Alcohol Consumption in Relation to Metabolic Regulation, Inflammation, and Adiponectin in 64-Year-Old Caucasian Women

A population-based study with a focus on impaired glucose regulation

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OBJECTIVE — The aims of this study were to examine alcohol drinking patterns in women with type 2 diabetes, impaired glucose tolerance (IGT), and normal glucose tolerance (NGT) and to investigate whether alcohol intake was associated with improved insulin sensitivity, decreased biomarkers of inflammation, and increased adiponectin levels and if these effects were limited to dysmetabolic women.

RESEARCH DESIGN AND METHODS — From a cohort of 64-year-old Caucasian women, 209 with type 2 diabetes, 205 with IGT, and 186 with NGT were recruited. Alcohol consumption and medication use were assessed by questionnaires. Anthropometric data were collected, and blood glucose, insulin, HDL cholesterol, triglycerides, C-reactive protein, white blood cell count, and serum adiponectin were measured.

RESULTS — Compared with the NGT group, alcohol consumption was lower in the IGT group and lowest in the diabetes group. Mean alcohol intakes of >9.2 and ≥3–9 g/day were positively associated with adiponectin and insulin sensitivity (homeostasis model assessment [HOMA]), respectively, independently of obesity, metabolic control, and other confounders. Alcohol intake correlated negatively with inflammatory markers, although this did not remain after adjustment for HOMA and waist circumference. The inverse associations between alcohol consumption and factors related to the metabolic syndrome such as HOMA, waist circumference, and inflammatory markers were more obvious among women with diabetes and IGT than in healthy women.

CONCLUSIONS — In these women, moderate alcohol consumption showed beneficial associations with the prevalence of type 2 diabetes, IGT, insulin sensitivity, and serum adiponectin. There is a need to clarify whether adiponectin may be a mechanistic link and also to clarify the clinical implications of these observations.

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Although extensive alcohol use leads to increased morbidity, it is well established that moderate consumption is associated with a lower risk of coronary heart disease. Moderate intake of alcohol reduces overall mortality compared with abstaining and heavy drinking (1,2). This benefit may be only partly explained through favorable effects on lipids (3,4). Other potential mechanisms include changes in insulin sensitivity and inflammatory cytokines (4,5).

In prospective studies moderate and frequent alcohol intake seems to decrease the incidence of type 2 diabetes (6). Lowered insulin sensitivity is a key factor in the development of type 2 diabetes, and many studies have shown that moderate alcohol consumption is associated with improved insulin sensitivity (7,8). These associations have been both linear and U-shaped with different upper limits of alcohol intake (8). However, these findings are not totally consistent (9).

Inflammatory biomarkers, such as C-reactive protein (CRP), predict cardiovascular disease and diabetes (10,11). Subclinical inflammation is probably an important etiological factor for the metabolic syndrome, insulin resistance, and type 2 diabetes (11,12). However, the levels of inflammatory biomarkers are reduced by moderate alcohol consumption (5). Adiponectin, a plasma protein expressed in adipocytes, might link type 2 diabetes, insulin resistance, and inflammation. The protein has insulin-sensitizing and anti-inflammatory properties (13), and recent reports have shown that moderate alcohol intake was associated with high adiponectin concentrations in diabetic men and in nondiabetic subjects (14,15). Further, increased alcohol consumption raised adiponectin concentrations in an intervention study (16). There are no available data on the relationship between alcohol and adiponectin in diabetic women or in subjects with impaired glucose tolerance (IGT).

In this study we examined a population sample of 64-year-old women with normal glucose tolerance (NGT), IGT, or type 2 diabetes. The aims were to examine the alcohol drinking patterns in these women and to investigate whether alcohol intake was associated with improved insulin sensitivity, decreased biomarkers of inflammation, and increased adiponec-

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Abbreviations: CRP, C-reactive protein; HOMA, homeostasis model assessment; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; WBC, white blood cell.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

tin levels and whether these effects were limited to dysmetabolic women.

RESEARCH DESIGN AND METHODS

The Diabetes, Impaired Glucose Tolerance in Women and Atherosclerosis (DIWA) study was powered to examine subclinical atherosclerosis in the carotid and femoral arteries in a population sample of 64-year-old women. Briefly, 2,595 women identified through the County Register were contacted and screened with questionnaire; measurement of weight, height, waist, and hip circumference; and an oral glucose tolerance test. Diabetes, IGT, and NGT were defined according to the World Health Organization classification (17). The diagnosis of IGT was based on results of two oral glucose tolerance tests fulfilling the criteria for IGT. The aim was to include strictly defined groups with type 2 diabetes ($n = 209$), IGT ($n = 205$), and NGT. The NGT group consisted of so many women that a random sample was drawn ($n = 101$). A group of women with NGT who were matched by BMI and waist-to-hip ratio to the women with IGT was also recruited ($n = 97$). Measurements of alcohol intake were available for 186 women with NGT. The randomized and matched NGT groups were combined into one group in the present study because they showed similar alcohol intakes.

For all subjects the exclusion criteria were malignant or inflammatory disease, severe psychiatric disorders, or other circumstances making participation not feasible. Diabetic women with anti-GAD antibodies were excluded. For subjects with NGT, additional exclusion criteria were coronary heart disease, intermittent claudication, previous stroke or transient ischemic attack, treatment or the need for treatment for hypertension, and dyslipidemia. Women with inflammatory diseases were excluded to avoid confounding.

The subjects received both written and oral information before they gave their consent to participate. The study was approved by the ethics committee at Sahlgrenska University Hospital.

Measurements

A questionnaire was used to obtain information on previous and present diseases, smoking, medication, education, and physical activity. Alcohol consumption was assessed by two different questionnaires completed at different occasions, 1–2 weeks apart. For one of the questionnaires, the subjects were to report the amount of alcoholic beverages consumed, expressed as bottles per week. The other was based on the number of glasses per week. Subjects were also asked to specify the amounts of beer, wine, and spirits. The alcohol intake was calculated as grams per day for each of the questionnaires, showing a good correlation ($r = 0.78$). The means of these measurements were used in the analysis. Information on the number of drinking occasions per week for the three kinds of alcoholic beverages was also obtained.

Table 1—*Characteristics of the 64-year-old women in the study*

	Diabetes	IGT	NGT
n	209	205	186
BMI (kg/m^2)	29.6 ± 4.9	27.7 ± 4.9	26.2 ± 3.4*
Waist (cm)	98.3 ± 12.4	91.3 ± 11.8	88.0 ± 9.1*
Smoker	51 (34)	38 (19)	37 (19)
Cigarette-years	25 (0–1,840)	40 (0–1,505)	40 (0–1,400)
Blood glucose (mmol/l)	7.2 ± 2.5	5.1 ± 0.6	4.8 ± 0.5*
HOMA	3.13 ± 5.79	1.47 ± 1.22	1.10 ± 0.65*
Systolic blood pressure (mmHg)	143 ± 20	142 ± 19	132 ± 17*
HDL cholesterol (mmol/l)	1.48 ± 0.41	1.62 ± 0.42	1.78 ± 0.43*
Triglycerides (mmol/l)	1.57 ± 0.99	1.36 ± 0.74	1.17 ± 0.56*
CRP (mg/l)	1.90 ± 10.73	1.30 ± 3.73	1.27 ± 2.55*
WBCs (10^9/l)	6.9 ± 1.8	6.3 ± 1.8	5.8 ± 1.5*
Previous myocardial infarction	13 (6)	2 (1)	0†
Previous stroke	6 (3)	6 (3)	0
Insulin	12 (6)	0	0
Metformin	40 (19)	0	0
Sulfonylurea	26 (12)	0	0
Glitazone	11 (5)	0	0
Statin/fibrate	58 (28)	22 (11)	0
Aspirin	43 (21)	21 (10)	1 (1)*
Hormonal replacement therapy	53 (25)	65 (32)	64 (34)†

Data are means ±SD, *n* (%), or median (minimum–maximum). *$P < 0.001$; †$P < 0.01$ for trend.

Biochemical analysis

At screening, capillary blood glucose was measured with the glucose oxidase technique. After inclusion, venous blood samples were drawn, and serum and plasma were frozen in aliquots at −70°C within 4 h.

Insulin was assayed at the Department of Clinical Biochemistry Addenbrookes NHS Trust (Cambridge, U.K.) on a 1235 AutoDELFIA automatic immunoassay system using a two-step time-resolved fluorometric assay. The kits were manufactured for Wallac Oy (Turku, Finland) by DAKO (Ely, Cambridgeshire, U.K.). Homeostasis model assessment (HOMA) was calculated (18).

Anti-GAD antibodies were measured by an autoantibody enzyme-linked immunosorbent assay kit (RSR, Cardiff, U.K.). Autoimmune diabetes was defined as anti-GAD antibodies >4.6 units/ml. CRP was measured by a photometric immunoturbidimetric test (Orion Diagnostica, Espoo, Finland). Serum adiponectin were determined by an ELISA kit (R&D Systems Europe, Abingdon, U.K.) at the Wallenberg Laboratory. Triglyceride levels were determined by fully enzymatic techniques (Thermo Clinical Labsystems, Espoo, Finland). HDL was determined after precipitation of apolipoprotein B–containing lipoproteins with magnesium sulfate and dextran sulfate (Thermo Clinical Labsystems). White blood cell (WBC) count was measured by using the Celldyn 4000 hematology analyzer (Abbott Laboratories, Santa Clara, CA).

Statistical analysis

The SPSS 12.0 program for Windows was used for the statistical analyses. Variables are given as means ± SD and *n* (%). Skewed variables such as alcohol intake are given as median (minimum–maximum). Blood glucose, HOMA, triglycerides, adiponectin, CRP, and WBC count are given as geometric means ± SD. The skewed variables were log-transformed before statistical analysis. Linear trend was tested, and ANOVA was used for testing between multiple groups. Student's *t* test was used to compare con-

Table 2—*Alcohol consumption patterns among the 64-year-old women in the study*

	Diabetes	IGT	NGT
n	209	205	186
Any alcohol intake	176 (84.2)	184 (89.8)	172 (92.5)*
Mean alcohol intake (g/day)	6.7 ± 7.8 (4.2, 0–38.2)	7.2 ± 7.0 (6.1, 0–46.3)	8.8 ± 7.8 (7.2, 0–37.2)*
Mean frequency of alcohol intake (occasions/week)	2.1 ± 2.2 (1.0–10)	2.4 ± 2.4 (2.0–13)	2.8 ± 2.3 (2.0–11)*
Abstainers with previous overconsumption	5 (2.4)	3 (1.5)	0 (0)†
Type of beverage, based on total g/day alcohol			
Beer (%)	31	28	31
Wine (%)	56	59	55
Spirits (%)	14	15	15

Data are means ±SD, *n* (%), or median (minimum–maximum) unless otherwise indicated. *$P < 0.01$; †$P < 0.05$ for trend.

tinuous data, and χ^2 tests were used for analysis of proportions between groups. Spearman's correlation coefficient was calculated. Multiple regression was used in covariance analyses. In these analyses alcohol consumption was categorized into tertiles used as dummy variables. $P < 0.05$ (two sided) was considered as statistically significant.

RESULTS — Table 1 presents the characteristics of the subjects. Obesity, blood glucose, HOMA, blood pressure, and dyslipidemia were gradually increased in the IGT and diabetes groups compared with the NGT group. The proportions of women with myocardial infarction and stroke are also shown in Table 1. Treatment with aspirin or lipid-lowering drugs was most common among women with diabetes, compared with the IGT group (Table 1). Hormonal replacement therapy was most common in the NGT group, least frequent in the diabetes group, and intermediate in the IGT group. Of the diabetic women, 31% ($n = 65$) were taking any antidiabetic medication.

Alcohol consumption

Alcohol consumption is presented in Table 2. The gradual increase in alcohol intake paralleled the impairment of glucose tolerance. Hence, women with NGT drank more alcohol than those with IGT, who in turn consumed more than women with diabetes. In all groups, most alcohol was consumed as wine. Among women drinking alcohol, the median (minimum–maximum) consumptions in the diabetes, IGT, and NGT groups were 5.6 (0.3–38.2), 7.0 (0.3–46), and 8.2 (0.3–37) g alcohol/day, respectively ($n = 532$, $P = 0.055$ for trend). The prevalence of previous overconsumption was highest in the diabetes group and lower in the IGT group, whereas none of the NGT women reported such problems (Table 2).

Education, measured by questionnaire as the total number of years in school (mean 10.8, median 10 years, range 4–24 years), was associated with alcohol consumption ($r = 0.18$, $P < 0.001$) and HOMA ($r = -0.18$, $P < 0.001$). Physical activity during leisure time was associated with HOMA ($r = -0.13$, $P = 0.003$) but not with alcohol consumption ($r = 0.05$, NS).

Table 3—*Correlations to mean daily alcohol intake in the entire group of 64-year old women and in the subgroups type 2 diabetes, IGT, and NGT*

	All	Diabetes	IGT	NGT
n		209	205	186
Waist	−0.22*	−0.25*	−0.19†	−0.10
Cigarette years	0.19*	0.14‡	0.24†	0.23†
HOMA	−0.26*	−0.27*	−0.27*	−0.10
Serum HDL cholesterol	0.32*	0.30*	0.34*	0.22†
Serum triglycerides	−0.17*	−0.16*	−0.10	−0.17‡
Adiponectin	0.22*	0.24*	0.16‡	0.15‡
CRP	−0.16*	−0.21†	−0.21†	−0.01
WBCs	−0.14†	−0.23*	−0.07	−0.03

*$P < 0.001$; †$P < 0.01$; ‡$P < 0.05$.

Alcohol consumption, metabolic factors, and smoking

Waist circumference, HOMA, HDL cholesterol, and cigarette-years were associated with mean daily alcohol intake in the entire group and within the diabetes and IGT groups (Table 3.) In the NGT group, only cigarette-years, HDL cholesterol, and triglycerides correlated with alcohol intake. Triglycerides correlated with alcohol intake in the diabetes and NGT groups and in all women taken together. Cigarette years and HOMA did not correlate (data not shown).

We performed a multivariate analysis with log HOMA as the dependent variable and alcohol intake in tertiles, log fasting blood glucose, log waist circumference, log school years, previous myocardial infarction, diabetes medication, aspirin, lipid-lowering drugs, and hormonal replacement treatment as independent variables. The results showed that the second tertile of alcohol intake (2.7–<9.2 g alcohol/day, $P = 0.049$), log glucose ($P < 0.001$), log waist circumference ($P < 0.001$), and aspirin treatment ($P = 0.020$) were independently associated with log HOMA ($R^2 = 65\%$). The corresponding partial correlation coefficients were −0.09, 0.59, 0.23, and 0.10, respectively. For the highest alcohol tertile, the partial correlation coefficient was −0.08 ($P = 0.057$).

Adiponectin

Serum adiponectin concentrations differed between women drinking alcohol and abstainers (14.66 ± 7.01 vs. 11.53 ± 6.47 mg/l, $P < 0.001$). The mean daily alcohol intake correlated with adiponectin in all women and in the separate

groups (Table 3). Cigarette years and adiponectin did not correlate (data not shown). A multivariate analysis was performed with adiponectin as a dependent variable and with alcohol consumption as tertiles, BMI, log waist circumference, glucose tolerance group (diabetes, IGT, and NGT), log HOMA, previous myocardial infarction, antidiabetic medication, aspirin, lipid-lowering drugs, and hormonal replacement treatment as independent variables. The results showed that alcohol consumption (tertile 3, ≥9.2 g/day, $P = 0.017$), log HOMA ($P < 0.001$), log waist circumference ($P = 0.017$), and aspirin treatment ($P = 0.028$), apart from glucose tolerance group, were independently associated with adiponectin ($R^2 = 24\%$). The corresponding partial correlation coefficients were 0.10, −0.28, −0.10, and 0.09, respectively.

Inflammatory markers

As shown in Table 1, CRP and WBC count increased with decreasing glucose tolerance. CRP and WBC count correlated negatively with alcohol consumption in the entire group and among diabetic women (Table 3). CRP was also inversely associated with alcohol consumption in the IGT group. In the NGT group there was no correlation between mean daily alcohol intake and CRP or WBCs. Adiponectin correlated negatively with CRP and WBC count ($r = -0.30$ and $r = -0.25$, respectively, $P < 0.001$). CRP did not correlate with cigarette-years (data not shown). A multivariate analysis was performed with log CRP as the dependent variable and alcohol consumption in tertiles, BMI, log waist circumference, log fasting glucose, log HOMA, previous myocardial infarction, antidiabetic medication, aspirin, lipid-lowering drugs, and hormonal replacement treatment as independent variables. Only log HOMA ($P = 0.005$) and log waist circumference ($P = 0.001$) were independently associated with log CRP ($R^2 = 23\%$). The corresponding partial correlation coefficients were 0.12 and 0.14. A corresponding analysis with WBC as the dependent variable showed that only log HOMA ($P = 0.001$) and log waist circumference ($P = 0.034$) were independent covariates (partial correlation coefficients = 0.15, and 0.09, respectively) ($R^2 = 9\%$).

After exclusion of all women with previous myocardial infarction and stroke and who were using antidiabetic medication, aspirin, lipid-lowering drugs, and hormonal replacement therapy, mean daily alcohol intake still correlated with HOMA ($r = -0.19$, $P < 0.01$), adiponectin ($r = 0.19$, $P < 0.01$), and CRP ($r = -0.17$, $P < 0.01$) but not with WBC ($r = -0.10$, $P = 0.085$) ($n = 305$).

CONCLUSIONS — The results from this population-based cohort of 64-year old women showed a consistently different pattern of alcohol consumption between subjects with type 2 diabetes, IGT, and NGT. Worsening glucose tolerance was accompanied by more abstaining, less frequent intake of alcohol, and smaller amounts consumed. The mean daily alcohol intake was positively associated with serum adiponectin and insulin sensitivity, independent of potential confounders such as concomitant disease, different medications, central obesity, or various lifestyle factors. Increased alcohol intake was accompanied by lower levels of CRP and a lower WBC count, although these did not remain after adjustment for HOMA and waist circumference. The inverse association between alcohol and factors related to the metabolic syndrome (i.e., HOMA, waist circumference, and inflammation) was stronger among subjects with type 2 diabetes and IGT than among those with NGT.

The study design warrants some methodological considerations. First, in this cross-sectional study, causality cannot be analyzed. It may be argued that more restricted drinking habits could be a response to the diagnosis of diabetes or IGT. However, we do not believe that this is the case. The associations between alcohol intake and HOMA and the other components of the metabolic syndrome were observed in the entire cohort after adjustment for glucose tolerance and also within each of the diabetes and IGT groups. Further, half of the diabetic women and all women with IGT were detected during the study. In the IGT group all women got the same information about lowered glucose tolerance without any classification of severity. No systematic information on alcohol intake was given.

Second, alcohol intake is difficult to assess. It may also covariate with lifestyle and psychosocial factors which, in turn, could exert metabolic effects. We handled these difficulties by evaluating alcohol consumption at two different occasions with two questionnaires, using different approaches. Several measures of intake were used, including both the frequency of drinking and mean alcohol intake. In addition, we assessed and adjusted for lifestyle and psychosocial factors.

Finally, there are other potential confounders. Hence, concomitant cardiovascular diseases may be associated with insulin resistance, inflammatory response (19), and lower adiponectin concentration (20). In addition antidiabetic treatment and lipid-lowering therapy may reduce CRP and also affect adiponectin levels (21). Aspirin may reduce CRP concentrations (22). However, in the present study the associations between alcohol intake and HOMA, adiponectin, CRP, and WBC count remained in covariance analyses in which concomitant diseases and medication were included as covariates. In a further analysis after exclusion of women with previous myocardial infarction or stroke and those presently taking medication, the correlations between alcohol consumption and HOMA, adiponectin, and CRP still remained.

The results are in line with previous studies. So far, serum adiponectin concentrations in relation to alcohol consumption have only been reported for nondiabetic men and women (15) and diabetic men (16). We extend this knowledge to Caucasian women with type 2 diabetes, IGT, and NGT, showing that a daily alcohol intake of >9 g was associated with an increase in serum adiponectin. Adiponectin levels are reduced in patients with obesity and cardiovascular disease, in those treated with an insulin sensitizer (23), and in patients with cardiovascular disease and has been shown to increase after weight reduction or treatment with insulin sensitizers (23). However, our findings were independent of these confounding factors.

To our knowledge, there are no data published on alcohol drinking patterns in middle-aged women, comparing subjects with diabetes or IGT with healthy women. In a recent review, we showed that in most studies, increased alcohol intake was related to higher insulin sensitivity (8). We found that alcohol consumption corresponding to >3–9 g/day was associated with high insulin sensitivity after adjustment for potential confounders, which is in line with findings by Freiberg et al. (7). Any established level for alcohol-induced improvement of insulin action is not well defined in the literature. Suggested alcohol consumption levels range from 6 to 12 g/day, up to <40 g/day (8).

Our interpretation of the results is

that women with impaired glucose regulation consumed less alcohol than those with NGT. Conversely, moderate alcohol consumption was associated with lesser degrees of impaired glucose regulation, higher insulin sensitivity, less dyslipidemia, central obesity, and higher adiponectin levels. We can only speculate on the underlying mechanisms. Adiponectin has anti-inflammatory (24) and insulin-sensitizing effects (23) and appears to protect from the development of the metabolic syndrome and type 2 diabetes (25). Hence, a hypothetical concept of adiponectin mediating the effect of alcohol consumption on metabolism is supported by these accumulating data and the results from the present study, in combination with data from a previous intervention study showing that alcohol consumption raised serum adiponectin levels (26). The primary effect of alcohol may also be to improve insulin sensitivity, thereby improving adiponectin production by the adipocytes. It has been proposed that the inhibitory effect of alcohol on lipolysis, leading to a decrease in free fatty acids, may be the mechanism that initiates an improvement of insulin sensitivity (27).

The results cannot be generalized beyond this population-based cohort of Caucasian 64-year-old women. However, an advantage of this study is that potential confounders related to ethnicity, sex, and age were constant. Further, the diagnoses of type 2 diabetes and IGT were based on repeated testing and measurement of anti-GAD antibodies.

In summary, moderate alcohol consumption was accompanied by less incidence of type 2 diabetes, IGT, insulin sensitivity, dyslipidemia, and inflammation, whereas serum adiponectin was increased. There is a need to clarify whether adiponectin may be a mechanistic link and also the clinical implications of these observations.

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References

1. Gaziano JM, Gaziano TA, Glynn RJ, Sesso HD, Ajani UA, Stampfer MJ, Manson JE, Hennekens CH, Buring JE: Light-to-moderate alcohol consumption and mortality in the Physicians' Health Study enrollment cohort. *J Am Coll Cardiol* 35: 96–105, 2000
2. Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ: Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. *BMJ* 319:1523–1528, 1999
3. Gaziano JM, Buring JE, Breslow JL, Goldhaber SZ, Rosner B, VanDenburgh M, Willett W, Hennekens CH: Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. *N Engl J Med* 329:1829–1834, 1993
4. Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC: Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. *BMJ* 310:555–559, 1995
5. Imhof A, Woodward M, Doering A, Helbecque N, Loewel H, Amouyel P, Lowe GD, Koenig W: Overall alcohol intake, beer, wine, and systemic markers of inflammation in western Europe: results from three MONICA samples (Augsburg, Glasgow, Lille). *Eur Heart J* 25:2092–2100, 2004
6. Carlsson S, Hammar N, Grill V, Kaprio J: Alcohol consumption and the incidence of type 2 diabetes: a 20-year follow-up of the Finnish twin cohort study. *Diabetes Care* 26:2785–2790, 2003
7. Freiberg MS, Cabral HJ, Heeren TC, Vasan RS, Curtis Ellison R: Alcohol consumption and the prevalence of the metabolic syndrome in the U.S.: a cross-sectional analysis of data from the Third National Health and Nutrition Examination Survey. *Diabetes Care* 27:2954–2959, 2004
8. Hulthe J, Fagerberg B: Alcohol consumption and insulin resistance—a review. *Metab Syndr Relat Disord* 3:13–18, 2005
9. Cordain L, Melby CL, Hamamoto AE, O'Neill DS, Cornier MA, Barakat HA, Israel RG, Hill JO: Influence of moderate chronic wine consumption on insulin sensitivity and other correlates of syndrome X in moderately obese women. *Metabolism* 49:1473–1478, 2000
10. Han TS, Sattar N, Williams K, Gonzalez-Villalpando C, Lean ME, Haffner SM: Prospective study of C-reactive protein in relation to the development of diabetes and metabolic syndrome in the Mexico City Diabetes Study. *Diabetes Care* 25: 2016–2021, 2002
11. Ridker PM, Buring JE, Cook NR, Rifai N: C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. *Circulation* 107:391–397, 2003
12. Leinonen E, Hurt-Camejo E, Wiklund O, Hulten LM, Hiukka A, Taskinen MR: Insulin resistance and adiposity correlate with acute-phase reaction and soluble cell adhesion molecules in type 2 diabetes. *Atherosclerosis* 166:387–394, 2003
13. Spranger J, Kroke A, Mohlig M, Bergmann MM, Ristow M, Boeing H, Pfeiffer AF: Adiponectin and protection against type 2 diabetes mellitus. *Lancet* 361:226–228, 2003
14. Shai I, Rimm EB, Schulze MB, Rifai N, Stampfer MJ, Hu FB: Moderate alcohol intake and markers of inflammation and endothelial dysfunction among diabetic men. *Diabetologia* 47:1760–1767, 2004
15. Thamer C, Haap M, Fritsche A, Haering H, Stumvoll M: Relationship between moderate alcohol consumption and adiponectin and insulin sensitivity in a large heterogeneous population. *Diabetes Care* 27: 1240, 2004
16. Sierksma A, Patel H, Ouchi N, Kihara S, Funahashi T, Heine RJ, Grobbee DE, Kluft C, Hendriks HF: Effect of moderate alcohol consumption on adiponectin, tumor necrosis factor-α, and insulin sensitivity. *Diabetes Care* 27:184–189, 2004
17. Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 15:539–553, 1998
18. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
19. Wannamethee SG, Lowe GD, Shaper AG, Rumley A, Lennon L, Whincup PH: The metabolic syndrome and insulin resistance: relationship to haemostatic and inflammatory markers in older non-diabetic men. *Atherosclerosis* 181:101–108, 2005
20. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K, Nishida M, Kihara S, Sakai N, Nakajima T, Hasegawa K, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Hanafusa T, Matsuzawa Y: Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 20:1595–1599, 2000
21. Satoh N, Ogawa Y, Usui T, Tagami T, Kono S, Uesugi H, Sugiyama H, Sugawara A, Yamada K, Shimatsu A, Kuzuya H, Nakao K: Antiatherogenic effect of pioglitazone in type 2 diabetic patients irrespective of the responsiveness to its antidiabetic effect. *Di-*

abetes Care 26:2493–2499, 2003
22. Woodward M, Lowe GD, Francis LM, Rumley A, Cobbe SM: A randomized comparison of the effects of aspirin and clopidogrel on thrombotic risk factors and C-reactive protein following myocardial infarction: the CADET trial. *J Thromb Haemost* 2:1934–1940, 2004
23. Diez JJ, Iglesias P: The role of the novel adipocyte-derived hormone adiponectin in human disease. *Eur J Endocrinol* 148: 293–300, 2003
24. Ouchi N, Kihara S, Funahashi T, Matsuzawa Y, Walsh K: Obesity, adiponectin and vascular inflammatory disease. *Curr Opin Lipidol* 14:561–566, 2003
25. Choi KM, Lee J, Lee KW, Seo JA, Oh JH, Kim SG, Kim NH, Choi DS, Baik SH: Serum adiponectin concentrations predict the developments of type 2 diabetes and the metabolic syndrome in elderly Koreans. *Clin Endocrinol (Oxf)* 61:75–80, 2004
26. Pai JK, Hankinson SE, Thadhani R, Rifai N, Pischon T, Rimm EB: Moderate alcohol consumption and lower levels of inflammatory markers in US men and women. *Atherosclerosis* [Epub ahead of print]
27. Avogaro A, Watanabe RM, Dall'Arche A, De Kreutzenberg SV, Tiengo A, Pacini G: Acute alcohol consumption improves insulin action without affecting insulin secretion in type 2 diabetic subjects. *Diabetes Care* 27:1369–1374, 2004