European Journal of Clinical Nutrition (2008) 62, 178–185
 0954-3007/08 $30.00
www.nature.com/ejcn

ORIGINAL ARTICLE

Coffee consumption, serum γ-glutamyltransferase and risk of type II diabetes

S Bidel[1,2], K Silventoinen[2], G Hu[1,2], D-H Lee[3], J Kaprio[2,4] and J Tuomilehto[1,2,5]

[1]*Department of Health Promotion and Chronic Disease Prevention, National Public Health Institute, Helsinki, Finland;* [2]*Department of Public Health, University of Helsinki, Helsinki, Finland;* [3]*Department of Preventive Medicine, School of Medicine, Kyungpook National University, Daegu, South Korea;* [4]*Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland and* [5]*South Ostrobothnia Central Hospital, Seinäjoki, Finland*

Objectives: To study the joint association of coffee consumption and serum γ-glutamyltransferase (GGT) levels on the risk of developing type II diabetes.
Design, setting and subjects: A total of 21 826 Finnish men and women who were 35–74 years of age and without any history of diabetes at baseline (years 1982, 1987, 1992 and 1997) were included in the present analyses. They were prospectively followed up for onset of type II diabetes ($n = 862$ cases), death or until the end of the year 2002. Coffee consumption, serum GGT and other study parameters were determined at baseline using standardized measurements. Analyses were stratified by the serum GGT level classified into two classes using the 75th sex-specific percentiles as the cut point.
Results: Coffee consumption was significantly and inversely associated with incident diabetes among both men and women. Serum GGT modified the association between coffee consumption and incident diabetes. Subjects in the high category of coffee consumption with the GGT level $\geqslant$75th percentile showed a significant inverse association for women, and for both sexes combined. The association was not significant in subjects with the GGT level $\leqslant$75th percentile. There was a significant interaction effect of GGT and coffee consumption on risk of type II diabetes in data of women ($P = 0.05$) and in both sexes combined ($P = 0.02$).
Conclusions: Habitual coffee consumption is associated with lower incidence of type II diabetes particularly in those with higher baseline serum GGT levels.
European Journal of Clinical Nutrition (2008) **62,** 178–185; doi:10.1038/sj.ejcn.1602712; published online 7 March 2007

Keywords: type II diabetes; coffee; γ-glutamyltransferase; oxidative stress; glutathione

Introduction

GGT is a plasma membrane enzyme, which may be raised with age (Schiele *et al*., 1977), obesity (Arnesen *et al*., 1986; Robinson and Whitehead, 1989; Nilssen *et al*., 1990; Wannamethee *et al*., 1995) and also diabetes (Barbieux *et al*., 1990). A raised serum GGT concentration has also been linked with cardiovascular risk factors, including hypertension, dyslipidemia and physical inactivity (Arnesen *et al*., 1986; Robinson and Whitehead, 1989; Nilssen *et al*., 1990). There is a strong association between the serum concentration of GGT and the risk for development of impaired fasting glucose or type II diabetes (Perry *et al*., 1998) and recent results have suggested that GGT may be used as a risk indicator for developing metabolic syndrome and type II diabetes (Nakanishi *et al*., 2004). In addition, age and obesity, two well-known risk factors in type II diabetes, have stronger association with diabetes in subjects with higher GGT levels (Lee *et al*., 2003a, b). The strong association between GGT and incident diabetes has been observed also in nonalcohol drinkers and individuals without increased concentrations of any other liver enzymes. Therefore, this

Correspondence: Dr S Bidel, Diabetes Unit, Department of Health Promotion and Chronic Disease Prevention, National Public Health Institute, Mannerheimintie 166, FIN-00300 Helsinki, Finland.
E-mail: siamak.bidel@ktl.fi
Guarantor: S Bidel.
Contributors: All contributors have made substantial contributions to the intellectual content of the paper. SB was primarily responsible for the conception and design analysis and interpretation of data and drafting of the manuscript. KS contributed in statistical analysis. KS, GH, DHL, JK and JT contributed in analysis and interpretation of data, and critical revision of the manuscript for important intellectual content.
Received 6 October 2006; revised 9 January 2007; accepted 24 January 2007; published online 7 March 2007

association would not to be explained by alcohol or any hepatic dysfunctions (Lee *et al*., 2003b), even though high GGT can be a marker of excessive alcohol drinking (Skinner *et al*., 1984; Shaper *et al*., 1985).

Several recent cohort studies (Van Dam and Feskens, 2002; Carlsson *et al*., 2004; Rosengren *et al*., 2004; Salazar-Martinez *et al*., 2004; Tuomilehto *et al*., 2004; Hu *et al*., 2006) and systematic reviews (van Dam and Hu, 2005; Greenberg *et al*, 2006) have been shown that long-term consumption of coffee may lower the risk of type II diabetes. The mechanism of the association has not been clarified yet, but several plausible mechanisms have been suggested (Tuomilehto *et al*., 2004). In the present study, we analyzed whether protective effects of coffee drinking on the risk of developing type II diabetes were affected by the baseline GGT concentration.

Subjects and methods

Baseline risk factor surveys were carried out in Kuopio and North Karelia provinces in eastern and in Turku-Loimaa area in southwestern Finland in 1982, 1987, 1992 and 1997. The Helsinki capital area was included in the survey in 1992 and 1997 and Oulu province in northern Finland in 1997 (Vartiainen *et al*., 2000). According to the international WHO MONICA (MONItoring trends and determinants in CArdiovascular disease) project protocol (Pajak *et al*., 1988), in each study year the sample was randomly drawn from the population aged 25–64 years and was stratified so that in each area at least 250 subjects were chosen from both sex and each 10-year age group. In 1997, an additional sample of subjects aged 65–74 years was conducted. In this study, we limited the analyses to participants aged 35–74 years. The surveys were independent, that is, the study subjects were randomly chosen from the population for each survey. Participants who belonged to more than one survey were included only into the first survey. The study was conducted according to the national data protection legislation, ethical rules of the Finnish National Public Health Institute, and the rules and principles of the Helsinki Declaration. The participation rates in the pooled data set were 75% in men and 82% in women. Of the 23 342 participants, 1247 were excluded from the analyses because of prevalent diabetes at baseline identified retrospectively from the National Social Insurance Institution's Drug Register that includes subjects receiving reimbursement for their diabetes medication, from the National Hospital Discharge Register and by a survey question about diabetes diagnosed by a physician. Another 247 participants were excluded because of missing data on GGT or coffee consumption. Additionally, we excluded 21 persons who had developed type I diabetes during the follow-up period; the diagnoses of the type of diabetes were based on the Finnish National Hospital Discharge register that provides separate diagnostic codes for type I and type II diabetes. A total of 10 666 men and 11 160 women were included in the present analyses. Coffee and alcohol consumption, smoking status and physical activity at baseline were assessed with a set of standardized questions in a self-administered questionnaire mailed to the participants in advance. Coffee consumption was asked as a number of cups of coffee per day on average, and it was classified as 0–2, 3–4, 5–6 and seven cups or more per day (Tuomilehto *et al*., 2004; Hu *et al*., 2006). We had information on type of coffee in the surveys in 1987, 1992 and 1997 and 82% of consumed coffee in these surveys was filtered coffee. Smoking status was classified as regular current smokers and former or never smokers. Alcohol consumption was assessed on the basis of the self-reported number of drinks consumed during the previous week. Alcohol consumption was classified as 0, 1–69, 70–139, 140–209, and 210 g or more in men and 0, 1–34, 35–69 and 70 g or more in women. The cut points were derived from the alcohol consumption distribution in these data and the lower cut points for women were used since the average alcohol consumption in Finland is much lower in middle-aged women than in men. Physical activity was estimated by asking whether the participant practiced leisure time physical activity at least 20–30 min two times or more per week (Hu *et al*., 2003, 2004).

At the survey site, specially trained research nurses measured height and weight in light clothing and without shoes by using the standardized WHO MONICA protocol. Body mass index (BMI, kg/m^2) was used as a measure of relative body weight as a continuous variable. GGT was determined from fresh venous blood serum samples using a kinetic method (Oy Medix Biochemica AB, Kauniainen, Finland) on the basis of recommendation of European Committee for Clinical Laboratory Standards in the same central laboratory located at the Finnish National Public Health Institute in Helsinki.

Data on the occurrence of new type II diabetes cases during the follow-up period until 31 December 2002 were obtained from the National Hospital Discharge Register and National Social Insurance Institution's register on persons entitled to special reimbursement for diabetes medication. To receive the special reimbursement, the diagnosis of diabetes is assigned by the person's own physician, usually general practitioner, internist or specialist in occupational medicine. The statements documenting the diagnosis have then been reviewed according to current criteria by expert physicians of the National Social Insurance Institution. Thus, the register data include the drug-treated diabetic, but not those who are on diet only. Under the Finnish law, all persons with type I or type II diabetes are eligible for the reimbursement, and thus this registry probably includes virtually all new cases that need medication for type II diabetes. Nevertheless, it is well known that the majority of type II diabetic patients sooner or later will require pharmacotherapy, and thus, it is likely that the date of ascertainment of diabetes is delayed in our cohort. The National Hospital Discharge Register includes in-hospital admissions of patients to hospitals with a primary or

secondary diagnosis of diabetes in Finland nationwide. The number of incident type II diabetes cases during the follow-up was 483 among men and 379 among women.

All analyses were performed separately in men and women and in both sexes together after adjusting for sex. Analyses were stratified by the serum GGT level classified into two classes using the 75th sex-specific percentiles as the cut points (40 U/l in men, 21 U/l in women). Follow-up time (in days) was calculated from the baseline examination to the registration date of type II diabetes diagnosis (cases), death (censored subjects) or 31 December 2002 (non-cases). Deaths were identified from the National Death Register maintained by Statistics Finland. Cox proportional hazard models were used to calculate multivariate-adjusted hazard ratios (HR) and the analyses were carried out by the PHREG procedure of the SAS statistical package (SAS institute, 2003). The assumption of Cox-model was tested using Schoenfeld residuals by the Stata statistical (package) (STATA press, 2001) and found not to be violated. Statistical significance for trends was computed using Wald's test. Age, BMI, alcohol consumption, smoking status and physical activity at baseline were used as covariates. Because the risk of type II diabetes differed between men and women, the STRATA option was used for sex in the pooled analyses in men and women together. Using the STRATA option, the model allows different baseline hazards for men and women and computes the overall hazard ratios from these stratified hazard ratios. Thus, the model does not expect the hazard ratios to be proportional in the whole data but only in each stratum.

Results

Table 1 presents the baseline characteristics of the participants. In general, older persons were less likely to drink coffee. GGT levels were inversely correlated with the amount of coffee consumption. Smoking rates increased as coffee consumption increased. People with sedentary lifestyle drank more coffee than people who practiced regular leisure-time physical activity.

Table 2 describes the association between coffee drinking and incidence of type II diabetes. After adjustment for age, BMI, alcohol consumption, smoking and physical activity, there was a significant inverse association among both men and women (P for trend $= 0.02$ for men and < 0.0001 for women). Additional adjustment for GGT did not change the association (P for trend $= 0.05$ for men and < 0.0001 for women). As the interaction of sex and coffee drinking, and that of sex and GGT on the risk of type II diabetes were not

Table 1 Baseline characteristics of participants by volume of coffee consumption

	Daily coffee consumption, cups			
	0–2	*3–4*	*5–6*	*⩾7*
Men				
No. of subjects, (%)	1994 (19)	2811 (26)	3275 (31)	2586 (24)
Age, mean (s.d.), years	52	52	50	48
GGT (U/l, mean)	46	39	33	31
BMI, mean (s.d.)	27	27	27	27
Alcohol consumption, No. (%)				
0 g	18	24	31	27
1–69 g	19	28	32	21
70–139 g	18	27	30	25
140–209 g	19	28	31	21
>210 g	24	29	24	23
Physical activity at least twice per week (%)	21	28	30	21
Current smoking, no. (%)	14	20	29	47
Women				
No. of subjects, (%)	2205 (20)	3849 (34)	3481 (31)	1625 (15)
Age, mean (s..d), years	51	51	50	47
GGT (U/l, mean)	26	20	18	17
BMI, mean (s.d.)	26	27	27	27
Alcohol consumption, No. (%)				
0 g	19	33	32	15
1–34 g	21	36	28	15
35–69 g	20	36	28	15
>70 g	12	10	9	9
Physical activity at least twice per week (%)	48	50	45	40
Current smoking, no. (%)	10	25	35	30

Abbreviation: BMI, body mass index.

Table 2 Relationship between coffee consumption and incident diabetes

	Coffee intake (frequency/day)				P-*value*
	0–2	*3–4*	*5–6*	*⩾7*	
Men					
No. of cases/pop.	87/1994	117/2811	164/3274	115/2586	
Person-years	22105	32919	40353	33190	
Incidence rate/1000 Person-years	3.94	3.55	4.06	3.46	
Age-adjusted RR	1.00	0.89 (0.67–1.17)	1.01 (0.78–1.13)	0.91 (0.69–1.21)	0.86
Multivariate[a] RR	1.00	0.89 (0.68–1.18)	0.87 (0.67–1.13)	0.71 (0.53–0.94)	0.02
Multivariate[b] RR	1.00	0.93 (0.7–1.22)	0.91 (0.69–1.18)	0.74 (0.55–0.99)	0.05
Women					
No. of cases/pop.	83/2206	131/3849	122/3481	43/1625	
Person-years	25860	48028	47612	23022	
Incidence rate/1000 Person-years	3.21	2.73	2.56	1.87	
Age-adjusted RR	1.00	0.80 (0.61–1.05)	0.76 (0.57–1.0)	0.64 (0.44–0.92)	0.02
Multivariate[a] RR	1.00	0.75 (0.57–0.98)	0.63 (0.47–0.83)	0.47 (0.33–0.69)	<0.0001
Multivariate[b] RR	1.00	0.78 (0.59–1.03)	0.66 (0.49–0.87)	0.50 (0.34–0.72)	<0.0001
Men and women[c]					
No. of cases/pop.	170/4200	248/6660	286/6756	158/4211	
Person-years	47966	80947	87965	56212	
Incidence rate/1000 Person-years	3.54	3.06	3.25	2.81	
Age-adjusted RR	1.00	0.85 (0.70–1.04)	0.89 (0.73–1.07)	0.80 (0.64–0.99)	0.10
Multivariate[a] RR	1.00	0.83 (0.68–1.0)	0.75 (0.62–0.91)	0.61 (0.49–0.76)	<0.0001
Multivariate[b] RR	1.00	0.85 (0.70–1.04)	0.78 (0.65–0.95)	0.64 (0.51–0.80)	<0.0001

[a]Adjusted for age, BMI, alcohol consumption, smoking and physical activity.
[b]Additional adjustment for GGT.
[c]All analyses additionally adjusted for sex.

statistically significant, the data for men and women were pooled together. Sex- and multivariate-adjusted HRs of incident type II diabetes by coffee consumption decreased linearly with increasing amount of coffee, being 0.64 for people drinking seven cups or more per day compared with those drinking 0–2 cups of coffee.

Table 3 shows the association between coffee consumption and incident type II diabetes stratified by the baseline GGT level. We also measured the interaction between coffee, GGT and sex on the risk of type II diabetes. There was no association between coffee consumption and the incidence of type II diabetes among men with low GGT levels but at the high GGT level an inverse tendency appeared; however, *P*-value for the trend failed to reach the level of significance (P for trend $= 0.75$, P for interaction $= 0.18$). Among women with a low GGT level, a nonsignificant inverse trend between coffee consumption and incident diabetes was detected (P for trend $= 0.20$). At high GGT level, there was a strong inverse association (P for trend $= 0.002$) and multivariate adjusted HRs of diabetes in women who drank 0–2, 3–4, 5–6, $\geqslant 7$ cups of coffee were 1.00, 0.75, 0.59, 0.44 (P of interaction $= 0.002$). When data for men and women were combined, in the highest quartile of GGT level sex-adjusted and multivariate-adjusted HRs for type II diabetes were 1.00, 0.77, 0.70, 0.65 (P for trend $= 0.001$), respectively, but no association between coffee and risk for type II diabetes was found in pooled data at lower levels of GGT ($\leqslant$75th percentile) (P for trend $= 0.95$).

Discussion

In this study, we found that coffee consumption was inversely and significantly associated with type II diabetes as has been reported in our earlier study (Tuomilehto *et al*., 2004). However, the present study had a larger sample size and longer follow-up period and thus adds to the previous findings. We also found that the results were influenced by baseline GGT levels. At high GGT levels ($\geqslant$75% percentile), coffee drinking was inversely associated with type II diabetes in women and both sexes combined, but this association was nonsignificant in men.

The strong association between the serum concentration of GGT and the risk for the development of impaired fasting glucose or type II diabetes has already been documented (Perry *et al*., 1998). Recent prospective studies showed that the risk of the metabolic syndrome and type II diabetes increases with increasing serum GGT level (Perry *et al*., 1998; Lee *et al*., 2003a, b; Nakanishi *et al*., 2004, 2003) and GGT has been suggested as an important risk indicator for developing type II diabetes. Despite apparent relation between the GGT level and alcohol intake (Skinner *et al*., 1984; Shaper *et al*., 1985), the association between GGT concentration and type II diabetes has been found to be independent of alcohol intake (Lee *et al*., 2003a, b). Also among subjects with high normal GGT levels, BMI and age are strong risk factors for incident type II diabetes (Lee *et al*., 2003a, b). A previous study based on the almost same study population as our

Table 3 Relationship between coffee consumption and incident diabetes stratified by baseline γ-glutamyltransferase level

	Coffee intake (frequency/day)				P *for trend*
	0–2	*3–4*	*5–6*	*> = 7*	
Men		(*P* of interaction = 0.18)			
GGT < 75th percentile (40 U/l)					
No. of cases	38/1335	64/2032	110/2519	73/2049	
Person-years	16019	24992	32838	27181	
Incidence rate/1000 Person-years	2.37	2.56	3.35	2.68	
Age-adjusted RR	1.00	1.06 (0.71–1.58)	1.36 (0.94–1.97)	1.18 (0.80–1.75)	0.22
Multivariate[a] RR	1.00	1.06 (0.71–1.59)	1.14 (0.79–1.66)	0.94 (0.63–1.40)	0.75
GGT > = 75th percentile (40 U/l)					
No. of cases	49/659	53/779	54/756	42/537	
Person-years	6087	7927	7515	6009	
Incidence rate/1000 Person-years	8.05	6.69	7.18	6.99	
Age-adjusted RR	1.00	0.82 (0.56–1.21)	0.93 (0.63–1.37)	0.92 (0.61–1.41)	0.89
Multivariate[a] R	1.00	0.85 (0.58–1.26)	0.81 (0.55–1.20)	0.68 (0.44–1.05)	0.08
Women		(*P* of interaction = 0.05)			
GGT < 75th percentile (21 U/l)					
No. of cases	33/1452	59/2710	76/2710	30/1322	
Person-years	18390	36692	39428	19615	
Incidence rate/1000 Person-years	1.79	1.61	1.93	1.53	
Age-adjusted RR	1.00	0.82 (0.53–1.25)	0.95 (0.63–1.43)	0.85 (0.52–1.40)	0.85
Multivariate[a] RR	1.00	0.84 (0.55–1.30)	0.86 (0.57–1.30)	0.68 (0.41–1.13)	0.20
GGT ⩾ 75th percentile (21 U/l)					
No. of cases	50/754	72/1139	46/771	13/303	
Person-years	7471	11336	8184	3407	
Incidence rate/1000					
Person-years	6.69	6.35	5.62	3.82	
Age-adjusted RR	1.00	0.92 (0.64–1.31)	0.85 (0.57–1.27)	0.67 (0.36–1.24)	0.19
Multivariate[a] RR	1.00	0.75 (0.52–1.09)	0.59 (0.39–0.88)	0.44 (0.24–0.82)	0.002
Men and women[b]			(*P* of interaction = 0.02)		
GGT < 75th percentile					
No. of cases	71/2787	123/4742	186/5229	103/3371	
Person-years	34409	61684	72266	46796	
Incidence rate/1000					
Person-years	2.06	1.99	2.57	2.20	
Age-adjusted RR	1.00	0.95 (0.71–1.27)	1.17 (0.89–1.54)	1.04 (0.77–1.41)	0.38
Multivariate[a] RR	1.00	0.96 (0.71–1.28)	1.01 (0.76–1.33)	0.82 (0.60–1.12)	0.95
GGT ⩾ 75th percentile					
No. of cases	99/1413	125/1918	100/1527	55/840	
Person-years	13557	19263	15699	9417	
Incidence rate/1000					
Person-years	7.30	6.49	6.37	5.84	0.51
Age-adjusted RR	1.00	0.88 (0.68–1.14)	0.89 (0.68–1.18)	0.85 (0.61–1.19	
Multivariate[a] RR	1.00	0.77 (0.59–1.01)	0.70 (0.53–0.93)	0.65 (0.46–0.91)	0.001

[a]Adjusted for age, BMI, alcohol consumption, smoking and physical activity.
[b]All analyses additionally adjusted for sex.

present study revealed that a higher serum GGT concentration within normal ranges was directly associated with the increased risk of type II diabetes (Lee *et al*., 2004c), but present analysis have now indicated that the risk of type II diabetes among people with high normal serum GGT levels is not necessarily increased, but actually decreased among habitual coffee consumers.

On the other hand, the relation between coffee consumption and GGT concentration, which has been studied before (Nilssen *et al*., 1990; Casiglia *et al*., 1993; Kono *et al*., 1994),

revealed an inverse association between coffee consumption and GGT level. The effects of regular daily coffee consumption on liver enzymes were studied in a large number of subjects from the general population by Casiglia *et al*. (1993). They found that in coffee drinkers, GGT and other liver enzymes (alkaline-amino transferase, and alkaline phosphatase) were lower than in non-coffee-drinking subjects or in those consuming less than three cups daily. In addition, a study by Esposito *et al*. (2003) revealed that moderate coffee consumption significantly increased the plasma glutathione (GSH) level among healthy subjects. It is well known that with increasing GSH levels, GGT concentration decreases consequently (Zhang *et al*. 2005).

Better knowledge of GGT and its important physiologic role in pathological conditions is necessary to explain our finding in present study. It is known that GGT is a plasma membrane enzyme which facilitates the transport of extracellular GSH into most type of cells and GSH is the major intracellular non-protein thiol defence against free radicals (oxidative stress) (Kugelman *et al*., 1994; Karp *et al*., 2001). In any condition, accumulation of free radicals, which means elevated oxidative stress, leads to rise in the GGT level in order to modify the existing oxidative stress by reproducing GSH. The γ-glutamyl cycle involving GGT is the major pathway by which cells utilize extracellular GSH for the *de novo* synthesis of intracellular GSH (Griffith *et al*., 1978) so this is the main way that membrane GGT is protecting cells from oxidative stress (Karp *et al*., 2001). The elevation of GGT could be expression of excess deposition of fat in liver (hepatic steatosis), and/or may reflect inflammation (Marchesini *et al*., 2001; Hotalamsligil, 2003; Malnick *et al*., 2003), both expressing the presence of oxidative stress and it plays a major role in pathological conditions such as inflammation, malignant diseases, aging, cardiovascular disease (Droge, 2002), and also in pathophysiology of diabetes (West, 2000; Haluzik and Nedvidkova, 2000; Rosen *et al*., 2001). A decrease in antioxidant capacity has been observed in the plasma of diabetic patients (Jones *et al*., 1988; Maxwell *et al*., 1997; Haluzik and Nedvidkova, 2000; Rosen *et al*., 2001), and evidence from numbers of experimental studies revealed that the formation of free radicals and presence of oxidative stress is a direct consequence of hyperglycemia (Diedrich *et al*., 1994; Graier *et al*., 1996; Ceriello *et al* 1999). So, we know that coffee contains many compounds, which may have potential to influence glucose metabolism process to prevent hyperglycemia and oxidative stress consequently. For instance, chlorogenic acid inhibits glucose transporters (Na^+-dependent glucose transporter) (Kobayashi *et al*., 2000). Chlorogenic acid also reduces or inhibits glucose-6-phosphatase (Glc-6-phase) hydrolysis, which may reduce plasma glucose output from the liver, leading to reduced plasma glucose concentration (Newgard *et al*., 1984; Arion *et al*., 1997). In addition, coffee may also influence the secretion of gastrointestinal peptides such as glucagon-like peptide-1 and gastric inhibitory polypeptide; both of them are known for their glucose-lowering effects (Nauck *et al*., 1993; Meier *et al*., 2001). Recently, published results in diverse countries revealed that higher coffee consumption was consistently associated with a lower prevalence of hyperglycemia and in particular, coffee consumption seems to lower post-prandial hyperglycemia (Agardh *et al*., 2004; Van Dam *et al*., 2004; Yamaji *et al*, 2004; Bidel *et al*., 2006). Although acute administration of caffeine may reduce insulin sensitivity (Keijzers *et al*., 2002), we have found nonetheless lower fasting insulin values and a lower prevalence of hyperinsulinemia among coffee consumers with long-term exposure. This may be interpreted as an improvement in insulin sensitivity by coffee consumption to prevent hyperglycemia and oxidative stress consequently (Bidel *et al*., 2006).

Finally, increased GGT levels for any reason is related to excess oxidative stress and excessive oxidative stress may play a role in initiating developing type II diabetes; thus, increasing frequency of the disease in people with high GGT levels may be expected as reported earlier (Lee *et al*., 2003a). However, in this study we found fewer cases of incident diabetes among habitual coffee consumers with high normal GGT levels, which indicate stronger protective effects of coffee in these levels. It may be interpreted that antioxidant capacity of coffee may be more activated at the particular oxidative stress level which it would be helpful to prevent diabetes in subjects who are more susceptible to develop diabetes. In consistence is the recent study by Ruhl and Everhart (2005) who investigated the association of coffee and tea consumption on chronic liver disease. They found lower risk associated with higher levels of coffee and/or tea consumption only in persons at higher risk for liver disease from heavier alcohol intake, overweight, diabetes or high iron saturation. These findings suggest hypotheses for future research.

Reliance on self-report for data on coffee drinking may be one of the limitation of this study. However, any possible misclassification of the exposure is unlikely to be systematically related to the outcome; thus, it should not cause biased results but may only weaken the true association. Secondly, an under-ascertainment of cases of incident type II diabetes is another limitation of this study, because we may have missed some cases of asymptomatic and diet-treated diabetes, although the clinical diagnosis of diabetes from the hospital discharge register may in part avoid this potential under diagnosis. On the other hand, type II diabetes is a progressive disease, and most of the cases sooner or later require pharmacologic treatment. Thus, rather than having underestimated the absolute number of diabetic cases in this cohort, we might have had a delayed date of diagnosis for some cases. Finally, we cannot completely exclude either the effects of residual confounding owing to measurement error in the assessment of confounding factors, or some unmeasured factors including coffee additives (sugar and/or milk) and several dietary factors (such as intake of whole grain, intake of fiber, magnesium, calcium, sodium, saturated and polyunsaturated fat, glycaemic load of the diet and total energy intake) (Steyn *et al*., 2004; Hu *et al*., 2005).

In conclusion, this study revealed that the inverse association between coffee consumption and incident type II diabetes is modified by serum GGT levels. The mechanism of this association has not been clarified, yet. Nevertheless, the antioxidant activity of coffee by interfering in glucose metabolism process is the most probable mode of action, as a high GGT level can be taken as a marker of oxidative stress.

Acknowledgements

This study was supported by grants from Juho Vainio foundation and the Academy of Finland (46558, 204274, 108297 and 205657). JK is supported by the Academy of Finland Center of Excellence in Complex Disease Genetics.

References

Agardh EE, Carlsson S, Ahlbom A, Efendic S, Grill V, Hammar N *et al.* (2004). Coffee consumption, type 2 diabetes and impaired glucose tolerance in Swedish men and women. *J Intern Med* **255**, 645–652.

Arion WJ, Canfield WK, Ramos FC, Schindler PW, Burger HJ, Hemmerle H *et al.* (1997). Chlorogenic acid and hydroxynitrobenzaldehyde: new inhibitors of hepatic glucose 6-phosphatase. *Arch Biochem Biophys* **339**, 315–322.

Arnesen E, Huseby NE, Brenn T, Try K (1986). The Tromsø Heart Study: distribution of, and determinants for, gamma-glutamyltransferase in a free living population. *Scand J Clin Lab Invest* **46**, 63–70.

Barbieux JP, Bacq Y, Schellenberg F, Weill J, Constans T, Lamisse F (1990). Increase of serum gamma-glutamyltransferase activity in diabetic patients is not linked to diabetes itself. *Pathol Biol* **138**, 93–98.

Bidel S, Hu G, Sundvall J, Kaprio J, Tuomilehto J (2006). Effects of coffee consumption on glucose tolerance and serum glucose and insulin levels-A cross sectional analysis. *Horm Metab Res* **38**, 38–43.

Carlsson S, Hammar N, Grill V, Kaprio J (2004). Coffee consumption and risk of type 2 diabetes in Finnish twins. *Int J Epidemiol* **3**, 616–617.

Casiglia E, Spolaore P, Ginocchio G, Ambrosio GB (1993). Unexpected effects of coffee consumption on liver enzymes. *Eur J Epidemiol* **9**, 293–297.

Ceriello A, Bortolotti N, Motz E, Pieri C, Marra M, Tonutti L *et al.* (1999). Meal-induced oxidative stress and low-density lipoprotein oxidation in diabetes: the possible role of hyperglycemia. *Metabolism* **48**, 1503–1508.

Diedrich D, Skopec J, Diedrich A, Dai FX (1994). Endothelial dysfunction in mesenteric resistance arteries of diabetic rats: role of free radicals. *Am J Physiol* **266**, H1153–H1161.

Droge W (2002). Free radicals in the physiological control of cell function. *Physiol Rev* **82**, 47–95.

Esposito F, Morisco F, Verde V, Ritieni A, Alezio A, Caporaso N *et al.* (2003). Moderate coffee consumption increases plasma glutathione but not homocysteine in healthy subjects. *Aliment Pharmacol Ther* **17**, 595–601.

Graier WF, Simecek S, Kukovetz WR, Kostner GM (1996). High glucose-induced changes in endothelial Ca2+/EDRF signaling are due to generation of superoxide anions. *Diabetes* **45**, 1386–1395.

Greenberg JA, Boozer CN, Geliebter A (2006). Coffee, diabetes, and weight control. *Am J Clin Nutr* **84**, 682–693.

Griffith OW, Bridges RJ, Meister A (1978). Evidence that the γ-glutamyl cycle functions *in vivo* using intracellular glutathione: effects of amino acids and selective inhibition of enzymes. *Proc Natl Acad Sci USA* **75**, 5405–5408.

Haluzik M, Nedvidkova J (2000). The role of nitric oxide in the development of streptozotocin-induced diabetes mellitus: experimental and clinical implications. *Physiol Res* **49** (Suppl 1), S37–S42.

Hotalamsligil GS (2003). Inflammatory pathways and insulin action. *Int J Obes Relat Metab Disord* **27** (Suppl 3), S53–S55.

Hu G, Jousilahti P, Peltonen M, Bidel S, Tuomilehto J (2006). Joint association of coffee consumption and other factors to the risk of type 2 diabetes: a prospective study in Finland. *Int J Obes Relat Metab Disord (London)* **30**, 1742–1749.

Hu G, Jousilahti P, Peltonen M, Lindstrom J, Tuomilehto J (2005). Urinary sodium and potassium excretion and the risk of type 2 diabetes: a prospective study in Finland. *Diabetologia* **48**, 1477–1483.

Hu G, Lindstrom J, Valle TT, Eriksson JG, Jousilahti P, Silventoinen K *et al.* (2004). Physical activity, body mass index, and risk of type 2 diabetes in patients with normal or impaired glucose regulation. *Arch Intern Med* **164**, 892–896.

Hu G, Qiao Q, Silventoinen K, Eriksson JG, Jousilahti P, Lindstrom J *et al.* (2003). Occupational, commuting, and leisure-time physical activity in relation to risk for type 2 diabetes in middle-aged Finnish men and women. *Diabetologia* **46**, 322–329.

Jones AF, Winkles JW, Jennings PE (1988). Serum antioxidant activity in diabetes mellitus. *Diabetes Res* **7**, 89–92.

Karp DR, Shimooku K, Lipsky PE (2001). Expression of gamma-glutamyl transpeptidase protects ramos B cells from oxidation-induced cell death. *J Biol Chem* **276**, 3798–3804.

Keijzers GB, De Galan BE, Tack CJ, Smiths P (2002). Caffeine can decrease insulin sensitivity in humans. *Diabetes Care* **25**, 364–369.

Kobayashi Y, Suzuki M, Satsu H, Arai S, Hara Y, Suzuki K *et al.* (2000). Green tea polyphenols inhibit the sodium-dependent glucose transporter of intestinal epithelial cells by a competitive mechanism. *J Agric Food Chem* **48**, 5618–5623.

Kono S, Shinchi K, Imanishi K, Todoroki I, Hatsuse K (1994). Coffee and serum gamma-glutamyltransferase: a study of self-defense officials in Japan. *Am J Epidemiol* **139**, 723–727.

Kugelman A, Choy HA, Liu R, Shi MM, Gozal E, Forman HJ (1994). Gamma-glutamyl teranspeptidase is increased by oxidative stress in rat alveolar L2 epithelial cells. *Am J Respir Cell Mol Biol* **11**, 5865–5892.

Lee DH, Jacobs Jr DR, Gross M, Kiefe CI, Roseman J, Lewis CE *et al.* (2003a). Gamma-glutamyltransferase is a predictor of incident diabetes and hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Clin Chem* **49**, 1358–1366.

Lee DH, Ha MH, Kim JH, Christiani DC, Gross MD, Steffes M *et al.* (2003b). Gamma-glutamyltransferase and diabetes: a 4 year follow-up study. *Diabetologia* **46**, 359–364.

Lee DH, Silventoinen K, Jacobs Jr DR, Jousilahti P, Tuomilehto J (2004c). Gamma-glutamyltransferase, obesity, and the risk of type 2 diabetes: observational cohort study among 20158 middle-aged men and women. *J Clin Endocrinol Metab* **11**, 5410–5414.

Malnick SD, Beergabel M, Knobler H (2003). Nonalcoholic fatty liver: a common manifestation of a metabolic disorder. *Q J Med* **96**, 699–709.

Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M *et al.* (2001). Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. *Diabetes* **50**, 1844–1850.

Maxwell SRJ, Thomason H, Sandler D, Leguen C, Baxter MA, Thorpe GH *et al.* (1997). Antioxidant status in patients with uncomplicated insulin-dependent and non insulin-dependent diabetes mellitus. *Eur J Clin Invest* **27**, 484–490.

Meier JJ, Hucking K, Holst JJ, Deacon CF, Schmiegel WH, Nauck MA (2001). Reduced insulinotropic effect of gastric inhibitory polypeptide in first-degree relatives of patients with type 2 diabetes. *Diabetes* **50**, 2497–2504.

Nakanishi N, Suzuki K, Tatar K (2004). Serum γ-glutamyltransferase and risk of metabolic syndrome and type 2 diabetes in middle-aged Japanese men. *Diabetes Care* **27**, 1427–1432.

Nakanishi N, Nishina K, Li W, Sato M, Suzuki K, Tatara K (2003). Serum gamma-glutamyltransferase and development of impaired

fasting glucose or type 2 diabetes in middle-aged Japanese men. *J Intern Med* **254**, 287–295.
Nauck MA, Heimesaat MM, Orskov C, Holst JJ, Ebert R, Creutzfeldt W (1993). Preserved incretin activity of glucagon-like peptide 1 [7–36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. *J Clin Invest* **91**, 301–307.
Newgard CB, Foster DW, McGarry JD (1984). Evidence for suppression of hepatic glucose-6-phosphatase with carbohydrate feeding. *Diabetes* **33**, 192–195.
Nilssen O, Førde OH, Brenn T (1990). The Trömsø study: distribution and population determinants of gamma-glutamyltransferase. *Am J Epidemiol* **132**, 318–326.
Nilssen O, Førde OH (1990). Seven-year longitudinal population study of change in gamma-glutamyltransferase: the Troms0 Study. *Am J Epidemiol* **139**, 787–792.
Pajak A, Kuulasmaa K, Tuomilehto J, Ruokokoski E (1988). The WHO MONICA Project. Geographical variation in the major risk factors of coronary heart disease in men and women aged 25–64 years. *World Health Stat Q* **41**, 115–140.
Perry IJ, Wannamethee SG, Sharper AG (1998). Prospective study of serum γ-glutamyltransferase and risk of NIDDM. *Diabetes Care* **21**, 732–737.
Robinson D, Whitehead TP (1989). Effect of body mass and other factors on serum liver enzyme in men attending for well population screening. *Ann Clin Biochem* **26**, 393–400.
Rosen P, Nawroth PP, King G, Moller W, Tritschler HJ, Packer L (2001). The role of oxidative stress in the onset and progression of diabetes and its complications: a summary of a Congress Series sponsored by UNESCO-MCBN, the American Diabetes Association and the German Diabetes Society. *Diabetes Metab Res Rev* **17**, 189–212.
Rosengren A, Dotevall A, Wilhelmsen L, Thelle D, Johansson S (2004). Coffee and incidence of diabetes in Swedish women: a prospective 18-year follow-up study. *J Intern Med* **255**, 89–95.
Ruhl CE, Everhart JE (2005). Coffee and tea consumption are associated with a lower incidence of chronic liver disease in the United States. *Gastroenterology* **129**, 1928–1936.
Salazar-Martinez E, Willett WC, Ascherio A, Leitzmann M, Manson JE, Stampfer MJ *et al*. (2004). Coffee consumption and risk for Type 2 diabetes. *Ann Intern Med* **140**, 1–8.
SAS Institute (2003). *SAS Online Doc* Retrieved from Version Eight SAS Institute, Inc.: Cary, NC, USA http://v8doc.sas.com/sashtml/.
Schiele F, Guilmin AM, Detienne H, Siest G (1977). Gamma-Glutamyletransferase activity in plasma: statistical distributions, individual variations, and reference intervals. *Clin Chem* **23**, 1023–1028.
Shaper AG, Pocock SJ, Ashby D, Walker M, Whitehead TP (1985). Biochemical and haematological response to alcohol intake. *Ann Clin Biochem* **22**, 50–61.
Skinner HA, Holt S, Schuller R, Roy J, Israel Y (1984). Identification of alcohol abuse using laboratory tests and a history of trauma. *Ann Intern Med* **101**, 847–851.
STATA Press (2001). *STATA User's Guide Release*. Stata Press: College Station, TE.
Steyn NP, Mann J, Bennett PH, Temple N, Zimmet P, Tuomilehto J, Lindstrom J, Louheranta A (2004). Diet, nutrition and the prevention of type 2 diabetes. *Public Health Nutr* **7**, 147–165.
Tuomilehto J, Hu G, Bidel S, Lindstrom J, Jousilahti P (2004). Coffee consumption and risk of type 2 diabetes mellitus among middle-aged Finnish men and women. *JAMA* **291**, 1213–1219.
Van Dam RM, Feskens EJ (2002). Coffee consumption and risk of type 2 diabetes mellitus. *Lancet* **360**, 1477–1478.
Van Dam RM, Hu FB (2005). Coffee consumption and risk of type 2 diabetes: a systematic review. *JAMA* **294**, 97–104.
Van Dam RM, Dekker JM, Nijpels G, Stehouwer CD, Bouter LM, Heine RJ (2004). Coffee consumption and incidence of impaired fasting glucose, impaired glucose, and type 2 diabetes: the Hoorn Study. *Diabetologia* **47**, 2152–2159.
Vartiainen E, Jousilahti P, Alfthan G, Sundvall J, Pietinen P, Puska P (2000). Cardiovascular risk factor changes in Finland, 1972–1997. *Int J Epidemiol* **29**, 49–56.
Wannamethee G, Ebrahim S, Shaper AG (1995). Gamma-glutamyltransferase: determinants and associations with mortality from ischemic heart disease and all causes. *Am J Epidemiol* **142**, 699–708.
West IC (2000). Radicals and oxidative stress in diabetes. *Diabet Med* **17**, 171–180.
Yamaji T, Mizoue T, Tabata S, Ogawa S, Yamaguchi K, Shimizu E *et al*. (2004). Coffee consumption and glucose tolerance status in middle-aged Japanese men. *Diabetologia* **47**, 2145–2151.
Zhang H, Forman HJ, Choi J (2005). Gamma-glutamyl transpeptidase in glutathione biosynthesis. *Methods Enzymol* **401**, 468–483.