was estimated on the basis of the types of regular exercise, weekly frequency and time spent per occasion for each activity. The type of exercise was categorized into four activities in terms of Metabolic Equivalent (MET), and MET-hours per week were calculated. The study subjects were classified into four categories (<5, 5-14, 15-24 and ≥25 MET-hours per week). Body weight and height were recorded, and body mass index (BMI, kg/m^2) was calculated as a measure of obesity. With regard to BMI, individuals were divided into four groups (<22.5, 22.5-24.9, 25.0-27.4 and ≥27.5 kg/m^2) arbitrarily, but with consideration to the definition of overweight (BMI ≥ 25 kg/m^2).

Genotyping

DNA was extracted from the buffy coat using a commercial kit (Qiagen, Hilden, Germany). Genotyping was carried out using the PCR-RFLP method with electrophoresis on a 3% agarose gel (NuiSieve GTG) and visualization by ethidium bromide. The PCR was carried out in a reaction mixture of 10 μL containing 0.5 U *Taq* DNA polymerase and 1 μL template DNA with a concentration of approximately 50-150 ng/μL. The *CYP1A2* -3860G>A (*CYP1A2*1C*) genotype was determined, as described by Chida et al. [21], using primers 5'-GCTAC ACATG ATCGA GCTAT AC-3' (sense) and 5'-CAGGT CTCTT CACTG TAAAG TTA-3' (antisense). The PCR product was digested with *Dde*I, which cleaves the 596-bp PCR product into two fragments of 464 bp and 132 bp for the -3860A allele. The *CYP1A2* -163C>A (*CYP1A2*1F*) polymorphism was determined using primers 5'-CCCAG AAGTG GAAAC TGAGA-3' (sense) and 5'-GGGTT GAGAT GGAGA CATTC-3' (antisense). The restriction enzyme *Apa*I digested the 243-bp PCR product into two fragments of 124 bp and 119 bp for the -163C allele. The assay was repeated when the PCR was unsuccessful or when the gel pattern was indeterminable. The re-assay was done for 102 samples (4.5%) regarding *CYP1A2*1C* and for 154 samples (6.8%) regarding *CYP1A2*1F*. Finally, genotypes of *CYP1A2*1C* and *CYP1A2*1F* were not determined for 19 and 13 samples, respectively.

Statistical Analysis

Odds Ratio (OR) and 95% Confidence Interval (CI) were obtained by logistic regression analysis; 95% CI was derived from the standard error for the logistic regression coefficient. Statistical adjustment was made for age (continuous variable), hospital, Self-Defense Forces rank (low, middle and high), cigarette smoking, alcohol intake, green tea intake, leisure-time physical activity and BMI. Trend of the association was evaluated with ordinal scores assigned to coffee categories. In evaluating the effect modification of the *CYP1A2* polymorphisms, homozygous and heterozygous genotypes of the minor allele were combined because the minor-allele homozygotes were relatively few. Statistical assessment of the interaction was based on the Wald statistic for the product term of an ordinal variable for coffee consumption and a dichotomous variable for the genotype. Two-sided P-values less than 0.05 were regarded as statistically significant. All computations in these analyses were carried out using Statistically Analysis System (SAS), Version 9.2 (SAS Institute, Cary, NC, USA).

Results

Characteristics of the study subjects are summarized in Table 1. The mean age of the 2263 men was 52.4 years with a range of 46 to 59 years. There were 139 (6%) prevalent cases of IFG, 421 (19%) of IGT and 180 (8%) of type 2 diabetes. The remaining 1523 men had normal glucose tolerance. Those with normal glucose tolerance were defined as controls.

As regards -3860G>A (*CYP1A2*1C*), the frequencies of the GG, GA and AA genotypes among controls were 57%, 37% and 6%, respectively.

Variable	Value[a]
Age (year)	52.4 ± 0.9
Body mass index (kg/m^2)	23.8 ± 2.5
Leisure-time physical activity (MET-hours/week)	18 ± 18
Current smoking, n (%)	1072 (47.4)
Current alcohol use, n (%)	1892 (83.6)
Daily use of green tea, n (%)	1989 (87.9)
Daily use of coffee, n (%)	1473 (65.1)
Glucose tolerance status, n (%)	
Normal	1523 (67.3)
Impaired fasting glycemia	139 (6.1)
Impaired glucose tolerance	421 (18.6)
Type 2 diabetes	180 (8.0)

MET, metabolic equivalent.
[a]Values are mean ± SD unless otherwise specified.

Table 1: Characteristics of the study subjects (n=2263).

	Type 2 diabetes		IFG/IGT		NGT
Genotype	*n* (%)	OR (95% CI)[a]	*n* (%)	OR (95% CI)[a]	*n* (%)
*CYP1A2*1C*					
GG	101 (56.7)	1.00 (referent)	313 (56.2)	1.00 (referent)	862 (57.1)
GA	70 (39.3)	1.04 (0.75-1.45)	210 (37.7)	1.02 (0.83-1.26)	555 (36.8)
AA	7 (3.9)	0.61 (0.27-1.37)	34 (6.1)	0.98 (0.64-1.50)	92 (6.1)
GA + AA	77 (43.3)	0.98 (0.71-1.35)	244 (43.8)	1.02 (0.83-1.24)	647 (42.9)
*CYP1A2*1F*					
AA	71 (39.7)	1.00 (referent)	253 (45.3)	1.00 (referent)	654 (43.3)
CA	81 (45.3)	1.15 (0.82-1.63)	242 (43.3)	0.96 (0.78-1.19)	661 (43.7)
CC	27 (15.1)	1.33 (0.82-2.16)	64 (11.4)	0.86 (0.62-1.19)	197 (13.0)
CA + CC	108 (60.3)	1.19 (0.86-1.65)	306 (54.7)	0.94 (0.77-1.15)	858 (56.7)

IFG, impaired fasting glycemia; IGT impaired glucose tolerance; NGT, normal glucose tolerance; OR, odds ratio; CI, confidence interval.

[a] Adjusted for age, hospital, rank in the Self-Defense Forces, cigarette smoking, leisure-time physical activity, body mass index, current use of alcoholic beverages (sake, shochu, beer, whisky and wine), past alcohol use and green tea intake.

Table 2: Relationship between *CYP1A2*1C* and *CYP1A2*1F* polymorphisms and impaired glucose metabolism.

	Coffee use							
	Null		Weekly		Daily		Trend *P*	Interaction *P*
Genotype	*n*[a]	OR[b]	*n*[a]	OR (95% CI)[b]	*n*[a]	OR (95%CI)[b]		
*CYP1A2*1C*								
GG	25/88	1.00 (referent)	21/171	0.39 (0.20-0.76)	55/603	0.29 (0.16-0.51)	<0.0001	0.07
GA + AA	12/93	1.00 (referent)	18/128	1.26 (0.55-2.90)	47/426	0.89 (0.41-1.90)	0.55	
*CYP1A2*1F*								
AA	12/86	1.00 (referent)	18/118	1.03 (0.43-2.44)	41/450	0.46 (0.20-1.03)	0.02	0.61
CA + CC	25/98	1.00 (referent)	22/181	0.48 (0.25-0.92)	61/579	0.42 (0.24-0.74)	0.006	

OR, odds ratio; CI, confidence interval.

[a]Number of cases/controls.

[b]Adjusted for age, hospital, rank in the Self-Defense Forces, cigarette smoking, leisure-time physical activity, body mass index, current use of alcoholic beverages (sake, shochu, beer, whisky and wine), past alcohol use and green tea intake.

Table 3: Relationship between coffee consumption and type 2 diabetes with stratification by *CYP1A2* genotype.

The frequencies of the AA, CA and CC genotypes of -163C>A (*CYP1A2*1F*) among controls were 43%, 44% and 13%, respectively. Frequencies of the minor allele were 0.245 for *CYP1A2*1C* and 0.349 for *CYP1A2*1F*. Distribution of the genotypes in controls were compatible with the Hardy-Weinberg equilibrium for both *CYP1A2*1C* (*P*=0.83) and *CYP1A2*1F* (*P*=0.14). The genotype distribution among type 2 diabetes or IFG/IGT cases did not differ from that among those with normal glucose tolerance in regard to either *CYP1A2*1C* or *CYPA2*1F* polymorphism (Table 2). Neither of the *CYP1A2* polymorphisms showed a measurable association with IFG/IGT or type 2 diabetes.

Coffee consumption was strongly inversely associated with IFG/IGT and type 2 diabetes. The adjusted OR of IFG/IGT for null, weekly and daily consumption of coffee were 1.00 (referent), 0.75 (95% CI 0.54-1.04) and 0.60 (95% CI 0.45-0.79), respectively (trend *P*=0.0003), and the corresponding values of type 2 diabetes were 1.00 (referent), 0.69 (95% CI 0.42-1.13) and 0.44 (0.29-0.68), respectively (trend *P*=0.0001).

There was a suggestive effect modification of *CYP1A2*1C* polymorphism on the association between coffee consumption and type 2 diabetes (interaction *P*=0.07) (Table 3). The inverse association was highly significant in the GG genotype of *CYP1A2*1C*, but coffee use was almost unrelated to type 2 diabetes in the GA and AA genotypes combined. The inverse association between coffee consumption and

	Coffee use							
	Null		Weekly		Daily		Trend *P*	Interaction *P*
Genotype	*n*[a]	OR[b]	*n*[a]	OR (95% CI)[b]	*n*[a]	OR (95%CI)[b]		
Current smokers								
*CYP1A2*1C*								
GG	12/23	1.00 (referent)	11/63	0.28 (0.10-0.80)	31/322	0.16 (0.06-0.39)	<0.0001	0.03
GA + AA	3/30	1.00 (referent)	9/41	2.27 (0.49-10.5)	30/235	1.37 (0.35-5.38)	0.92	
*CYP1A2*1F*								
AA	5/23	1.00 (referent)	8/38	0.64 (0.15-2.75)	30/241	0.39 (0.11-1.37)	0.10	0.52
CA+CC	10/31	1.00 (referent)	13/66	0.63 (0.23-1.72)	31/316	0.33 (0.14-0.81)	0.008	
Nonsmokers								
*CYP1A2*1C*								
GG	13/65	1.00 (referent)	10/108	0.44 (0.17-1.14)	24/281	0.43 (0.19-0.96)	0.07	0.59
GA+AA	9/63	1.00 (referent)	9/87	1.04 (0.33-3.27)	17/191	0.73 (0.26-2.04)	0.48	
*CYP1A2*1F*								
AA	7/63	1.00 (referent)	10/80	1.56 (0.43-5.72)	11/209	0.38 (0.11-1.30)	0.06	0.53
CA+CC	15/67	1.00 (referent)	9/115	0.34 (0.13-0.87)	30/263	0.51 (0.24-1.10)	0.20	

OR, odds ratio; CI, confidence interval.

[a]Number of cases/controls.

[b]Adjusted for age, hospital, rank in the Self-Defense Forces, leisure-time physical activity, body mass index, current use of alcoholic beverages (sake, shochu, beer, whisky and wine), past alcohol use and green tea intake.

Table 4: Relationship between coffee consumption and type 2 diabetes with stratification by *CYP1A2* genotype among current smokers and nonsmokers.

type 2 diabetes did not differ by *CYP1A2*1F* polymorphism. The prevalence odds of IFG/IGT decreased with increasing consumption of coffee regardless of *CYP1A2*1C* or *CYP1A2*1F* genotypes (Supplementary Table 1).

The effect modifications of *CYP1A2*1C* genotype on the association between coffee and type 2 diabetes was statistically significant among current smokers (Table 4). Among nonsmokers, the inverse association between coffee and type 2 diabetes seemed to be more pronounced in the GG genotype of *CYP1A2*1C* than in the GA and AA genotypes, but the interaction was far from statistical significance. Neither *CYP1A2*1C* nor *CYP1A2*1F* polymorphism modified the association between coffee and IFG/IGT among current smokers and nonsmokers each (Supplementary Table 2).

Discussion

The present study first investigated the associations between functional *CYP1A2* polymorphisms and impaired glucose metabolism and the effect modification of the *CYP1A2* polymorphisms on the association between coffee and impaired glucose metabolism. Overall, neither *CYP1A2*1C* nor *CYP1A2*1F* polymorphism was associated with impaired glucose metabolism. While decreased prevalence odds of IFG/IGT associated with coffee consumption did not modified by either of the two polymorphisms, the inverse association between coffee and type 2 diabetes differed by *CYP1A2*1C* genotype. This effect modification was more evident in current smokers. It is documented that cigarette smoking induces CYP1A2 activity in humans [22,23], and both *CYP1A2*1C* and *CYP1A2*1F* affect the inducibility of the enzyme [15,17]. Thus it is of interest whether the interactions between these polymorphisms and coffee on impaired glucose metabolism may differ by smoking status.

The present findings on *CYP1A2*1C* and coffee suggest that caffeine may play a potential role in the coffee-diabetes association. Caffeine metabolites were shown to have an antioxidant potential [13,14]. Although an in vitro antioxidant effect of caffeine metabolites was lower than that of phenolic compounds of coffee, the antioxidant effect of caffeine metabolites may not be neglected when physiological concentrations of caffeine metabolites are taken into consideration [14]. The GG genotype of the *CYP1A2*1C* polymorphism is associated with increased enzyme activity among smokers [15]. Thus the stronger inverse association between coffee and type 2 diabetes among current smokers with higher enzyme activities (GG genotype) is compatible with the protective effect of caffeine metabolites. On the other hand, substantial evidence from human studies indicates that caffeine ingestion deteriorates insulin sensitivity acutely [24-26]. Faster metabolism of caffeine may attenuate the adverse effects of caffeine, and the potential protective effect of coffee compounds other than caffeine may be more discernible among smokers with *CYP1A2*1C* GG genotype. It should be noted that *CYP1A2*1C* polymorphism did not affect the inverse association between coffee and IFG/IGT. A possible protective effect of caffeine metabolites may be more relevant to the progression of impaired glucose metabolism.

Previous studies have examined the effect modification of *CYP1A2*1F* on the associations of coffee consumption with the risks of myocardial infarction and hypertension [27,28]. Coffee consumption was associated with an increased risk of myocardial infarction among carriers of the inactive allele (C allele) of *CYP1A2*1F* in the former study [27]. Furthermore, coffee consumption was associated with an increased risk of hypertension among those with the inactive allele of *CYP1A2*1F*, and with a decreased risk among those without the inactive allele [28]. None had examined the interaction between *CYP1A2*1C* and coffee in relation to disease risk.

Use of the standard glucose tolerance test and the ethnic homogeneity of subjects were among strengths of the present study. The *CYP1A2*1C* polymorphism is relatively common in Japanese, and it is difficult to address the effect of this polymorphism in Caucasians. Allele frequencies of *CYP1A2*1C* and *CYP1A2*1F* observed in the

present study were similar to those reported for Japanese elsewhere. In a study of 159 healthy Japanese [21], the frequencies of *CYP1A2*1C* and *CYP1A2*1F* were 21% and 61%, respectively. Another Japanese study reported that the corresponding frequencies were 25% and 67%, respectively [29]. A limitation was that the number of cases with type 2 diabetes was rather small, and the statistical power may have been low for type 2 diabetes. Thus the present observation needs to be replicated in different studies. Another weakness was that decaffeinated coffee was not distinguished from caffeinated coffee. However, decaffeinated coffee is not commonly consumed in Japan. We considered only the known functional *CYP1A2* polymorphisms. Although CYP1A2 is a primary enzyme in caffeine metabolism, other enzymes such as CYP2A6 and NAT2 are also involved in the metabolism [5].

In conclusion, the *CYP1A2*1C* polymorphism modified the association between coffee consumption and type 2 diabetes, especially among current smokers, suggesting that caffeine may not be negligible in the association between coffee and type 2 diabetes.

Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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