Elevated Alanine Aminotransferase Predicts New-Onset Type 2 Diabetes Independently of Classical Risk Factors, Metabolic Syndrome, and C-Reactive Protein in the West of Scotland Coronary Prevention Study

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We examined the association of serum alanine aminotransferase (ALT) with features of the metabolic syndrome and whether it predicted incident diabetes independently of routinely measured factors in 5,974 men in the West of Scotland Coronary Prevention Study. A total of 139 men developed new diabetes over 4.9 years of follow-up. ALT, but not aspartate aminotransferase, levels increased progressively with the increasing number of metabolic syndrome abnormalities from (means ± SD) 20.9 ± 7.6 units/l in those with none to 28.1 ± 10.1 units/l in those with four or more (P < 0.001). In a univariate analysis, men with ALT in the top quartile (ALT ≥29 units/l) had an elevated risk for diabetes (hazard ratio 3.38 [95% CI 1.99–5.73]) versus those in the bottom quartile (<17 units/l). ALT remained a predictor with adjustment for age, BMI, triglycerides, HDL cholesterol, systolic blood pressure, glucose, and alcohol intake (2.04 [1.16–3.58] for the fourth versus first quartile). In stepwise regression, incorporating ALT and C-reactive protein (CRP) together with metabolic syndrome criteria, elevated ALT (≥29 units/l), and CRP (≥3 mg/l) predicted incident diabetes, but low HDL cholesterol and hypertension did not. Thus, elevated ALT levels within the "normal" range predict incident diabetes. The simplicity of ALT measurement and its availability in routine clinical practice suggest that this enzyme activity could be included in future diabetes prediction algorithms.
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The role of the liver in the pathogenesis of type 2 diabetes is attracting increasing interest. In a recent study (1), directly determined liver fat content was shown to correlate with several features of insulin resistance in normal weight and moderately overweight subjects independent of BMI and intra-abdominal or overall obesity. However, direct measurements of liver fat require ultrasound, computed tomography scan, or proton spectroscopy, and such techniques are unlikely to be recommended for this purpose in routine clinical practice. Fortunately, circulating concentrations of a number of variables appear to give insight into the extent of liver fat accumulation. Among these are γ-glutamyltransferase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Of these three, ALT is the most specific marker of liver pathology and appears to be the best marker for liver fat accumulation (2). In addition, circulating concentrations of plasminogen activator inhibitor-1 may give insight into the extent of liver fat content (3) but, unlike ALT, its measurement is perhaps not as simple, standardized, or routinely available in laboratories.

In light of the above observations, it is of interest that ALT has been shown to predict incident type 2 diabetes in two prospective studies (4,5). Ohlson et al. (4) determined risk factors for diabetes in 766 men, 47 of whom developed diabetes over 13.5 years of follow-up. They reported that elevated ALT predicted diabetes independently of classical predictors inclusive of BMI, blood pressure, triglycerides, and family history. However, diabetes ascertainment was not uniform in their study, and the potential utility of ALT to predict diabetes was not examined in any detail. Vozarovoa et al. (5) examined the ALT levels in a cohort of 370 Pima Indians with normal glucose tolerance, 63 of whom developed diabetes over an average follow-up of 6.9 years. In their analyses, individuals in the top decile for ALT (≥70 units/l) had a relative risk of 2.5 (95% CI 1.7–3.7) for diabetes compared with those in the bottom decile (ALT ≤12 units/l), with adjustment for age, sex, percentage body fat, clamp-derived insulin resistance, and acute insulin response. The only minor weaknesses in that study were the absence of data on alcohol consumption and routine clinical measures known to predict diabetes, namely fasting lipids and blood pressure. Moreover, they

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ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; WOSCOPS, West of Scotland Coronary Prevention Study.

TABLE 1
Baseline characteristics

	Developed diabetes	No diabetes	*P*
n	139	5,835	
Age (years)	55.6 ± 5.7	55.4 ± 5.5	0.43
BMI (kg/m^2)	27.7 ± 3.6	26.0 ± 3.1	<0.0001
AST (units/l)	22.6 ± 6.2	21.9 ± 5.8	0.12
ALT (units/l)	27.5 ± 10.2	23.2 ± 9.1	<0.0001
Cholesterol–to–HDL cholesterol ratio	7.09 ± 1.5	6.40 ± 1.4	<0.0001
Triglycerides (log mmol/l)	0.78 ± 0.4	0.51 ± 0.4	<0.0001
HDL cholesterol (mmol/l)	1.05 ± 0.2	1.14 ± 0.24	<0.0001
LDL cholesterol (mmol/l)	5.00 ± 0.45	4.96 ± 0.45	0.26
Systolic blood pressure (mmHg)	138.4 ± 18.0	135.3 ± 17.1	0.039
Diastolic blood pressure (mmHg)	85.4 ± 10.0	83.8 ± 10.3	0.086
Fasting plasma glucose (mmol/l)	5.49 ± 0.7	4.70 ± 0.49	<0.0001
CRP (log mg/l)	1.05 ± 0.9	0.53 ± 1.08	<0.0001
Categorical			
Current smokers	64 (46.0)	2520 (43.2)	0.50
Alcohol consumption ≥20 units	21 (15.1)	1002 (17.2)	0.52

Data are means ± SD or *n* (%).

were not able to incorporate markers of inflammation in their prospective analyses, and the authors themselves suggested that inflammatory cytokines, via their ability to enhance de novo hepatic fatty acid synthesis, may contribute to both elevated ALT and diabetes. We and others (6–8) have previously shown elevated C-reactive protein (CRP) to be an independent predictor of incident diabetes.

We had the opportunity to address the predictive power of ALT for new-onset diabetes in the West of Scotland Coronary Prevention Study (WOSCOPS) in more detail and attempted to address many of the above issues in this study. In particular, we were able to examine whether ALT predicts new-onset diabetes independently of classical predictors, alcohol intake, and markers of inflammation. We were also able to address whether elevated ALT predicts new-onset diabetes independently of the metabolic syndrome, previously shown to predict new-onset diabetes in WOSCOPS (9). Finally, due to the larger size of WOSCOPS, it was possible to better approximate the level of ALT above which increased risk for diabetes is evident. We believe our study enhances knowledge on the prediction of incident diabetes by ALT, with potential implications for clinical practice and the development of future algorithms to predict diabetes.

RESEARCH DESIGN AND METHODS

The design of WOSCOPS has been described in detail (10–12). Briefly, 6,595 moderately hypercholesterolemic men (LDL cholesterol 4.5–6.0 mmol/l and triglycerides <6.0 mmol/l) with no history of myocardial infarction were randomized to 40 mg pravastatin daily or placebo and followed for an average of 4.9 years.

A battery of risk factors and other demographic variables were assessed at baseline (10–12), and, of particular relevance to this study, fasting glucose measurements at six monthly visits were recorded throughout the study, enabling us to determine the transition to and timing of diabetes development. We excluded men with frank diabetes (72 subjects with self-reported diabetes and 76 who had a baseline blood glucose ≥7.0 mmol/l [*n* = 148]). New-onset diabetes was defined by at least two postrandomization glucose measurements ≥7.0 mmol/l · mg^{-1} · dl^{-1} or commencement of hypoglycemic drugs. In addition, because we were primarily interested in examining subjects who experienced significant deterioration in their glucose control, a further restraint was incorporated into the definition whereby one glucose measurement must be ≥2.0 mmol/l above baseline, an approach validated in previous relevant publications (6,13). Inevitably, this strategy restricted the number of subjects classified as newly diabetic but increased our level of confidence that the subjects labeled as newly diabetic in this study were truly thus. Finally, subjects' time to becoming glucose intolerant was taken as the 6-month visit at which they first had two postrandomization glucose measurements of ≥7.0 mmol/l and one or more postrandomization glucose measurement of >2.0 mmol/l above the baseline glucose level or at the postrandomization visit at which they first indicated taking hypoglycemic drugs (6,13). Due to nonattendance at visits or end of study (with varying length of follow-up), subjects' time to becoming glucose intolerant was censored at the last 6-month visit at which their glucose level was measured. Since only 5,974 men had two or more postrandomization fasting glucose measurements, the analyses relating to new-onset diabetes used this reduced cohort. We used modified criteria for characterizing men with the metabolic syndrome, as described in detail previously (9). Men with ALT and AST levels >70 and >60 units/l, respectively, were excluded from entry into WOSCOPS.

Laboratory analyses and determination of alcohol intake. All biochemical analyses were performed in the biochemistry department at Glasgow Royal Infirmary, which is a Centers for Disease Control and Prevention (Atlanta) reference laboratory and accredited by Clinical Pathology Accreditation U.K. Plasma lipids and lipoproteins were measured twice before randomization, and the baseline level was taken as the average (10–12). Lipoprotein profiles were determined according to the Lipid Research Clinics protocol. Details of the CRP assay are given in the article by Packard et al. (11). Stored samples for CRP analysis were available for 5,657 men (11). ALT and AST were determined on fresh samples using standard reagents by reaction rate assay based on the conversion of NADH to NAD. All AST and ALT analyses were conducted in the same laboratory with adherence to external quality control. The between-batch coefficient of variation for their determination was <5%. Alcohol intake was determined by a nurse-administered standardized questionnaire.

Statistics. Data are presented as means ± SD for continuous variables and number of subjects (percentage) for categorical variables. The relationships among serum AST, ALT, and other continuous variables were measured using Spearman's rank correlations. Plasma triglycerides and CRP were log transformed. Univariate and multivariate Cox proportional hazards models were fitted to identify predictors of new-onset diabetes. The models contained a set of conventional risk factors known to predict diabetes, metabolic syndrome classification, and CRP. A stepwise regression model was also examined incorporating all individual metabolic syndrome criteria, CRP, and ALT. Cumulative time-to-event survival curves were estimated using the Kaplan-Meier method.

RESULTS

A total of 139 men (2.33%) developed diabetes over an average follow-up of 4.9 years. Their baseline characteristics are given in Table 1. Notably, mean ALT was 18% higher in those who subsequently developed diabetes ($P <$ 0.001).

TABLE 2
Spearman correlations of AST and ALT with other baseline measurements

	AST		ALT	
	Correlation	*P*	Correlation	*P*
Age (years)	−0.02	0.19	−0.16	<0.0001
BMI (kg/m^2)	0.10	<0.0001	0.29	<0.0001
Cholesterol (mmol/l)	0.11	<0.0001	0.13	<0.0001
Triglycerides (log mmol/l)	0.05	<0.0001	0.21	<0.0001
HDL cholesterol (mmol/l)	0.15	<0.0001	−0.03	0.034
LDL cholesterol (mmol/l)	0.01	0.47	0.05	<0.0001
Systolic blood pressure (mmHg)	0.05	<0.0001	0.05	<0.0001
Diastolic blood pressure (mmHg)	0.07	<0.0001	0.11	<0.0001
Fasting plasma glucose (mmol/l)	0.04	0.005	0.14	<0.0001
CRP (log mg/l)	−0.04	0.0024	0.02	0.07
Alcohol ≥20 units (yes/no)	0.13	<0.0001	0.09	<0.0001

In the correlation analysis (Table 2), elevated ALT was most strongly associated with BMI, triglycerides, fasting glucose, and diastolic blood pressure (all $r > 0.10$, $P < 0.001$). AST was less strongly associated with these variables. Both elevated ALT and AST were weakly associated with excessive alcohol intake, but neither was related substantially to CRP. Consistent with the above observations, ALT increased progressively with increasing number of metabolic syndrome abnormalities ranging from 20.9 ± 7.6 units/l in those with no abnormalities to 28.1 ± 10.1 units/l in those with four or more ($P < 0.0001$ for trend) (Fig. 1), whereas AST did not change significantly ($P = 0.27$).

ALT versus classical predictors. In a univariate analysis, ALT as a continuous variable was associated with risk of diabetes. A 5-units/l increment had a hazard ratio (HR) of 1.25 (95% CI 1.15–1.34, $P < 0.0001$). Men in the fourth quartile for ALT, but not those in the second or third quartiles, had a significantly increased risk for diabetes relative to men in the first quartile (Table 3). The relationship was clearly evident in the Kaplan-Meier curve (Fig. 2). In a multivariate analysis, after adjusting for other measured baseline parameters (including BMI, triglycerides, HDL cholesterol, blood pressure, glucose, and alcohol intake), men in the fourth quartile for ALT continued to have a significantly elevated risk for diabetes (HR 2.04 [1.1633–0.508]) (Table 3). Moreover, the predictive ability of ALT persisted when the fourth quartile was compared with the risk in men in the other three quartiles combined (HR 1.72 [1.20–2.48]) (Fig. 3). Similarly, an ALT cutoff of ≥29 units/l improved prediction of diabetes when combined with a fasting glucose cutoff of 6.1 mmol/l (data not shown). By contrast, AST did not predict incident diabetes in univariate or multivariate analyses (data not shown).

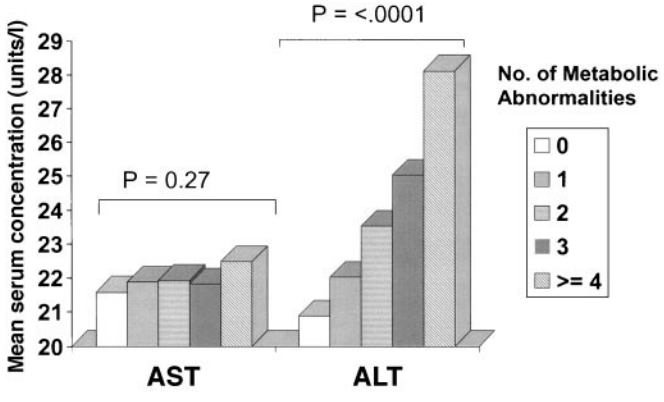

FIG. 1. The serum concentrations of ALT and AST in men fulfilling increasing numbers of metabolic syndrome criteria.

ALT versus metabolic syndrome classification. Elevated ALT continued to predict incident diabetes (HR 2.08 [95% CI 1.48–2.93] for ALT ≥29 versus ALT <29 units/l) even when subjects were categorized as having or not having the metabolic syndrome (Fig. 3). Similarly, further addition of a CRP cutoff 3 mg/l into the latter analysis did not alter the ability of ALT to predict incident diabetes. Finally, we performed a stepwise multivariate analysis of diabetes predictors, with all individual metabolic syndrome criteria cutoffs, a CRP cutoff of 3 mg/l and an ALT

TABLE 3
ALT as a predictor of incident diabetes in unvariate and multivariate analysis

	HR (95% CI)	*P*
ALT (in units/l) univariate analysis		
Second (ALT 17–21) versus first (<17) quartile	1.37 (0.76–2.48)	0.30
Third (22–28) versus first quartile	1.65 (0.93–2.92)	0.09
Fourth (≥29) versus first quartile	3.38 (1.99–5.73)	<0.0001
ALT multivariate analysis		
Second versus first quartile	1.22 (0.67–2.22)	0.51
Third versus first quartile	1.23 (0.69–2.22)	0.48
Fourth versus first quartile	2.04 (1.16–3.58)	0.01
Pravastatin treatment	0.69 (0.49–0.97)	0.03
Age (10 years)	1.28 (0.93–1.78)	0.13
BMI (5 kg/m^2)	1.62 (1.27–2.07)	0.0001
Current smoker tobacco (yes/no)	1.27 (0.90–1.81)	0.17
Systolic blood pressure (20 mm/Hg)	1.06 (0.87–1.28)	0.57
Cholesterol–to–HDL cholesterol ratio	1.07 (0.92–1.23)	0.38
Triglycerides (log mmol/l)	2.65 (1.52–4.62)	0.0006
Alcohol ≥20 units (yes/no)	0.74 (0.45–1.20)	0.22
Fasting glucose ≥6.1 mmol/l (yes/no)	12.73 (8.20–19.77)	<0.0001

Multivariate analysis examined prediction of ALT quartiles adjusting for other risk factors listed in the table.

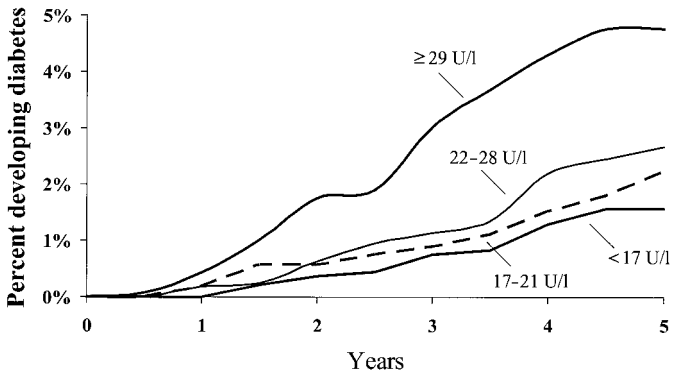

FIG. 2. Onset of new diabetes by quartiles of plasma ALT concentration.

TABLE 4
Results of stepwise regression on the predictors of incident diabetes in WOSCOPS

	HR (95% CI)	*P*
Fasting plasma glucose ≥6.1 mmol/l (yes/no)	13.17 (8.50–20.42)	<0.0001
BMI >28.8 kg/m^2 (yes/no)	2.56 (1.74–3.76)	<0.0001
Triglycerides >1.69 mmol/l (yes/no)	2.22 (1.49–3.29)	<0.0001
ALT ≥29 units/l (yes/no)	1.67 (1.17–2.38)	0.005
CRP ≥3 mg/l (yes/no)	1.60 (1.14–2.25)	0.007

Factors entered into model include the five individual National Cholesterol Education Program metabolic syndrome criteria, with BMI >28.8 kg/m^2 replacing the waist cutoff together with ALT ≥29 units/l and CRP ≥3 mg/l. Factors not entering final model were HDL cholesterol (<1.04 mmol/l), systolic (≥130 mm/Hg) or diastolic (≥85 mm/Hg) blood pressure, or antihypertensives.

cutoff of 29 units/l, entered into the model. In this case, both ALT and CRP continued to independently predict diabetes but low HDL cholesterol and blood pressure did not enter the final model (Table 4).

Pravastatin effect. All measurements in this analysis, except for repeated fasting glucose concentrations, were made before randomization to active therapy or placebo and are thus unaffected by treatment allocation. Since we have previously shown that pravastatin use did influence progression to diabetes (13), we included treatment allocation in the multivariate analysis and, in addition, noted that the ALT incident diabetes association was not dissimilar ($P = 0.89$) in men allocated to pravastatin or placebo.

DISCUSSION

Our study adds new information to the concept of ALT as a predictor of diabetes. First, a large sample size allowed us to identify the level of ALT above which the risk of diabetes is evident. Men with baseline ALT levels 29 units/l had more than three times the risk for diabetes than men with ALT <17 units/l. Second, we were able to exclude alcohol intake and CRP, a robust biomarker of low-grade inflammation, as potential confounders. Finally, we had prior data on metatolic syndrome in this population and again were able to adjust for this in our analysis. Significantly, ALT continued to predict type 2 diabetes independently of all the above factors whether we compared risk in the fourth versus the first quartile or examined risk in those above or below the 75th percentile for ALT (i.e., ≥ 29 units). Moreover, elevated ALT and CRP continued to predict, quite independently, incident diabetes, whereas low HDL cholesterol and blood pressure did not in a stepwise regression analysis that considered all individual metabolic syndrome criteria. Given the simplicity of ALT measurement and its universal standardization and availability in routine clinical practice, these novel observations indicate the potential for an ALT cutoff to be considered in diabetes prediction algorithms. Our observations perhaps also add further support for the role of the liver in the pathogenesis of type 2 diabetes.

Why should elevated ALT predict type 2 diabetes? There is now good evidence that elevated ALT, even within the normal range, correlates with increasing liver fat (2). Moreover, the condition of nonalcoholic fatty liver disease

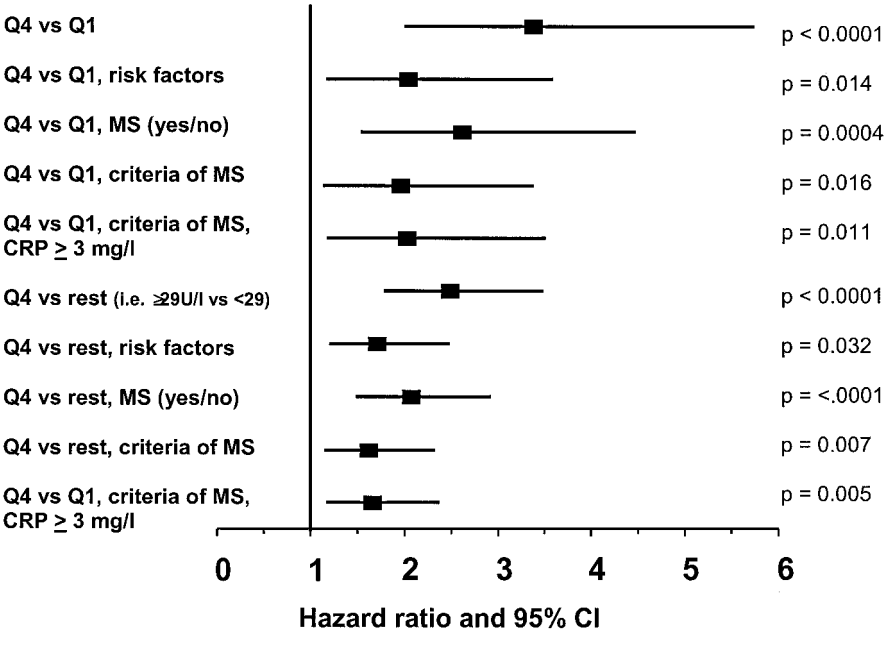

FIG. 3. Association of ALT quartiles with incident diabetes with and without adjustment for other risk factors as stated. Risk factors include all parameters considered in the multivariate analysis in Table 3.

is now well recognized, and an elevated ALT is a principal diagnostic feature (14,15). With respect to diabetes risk, it is therefore likely that elevated liver fat is part of the pathogenic mechanism. In line with this, Seppala-Lindross et al. (1) elegantly demonstrated that elevated liver fat in nondiabetic men with average BMI is linked to insulin resistance independently of total adiposity. These prior observations in turn explain why elevated ALT predicted decreasing hepatic insulin sensitivity independent of total adiposity and an increase in hepatic glucose output in a study of Pima Indians (5). Of more recent interest, an inverse correlation between ALT levels and adiponectin concentrations has been demonstrated (16). This observation is relevant since low adiponectin predicts incident diabetes in prospective studies (17–19) and may do so in part by enhancing hepatic fatty acid oxidation and thereby lessening fat accumulation and ALT levels. It would be clinically important in future studies, therefore, to compare ALT and adiponectin as predictors of diabetes in prospective cohorts.

Why then does the liver accumulate fat? One possibility is simply excess flux of fatty acids to liver from abdominal or visceral fat depots (20). However, others (2) suggest that increased liver fat content may relate better to dietary fat intake. Further possibilities include excessive intravascular lipolysis of triglyceride-rich lipoproteins or indeed impaired free fatty acid clearance. Whether acquired or genetic defects in hepatic β-oxidation are involved in liver fat accumulation requires direct examination.

Regardless of the mechanisms for fat accumulation, our results offer some potential clinical interest. Firstly, our data suggest that levels of ALT, even within the currently acceptable normal range, may indeed be prognostic with respect to the development of diabetes. A level of ~28–29 units/l (around the mean level of those developing diabetes and the approximate cutoff for the top quartile) is well within the current normal range in all laboratories and populations. This suggests that perhaps even modest degrees of hepatic fat accumulation may be relevant for the development of diabetes.

Given the increasing incidence of obesity and therefore the likelihood for diabetes worldwide, there is great interest in the development of predictive algorithms for type 2 diabetes. In this respect, it is of interest that the National Cholesterol Education Program–defined metabolic syndrome criteria have been shown to predict incident diabetes in different populations (9,21). However, we previously suggested that the National Cholesterol Education Program criteria could be modified to improve its prediction of diabetes and that differing definitions are likely to better predict risk for coronary heart disease (9). Our findings that elevated ALT and CRP continued to predict incident diabetes in stepwise regression analyses, whereas low HDL cholesterol and blood pressure did not, perhaps indicate the potential future use of ALT cutoffs in this respect. Future studies in other populations should address this potential in greater detail.

The strengths of our study have been indicated above and include its larger sample size and inclusion of alcohol intake, CRP, and metabolic syndrome in analyses. Moreover, our definition of diabetes used the American Diabetes Association criteria and was consistent and validated in prior analyses (6,9,13). We acknowledge that the current study represents a post hoc analysis of men with elevated cholesterol and that men with levels of ALT >70 units/l were excluded from WOSCOPS. However, since cholesterol and LDL cholesterol are not predictive of diabetes and since others have shown higher ALT levels to predict diabetes, we feel such limitations are not significant concerns. Clearly, our results were obtained in a cohort of men and are not applicable to women. We also acknowledge that we used a modified version of the American Diabetes Association criteria to predict diabetes but feel that our conservative approach (which may have contributed to only 2.33% developing diabetes) increased rather than decreased our confidence in the diagnosis of new-onset type 2 diabetes. Finally, although these results were conducted in the context of a statin trial, and statins can transiently raise transaminases, it is important to note that ALT and AST concentrations used herein were measured before randomization and treatment allocation and that further statistical analysis indicated no heterogeneity in the ALT–incident diabetes findings dependent on treatment allocation.

In conclusion, we have shown that elevated ALT within the "normal" range predicts diabetes independently of classical predictors, CRP, and the metabolic syndrome in middle-aged Caucasian men of average BMI. In this respect, it is noteworthy that ALT measurement is automated, internationally standardized, and universally available, unlike many other proposed novel markers of diabetes. Therefore, we believe that the results of our study have potential implications for clinical practice or development of future algorithms to predict diabetes. The results may also add some support for the notion that liver fat accumulation is important in the pathogenesis of type 2 diabetes.

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