Low Adiponectin Levels and Increased Risk of Type 2 Diabetes in Patients With Myocardial Infarction

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OBJECTIVE

Patients with acute myocardial infarction (MI) have increased risk of developing type 2 diabetes mellitus (T2DM). Adiponectin is an insulin-sensitizing hormone produced in adipose tissue, directly suppressing hepatic gluconeogenesis, stimulating fatty acid oxidation and glucose uptake in skeletal muscle and insulin secretion. In healthy humans, low plasma adiponectin levels associate with increased risk of T2DM; however, the relationship between adiponectin and T2DM in patients with MI has never been investigated.

RESEARCH DESIGN AND METHODS

We prospectively included 666 patients with ST-segment elevation MI, without diabetes, treated with percutaneous coronary intervention, from September 2006 to December 2008 at a tertiary cardiac center. Blood samples were drawn before intervention, and total plasma adiponectin was measured in all samples. During follow-up (median 5.7 years [interquartile range 5.3–6.1]) 6% (n = 38) developed T2DM. Risk of T2DM was analyzed using a competing risk analysis.

RESULTS

Low adiponectin levels were associated with increased risk of T2DM ($P < 0.001$). Even after adjustment for confounding risk factors (age, sex, hypertension, hypercholesterolemia, current smoking, previous MI, BMI, blood glucose, total cholesterol, HDL, LDL, triglyceride, estimated glomerular filtration rate, C-reactive protein, peak troponin I, and proatrial natriuretic peptide), low adiponectin levels remained an independent predictor of T2DM (hazard ratio [HR] 5.8 [2.3–15.0]; $P < 0.001$). Importantly, plasma adiponectin added to the predictive value of blood glucose, with the combination of high blood glucose and low plasma adiponectin, vastly increasing the risk of developing T2DM (HR 9.6 [3.7–25.3]; $P < 0.001$).

CONCLUSIONS

Low plasma adiponectin levels are independently associated with increased risk of T2DM in patients with MI and added significantly to the predictive value of blood glucose.

Adiponectin, a hormone almost exclusively secreted by adipocytes, participates in several anti-inflammatory and insulin-sensitizing processes (1). Plasma levels are decreased in several metabolic disorders, including obesity, inflammatory states, insulin resistance, and type 2 diabetes mellitus (T2DM) (2). Observational studies

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have consistently documented an inverse relationship between plasma adiponectin and incident T2DM in the general population (3–6).

In patients with acute myocardial infarction (AMI) and no history of T2DM, impaired glucose tolerance (IGT) and undiagnosed T2DM are common and strong predictors of poor prognosis (7). Even in nondiabetic patients, admission blood glucose levels remain an independent risk factor, in part related to impaired β-cell function (8,9).

Adiponectin asserts its effects through activation of the AMP-dependent kinase (AMPK), thereby directly suppressing hepatic gluconeogenesis and stimulating fatty acid oxidation in liver and muscle, glucose uptake in skeletal muscle, and insulin secretion (1,10). Adiponectin also improves pancreatic β-cell function by contributing to favorable glycometabolic properties through antiapoptotic effects (11).

Accordingly, one could hypothesize that high plasma adiponectin levels protect against the development of T2DM, thereby leading to a more favorable cardiovascular outcome. However, to the best of our knowledge, plasma adiponectin and risk of developing T2DM in patients with AMI has never been investigated.

RESEARCH DESIGN AND METHODS

Study Population

From September 2006 through December 2008, we prospectively enrolled 666 nondiabetic ST-segment elevation myocardial infarction (STEMI) patients treated with primary percutaneous coronary intervention (pPCI) at Gentofte University Hospital, Denmark (a high-volume percutaneous coronary intervention center with present on-site cardiac surgery performing >1,500 percutaneous coronary intervention procedures per year) (12). Inclusion criteria were patients admitted because of a suspected STEMI with presence of chest pain for >30 min and <12 h and persistent ST-segment elevation ≥2 mm in at least two contiguous precordial electrocardiogram leads or ≥1 mm in at least two contiguous limb electrocardiogram leads or a newly developed left bundle branch block. Exclusion criteria were a nonsignificant troponin I (TnI) increase (≤0.5 μg/L) or cancellation of pPCI (no occlusion on coronary artery angiography or coronary artery bypass surgery elected instead).

A total of 735 patients were included; however, in the current study, we excluded 69 patients because of prevalent diabetes, ending up with 666 STEMI patients.

Subsequent medical treatment included daily aspirin 75 mg, clopidogrel 75 mg (for 12 months), lipid-lowering drugs (statins), and β-receptor antagonists.

Hypertension was defined as use of blood pressure–lowering drugs and hypercholesterolemia as treatment with cholesterol-lowering drugs at time of admission. Multivessel disease was defined as two- or three-vessel disease.

All patients were followed for a median of 5.7 years (interquartile range 5.3–6.1), and follow-up was 100% complete (n = 666). Follow-up data on mortality were obtained through the civil registration system, which holds information on vital status (alive, death, or emigration). Diagnosis of T2DM was obtained from the highly validated National Patient Registry using ICD-10 code E11. All events found using this registry were carefully validated using medical records (e.g., laboratory tests, medical charts, and hospital summaries), excluding possibly misclassified events.

The study was approved by the local scientific ethics committee and the Danish Data Protection Agency and complied with the 2nd Declaration of Helsinki. Informed consent was obtained from all participants.

Laboratory Methods

Blood samples were drawn from the femoral sheath before the pPCI procedure. Blood was allocated to 4 mL EDTA containers and within 30 min centrifuged at 10.000 RPM for 10 min. Plasma was stored in Nunc cryo tubes at −80°C until analysis in a blinded fashion in a dedicated core laboratory. Plasma adiponectin was determined by a validated in-house time-resolved immunofluorometric assay as previously described (13). This assay recognizes all three major molecular forms of plasma adiponectin (14). All samples were analyzed in duplicate, with a detection limit of 1.5 μg/L and intra- and interassay coefficients of variation <5% and <7%, respectively. C-reactive protein (CRP), TnI, creatinine, and blood glucose were assayed by routine laboratory methods. TnI was measured at baseline and again after 6 and 12 h. Estimated glomerular filtration rate (eGFR) was calculated on the basis of serum creatinine, age, and sex using the MDRD formula (15).

Statistical Analysis

In Table 1, comparisons between groups were performed by χ^2 test for dichotomous variables and Kruskal-Wallis for continuous variables. Plasma adiponectin, CRP, TnI, and blood glucose concentrations were positively skewed and therefore logarithmically transformed using the base log of 2 before further analysis. The competing risk of death is important to take into account when examining the incidence of a cause-specific hazard like T2DM. A standard Cox proportional hazards regression analysis assumes that the risk of T2DM is similar in patients remaining alive and those censored at the time of death. By using a competing risk model, appropriate incidences of T2DM in patients remaining alive are calculated (16). To examine the association between adiponectin and risk of T2DM, we treated adiponectin as both a categorical (quartiles) and a continuous (per SD increase in log transformed) variable, using Cox proportional hazards regression analyses with competing risks by Fine and Gray (16). The dose-response relationship between adiponectin and risk of T2DM was examined by fitting restricted cubic splines to a Cox model (using three automated selected knots), testing for nonlinearity with a likelihood ratio test, comparing a model with only the linear term to a model with the linear and the cubic spline terms (17). Evaluation of first-order interactions was made in the final model, adjusting for multiple testing by the Bonferroni method. Deviation from linearity was assessed by simultaneous assessment of linear and quadratic effects. Misspecification of the functional form of the covariates and the assumption of proportional hazards were evaluated by plots of the cumulative martingale residuals. P values <5% on two-sided tests were considered significant. The competing risk calculations were performed using Stata/IC 11.1 for Windows, whereas all other statistical calculations were performed using the

Table 1—Baseline characteristics according to age- and sex-adjusted quartiles of plasma adiponectin

	Adiponectin quartiles				
Variables	1 (≤5.13)	2 (>5.13–7.16)	3 (>7.16–10.35)	4 (>10.35)	*P* value
Age (years)[a]	57 ± 12	61 ± 11	66 ± 11	70 ± 11	<0.001
Male sex	93%	84%	71%	49%	<0.001
Hypertension	26%	32%	34%	36%	0.27
Current smoking	58%	57%	49%	45%	0.05
Hypercholesterolemia	21%	16%	19%	11%	0.08
Previous MI	6%	5%	6%	4%	0.74
BMI (kg/m^2)[a]	27.7 ± 4.0	27.9 ± 4.6	26.1 ± 4.2	24.2 ± 4.1	<0.001
Blood glucose (mmol/L)[b]	8.2 (7.0–9.5)	8.1 (7.2–9.4)	8.2 (6.8–9.7)	8.2 (7.0–9.4)	0.95
Peak TnI (μg/L)[b]	100 (26–228)	94 (28–245)	83 (32–240)	134 (26–258)	0.86
Mid-regional proANP (μmol/L)[b]	127 (77–215)	141 (97–209)	167 (117–272)	244 (169–373)	<0.001
CRP (mg/L)[b]	3 (2–7)	3 (2–9)	4 (1–9)	4 (1–10)	0.98
Serum creatinine (μmol/L)[b]	95 (82–109)	91 (79–105)	91 (77–108)	89 (73–111)	0.17
eGFR (mL/min)[a]	76 ± 23	75 ± 21	72 ± 22	69 ± 24	0.023
Total cholesterol (mmol/L)[a]	4.9 ± 1.2	4.9 ± 1.1	4.9 ± 1.2	4.8 ± 1.0	0.55
HDL (mmol/L)[a]	1.2 ± 0.3	1.3 ± 0.3	1.4 ± 0.3	1.5 ± 0.4	<0.001
LDL (mmol/L)[a]	3.0 ± 1.1	3.1 ± 1.0	3.0 ± 1.0	2.9 ± 1.0	0.39
Triglyceride (mmol/L)[b]	1.3 (0.9–2.2)	1.0 (0.7–1.8)	0.9 (0.6–1.4)	0.8 (0.6–1.1)	<0.001
Symptom-to-balloon time (min)[b]	200 (127–349)	180 (120–319)	215 (140–330)	195 (135–303)	0.65
Multivessel disease	23%	32%	26%	25%	0.83
Culprit lesion					0.92
Left anterior descending artery	48%	47%	46%	48%	
Circumflex artery	11%	14%	11%	10%	
Right coronary artery	41%	39%	43%	42%	
Glycoprotein IIb/IIIa inhibitor	28%	28%	22%	22%	0.52

Dichotomous variables are presented in %. [a]Gaussian distribution presented as mean ± SD. [b]Non-Gaussian distribution presented as median (interquartile range).

SAS statistical software (SAS for Windows, version 9.2, SAS Institute Inc., Cary, NC).

RESULTS

The plasma level of adiponectin (geometric mean [5th to 95th percentile]) was 7.4 mg/L (2.4–22.4 mg/L). During the 5-year follow-up, 38 participants developed T2DM (6%). Table 1 describes baseline characteristics according to quartiles of plasma adiponectin.

As seen, adiponectin was associated positively with age, female sex, HDL, and proatrial natriuretic peptide (proANP) and inversely with BMI, triglyceride, and eGFR. Of interest, adiponectin was not associated with blood glucose (Table 1).

The risk of developing T2DM was evaluated using plasma adiponectin both as a continuous and as a categorical variable by Cox regression competing risk analyses; the results are shown in Table 2. After adjustment for age and sex, patients in the lowest quartile of adiponectin had approximately six times increased risk of T2DM as compared with patients in the highest quartile. Additional adjustment for cardiovascular risk factors, BMI, and blood test did not influence the association significantly; low adiponectin remained associated with risk of T2DM in all models. We also investigated the risk of T2DM per SD decrease in continuous adiponectin ($\log_2$ transformed), which yielded similar results with approximately two times the risk of T2DM per SD decrease in adiponectin. Again, multivariate adjusting only influenced the association weakly. Importantly, adiponectin was the only variable with increasing values associating with reduced risk of T2DM.

We also examined the dose-response relationship between plasma adiponectin and risk of developing T2DM (using multivariate model 2) by adding several cubic splines, thus allowing the relationship between adiponectin and T2DM to be nonlinear (Fig. 1).

The adjusted dose-response curve confirmed the linear inverse association with T2DM over the full spectrum of adiponectin levels (on the log-scale; $P_{linear} = 0.003$) (Fig. 1). By contrast, a nonlinear association was clearly nonsignificant ($P_{nonlinear} = 0.89$).

Using ROC curves, we identified an optimal cutoff value at a plasma adiponectin of 5.5 mg/L. Patients with adiponectin below the cutoff (low adiponectin) had a severely increased risk of developing T2DM (hazard ratio [HR] 5.1 [2.2–11.6]; $P < 0.001$ when adjusted for age and sex). When further adjusted for hypertension, hypercholesterolemia, current smoking, previous myocardial infarction (MI), BMI, blood glucose, total cholesterol, HDL, LDL, triglyceride, eGFR, CRP, peak TnI, and proANP (model 4), patients with low adiponectin had more than five times increased risk of T2DM (HR 5.8 [2.3–15.0]; $P < 0.001$).

Finally, we investigated risk of T2DM using a combination of blood glucose and adiponectin using cutoffs at 5.5 mg/L for adiponectin and 10 mmol/L for blood glucose (Fig. 2). As shown, plasma adiponectin was additive to

Table 2—Risk of T2DM according to plasma adiponectin

	Continuous adiponectin (per SD decrease in log_2 transformed)	*P* value	Categorized adiponectin (quartiles)				
			1	2	3	4	P_{trend} value
Univariate	1.69 (1.22–2.34)	0.001	4.14 (1.39–12.35)	2.02 (0.61–6.70)	1.99 (0.60–6.58)	Reference	0.008
Model 1	1.99 (1.34–2.94)	0.001	6.26 (1.51–25.80)	2.77 (0.67–11.42)	2.35 (0.66–8.32)	Reference	0.007
Model 2	1.97 (1.24–3.12)	0.004	5.86 (1.34–25.69)	2.26 (0.50–10.14)	2.29 (0.65–8.15)	Reference	0.017
Model 3	2.06 (1.23–3.46)	0.006	6.78 (1.11–41.28)	2.41 (0.44–13.06)	2.29 (0.57–9.14)	Reference	0.032
Model 4	1.91 (1.12–3.24)	0.017	7.18 (1.05–49.18)	2.39 (0.45–12.54)	1.95 (0.44–8.63)	Reference	0.040

Data are HR and 95% CI for risk of T2DM according to both continuous and categorized total plasma adiponectin calculated by Cox proportional hazards regression using competing risk analyses. Model 1, age and sex; model 2, model 1 + hypertension, hypercholesterolemia, current smoking, previous MI, BMI, and blood glucose; model 3, model 2 + total cholesterol, HDL, LDL, and triglyceride; model 4, model 3 + eGFR, CRP, peak TnI, and proANP.

blood glucose in predicting risk of T2DM. Patients with high adiponectin/low blood glucose had a very low risk of T2DM. By contrast, patients with low adiponectin/high blood glucose had a very high risk (HR 9.6 [3.7–25.3]; $P < 0.001$), compared with patients with high adiponectin/low blood glucose.

CONCLUSIONS

In the current study, we showed that in patients with AMI, low plasma adiponectin was associated independently with increased risk of developing T2DM in a linear dose-response relationship. Even in patients with low glucose, adiponectin still added significantly to the prognostic value, as the risk of developing T2DM was higher in patients with low adiponectin/low glucose compared with patients with high adiponectin/low glucose. However, the risk increased by ~10-fold in patients who were characterized by the combination of low adiponectin and high blood glucose.

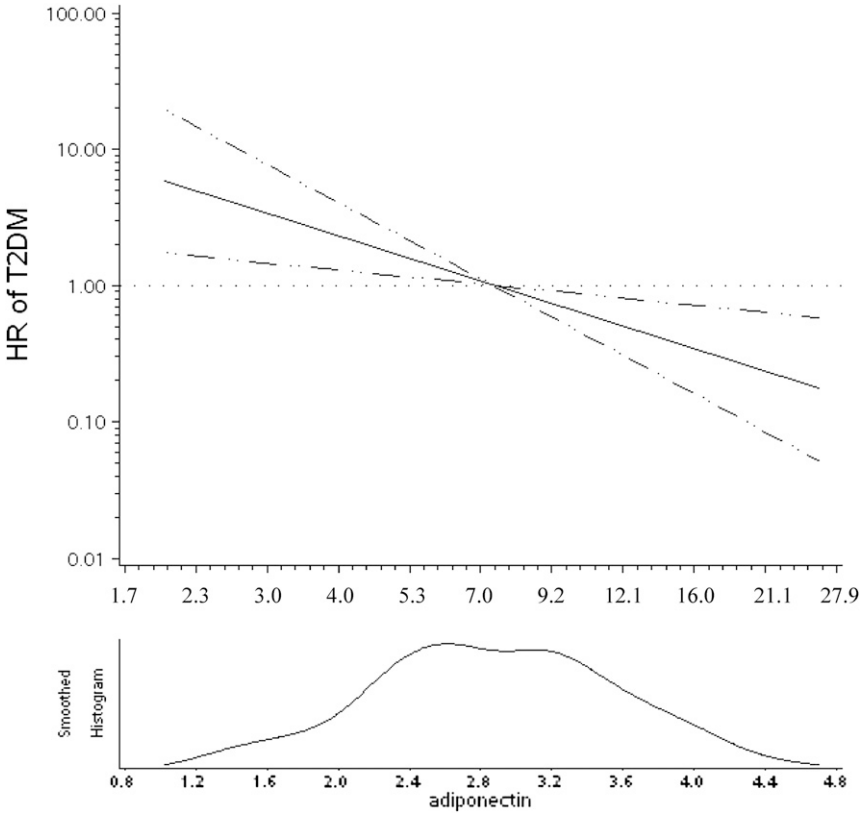

Figure 1—Dose-response relationship between total plasma adiponectin and risk of T2DM. The adjusted HR of T2DM risk as a function of log_2-transformed plasma adiponectin (back transformed for ease of interpretation). A histogram of the distribution of plasma adiponectin is shown underneath the graph. The 95% CI is indicated by the dashed lines. Model adjusted for age, sex, hypertension, hypercholesterolemia, current smoking, previous MI, BMI, and blood glucose (multivariate model 2).

Low plasma adiponectin has been suggested to be causally involved in pathways leading to T2DM. The binding of adiponectin to its receptors (adiR1/R2) directly suppresses hepatic gluconeogenesis and stimulates fatty acid oxidation in liver and muscle, glucose uptake in skeletal muscle, and insulin secretion (1,10).

In a study of 335 cases of incident T2DM from the Whitehall II study, adiponectin was measured three times per participant from 1991 to 2004. Lower plasma adiponectin was already observed 20 years prior to the diagnosis of T2DM (18). Similarly, Tabák et al. (5) showed that increasing adiponectin was associated with decreased HbA_{1c} during 10 years of follow-up. In several large observational studies in the general population, low plasma adiponectin was associated with increased risk of T2DM (3,4,6), and this was recently confirmed in 5,349 healthy participants from the Copenhagen City Heart Study (19).

In summary, both experimental and observational studies suggest adiponectin to be an important insulin-sensitizing hormone protecting against development of T2DM in the healthy population.

Increased insulin sensitivity is particularly important in patients with AMI who are at high risk of developing T2DM. Wallander et al. (9) showed that in nondiabetic patients with AMI, glucose abnormalities were related to impaired pancreatic β-cell secretion of insulin. Interestingly, adiponectin increases function of β-cells by contributing to favorable glycometabolic properties through antiapoptotic effects (11). The current study showed for the first time that in patients with

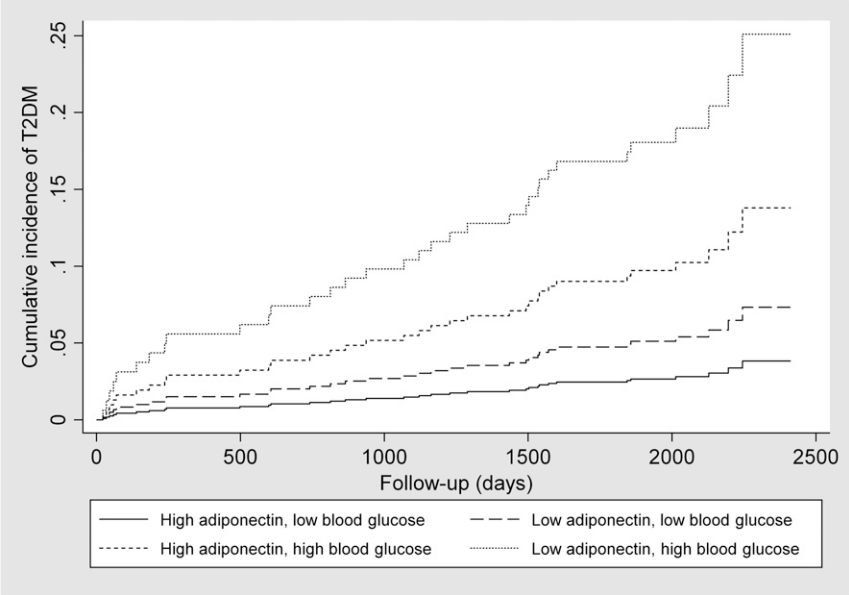

Figure 2—Risk of T2DM based on groups by adiponectin and blood glucose. Cumulative incidence of T2DM based on cutoffs of 5.5 mg/L for adiponectin and 10 mmol/L for blood glucose adjusted for age and sex. The curves are calculated using a competing risk analysis.

STEMI, low adiponectin was associated with increased risk of T2DM. Accordingly, raising adiponectin levels could seem advantageous in the management of IGT, diabetes, and metabolic syndrome, although this needs to be further investigated.

Surprisingly, we did not find any association between adiponectin and admission blood glucose. However, the early increase in blood glucose seen in AMI, known as stress-related hyperglycemia, is caused by the increased adrenal response (i.e., cortisol and adrenalin) (20). Still, admission blood glucose is a strong and independent risk factor of outcome (8,9). Importantly, adiponectin added significantly to the predictive value of admission blood glucose; low plasma adiponectin levels increased the risk of T2DM similar to high blood glucose, and the combination of low adiponectin/high blood glucose vastly increased the risk.

IGT is common in patients with AMI, increasing the risk of developing T2DM as well as mortality from cardiovascular disease (7). Interestingly, the increase in cardiovascular risk is also observed at lower blood glucose concentrations (21). Our finding that low adiponectin increased the risk of T2DM in patients with low admission blood glucose further suggests that low adiponectin may precede IGT.

Natriuretic peptides (NPs) and adiponectin are highly correlated, and recently NP was demonstrated to increase plasma adiponectin, possibly confounding the relationship between adiponectin and cardiovascular outcome through the strong association with prognosis (22,23). Indeed, we and others have recently demonstrated this. In 2,879 patients from the general population, Wannamethee et al. (24) demonstrated that adiponectin independently predicted cardiovascular mortality and coronary heart disease. However, when N-terminal pro-brain NP was included in the analysis, adiponectin was no longer significant. We have recently published similar results for risk of heart failure in the general population (25). Importantly, the findings of the current study showed that in contrast to cardiovascular outcome, the inverse association between adiponectin and risk of T2DM was not confounded by NP, even though NPs are elevated in patients with STEMI, thus emphasizing the beneficial insulin-sensitizing effects of adiponectin (26).

A direct link between NP, glucose metabolism, and T2DM has been suggested. Treatment of insulin-resistant human adipocytes with NP restored mitochondrial gene expression, suggesting that raising NPs may have a role in the management of obesity/insulin resistance (27).

In the Framingham Study, NP was associated inversely with several risk factors for metabolic syndrome, including insulin resistance (28). Mice treated with infusion of NP exhibited improved glucose tolerance, and in the Malmö Diet and Cancer Study, Magnusson et al. (29) showed that higher NPs were associated with increased glucose tolerance and lower risk of T2DM. However, the cause of the relationship between reduced NPs and long-term glucose deterioration and progression toward T2DM remains unknown. Based on our findings, we dare to suggest that the relationship between NP and reduced risk of T2DM is mediated through adiponectin.

Limitations and Strengths

The high molecule weight (HMW) isomer of adiponectin has been suggested as responsible for the majority of the insulin-sensitizing effects of adiponectin (30). However, in a large prospective cohort study, the association with incident T2DM was similar for both total and HMW adiponectin (31), indicating that measurement of total adiponectin is sufficient. In this context, we would like to stress that the assay used in the present investigation is, in fact, able to measure HMW adiponectin and, as the fraction corresponding to HMW adiponectin, constitutes the most abundant isoform; this may explain why measurements of total adiponectin and HMW adiponectin yield similar results (14). Furthermore, we did not have measurements of plasma insulin, previously shown to be inversely correlated with adiponectin, possibly confounding the results.

Finally, it is a limitation that cases of incident T2DM were identified using national registries, although we did validate all events.

Study strengths include the use of a homogeneous AMI population by only including patients with STEMI and the long follow-up time.

In conclusion, low plasma adiponectin levels were associated independently with increased risk of T2DM in patients with AMI in a dose-response relationship.

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