Effect of Change in Body Weight on Incident Diabetes Mellitus in Patients With Stable Coronary Artery Disease Treated With Atorvastatin (from the Treating to New Targets Study)

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Features of the metabolic syndrome are independent risk factors for new-onset diabetes mellitus (NODM) related to statin therapy. Obesity is the predominant underlying risk factor for the metabolic syndrome and diabetes mellitus. This study investigated whether change in body weight may predict NODM in statin-treated patients. A total of 7,595 patients without prevalent diabetes mellitus at baseline from the Treating to New Targets (TNT) study were included in this analysis. They were randomized to atorvastatin 10 or 80 mg/day and monitored for a median of 4.9 years. NODM developed in 659 patients (8.1% in the 10-mg group and 9.2% in the 80-mg group). There was a significant increase in body weight (0.9 kg, p <0.01 in both men and women) over 1 year after randomization. The increase in body weight was greater in patients with NODM than those without NODM (1.6 vs 0.9 kg, p <0.001). The association of change in body weight with NODM risk remained significant after adjusting for confounding factors (hazard ratios 1.33, 1.42, and 1.88 for quartiles 2, 3, and 4 compared with quartile 1, respectively). Similar results were obtained in patients with normal fasting glucose level. In conclusion, 1-year change in body weight is predictive of NODM in patients who underwent statin therapy from the TNT trial. Our study highlights the importance of weight control as a lifestyle measure to prevent statin-related NODM. **(Am J Cardiol 2014;113:1593−1598)**

There is an increasing awareness in the importance of weight loss as a lifestyle intervention to prevent the development of diabetes mellitus and cardiovascular diseases. It is not known however whether short-term change in body weight can affect subsequent risk of new-onset diabetes mellitus (NODM) related to statin therapy in the long term. Therefore, in this study we investigated whether change in body weight over 1 year could predict subsequent NODM. We studied patients in the Treating to New Targets (TNT) trial with stable coronary artery disease randomized to 10 or 80 mg/day of atorvastatin and monitored for a median of 4.9 years.[1,2] As statins have a slight effect on hepatic markers such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transaminase, and AST/ALT ratio, and because these hepatic markers have been reported to predict the development of the metabolic syndrome[3] and type 2 diabetes mellitus,[4−8] we also investigated the effect of body weight change on subsequent NODM risk, after taking the confounding effects of these hepatic markers into account.

Methods

The study design and results of the TNT trial have been published.[1,2] Briefly, 10,001 patients with stable coronary disease and a low-density lipoprotein cholesterol off therapy of 3.4 to 6.5 mmol/L (130 to 250 mg/dl), decreasing to <3.4 mmol/L (130 mg/dl) after an 8-week run-in period on atorvastatin 10 mg/day, were randomized to 10 or 80 mg/day of atorvastatin. Mean low-density lipoprotein cholesterol during follow-up was 2.6 mmol/L (101 mg/dl) in the 10-mg group and 2.0 mmol/L (77 mg/dl) in the 80-mg group. The primary end point, a composite of coronary heart disease death, myocardial infarction, stroke, and resuscitated cardiac arrest, occurred in 10.9% of patients in the 10-mg group and 8.7% of patients in the 80-mg group (hazard ratio [HR] 0.78, 95% confidence interval [CI] 0.69 to 0.89, p <0.001). All patients gave written informed consent, and the study was approved by the local research ethics committee or institutional review board at each center.

For this study, patients with a history of diabetes mellitus at baseline, missing baseline fasting blood glucose data, baseline fasting blood glucose ≥7.0 mmol/L (126 mg/dl), and <2 postbaseline measurements were excluded, leaving 7,595 subjects for this analysis, as described previously.[9] There was no significant difference in the proportion of patients excluded from this analysis between 10- and 80-mg atorvastatin groups (24.2% and 24.0%, respectively, p >0.05).

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Table 1
Number of subjects identified as having new-onset diabetes mellitus for different criteria according to the treatment group

Criteria	Total (n = 7,595)	Atorvastatin 10 mg (n = 3,797)	Atorvastatin 80 mg (n = 3,798)	p Value
AE alone	358 (4.7)	166 (4.4)	192 (5.1)	0.16
Blood glucose alone	84 (1.1)	38 (1.0)	46 (1.2)	0.38
Drug medication alone	3 (0.04)	3 (0.08)	0 (0.00)	0.95
AE + blood glucose	211 (2.8)	100 (2.6)	111 (2.9)	0.44
AE + drug medication	1 (0.01)	1 (0.03)	0 (0.00)	0.96
AE + blood glucose + drug medication	2 (0.03)	0 (0.00)	2 (0.05)	0.94
Any of the above	659 (8.7)	308 (8.1)	351 (9.2)	0.08

Data are expressed as n (%).
AE = adverse event.

Table 2
Baseline clinical characteristics between patients with and without new-onset diabetes mellitus (NODM)

Characteristics	Total (n = 7,595)	With NODM (n = 659)	No NODM (n = 6,936)	p Value
Age (yrs)	60.6 ± 8.9	60.1 ± 8.6	60.7 ± 8.9	0.10
Male gender	6,277 (82.6)	538 (81.6)	5,739 (82.7)	0.47
Current smokers	1,026 (13.5)	99 (15.0)	927 (13.4)	0.23
Hypertension	3,840 (50.6)	408 (61.9)	3,432 (49.5)	<0.001
Fasting glucose (mmol/L)	5.41 ± 0.59	5.99 ± 0.60	5.35 ± 0.56	<0.001
Body mass index (kg/m^2)	28.10 ± 4.24	30.65 ± 4.75	27.86 ± 4.11	<0.001
White blood cell count (10^3/mm^3)	6.0 (5.1−7.2)	6.4 (5.4−7.5)	6.0 (2.5−16.8)	<0.001
Systolic blood pressure (mm Hg)	129.7 ± 16.3	132.6 ± 17.2	129.4 ± 16.2	<0.001
Diastolic blood pressure (mm Hg)	78.1 ± 9.3	79.7 ± 9.5	77.9 ± 9.3	<0.001
Total cholesterol (mmol/L)	4.51 ± 0.61	4.61 ± 0.62	4.50 ± 0.61	<0.001
LDL cholesterol (mmol/L)	2.52 ± 0.45	2.55 ± 0.46	2.52 ± 0.45	0.11
HDL cholesterol (mmol/L)	1.24 ± 0.29	1.17 ± 0.27	1.25 ± 0.29	<0.001
Total/HDL cholesterol ratio	3.78 ± 0.84	4.10 ± 0.91	3.75 ± 0.83	<0.001
Triglycerides (mmol/L)	1.47 (1.12−1.99)	1.76 (1.32−2.38)	1.45 (1.10−1.95)	<0.001
Use of statin during screening	4,735 (62.3)	417 (63.3)	4,318 (62.3)	0.61
Use of β blockers before or at baseline	4,098 (54.0)	393 (59.6)	3,705 (53.4)	0.002
Treatment with atorvastatin 80 mg	3,798 (50.0)	351 (53.3)	3,447 (49.7)	0.08
AST (U/L)	16 (14−19)	16 (14−19)	16 (14−19)	0.94
ALT (U/L)	16 (13−20)	17 (13−23)	16 (13−20)	<0.001
AST/ALT ratio	1.00 (0.85−1.21)	0.93 (0.78−1.11)	1.00 (0.86−1.21)	<0.001

Data are expressed as mean ± SD, median (interquartile range), or n (%).
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Baseline was defined as the time of randomization, when all patients had been taking atorvastatin 10 mg/day for 8 weeks. AST and ALT levels were measured as part of the routine clinical biochemical test for liver function.

Fasting blood glucose was measured at each 6-month visit. NODM was defined prospectively as ≥2 postbaseline fasting blood glucose measurements ≥7.0 mmol/L (126 mg/dl) and at least 1 postbaseline glucose >2 mmol/L (36 mg/dl) above baseline.[5,9] We also included patients for whom NODM was identified through adverse event reporting.

Comparisons of baseline characteristics between patient groups were based on 1-way analysis of variance for continuous variables and logistic regression for categorical variables. Data are presented as mean ± SD or number (percentage). For variables that were not normally distributed, specifically ALT, AST, AST/ALT ratio, white blood cell count, and triglycerides, data are presented as median (interquartile range) and were natural log transformed before analysis. As there is a gender difference in AST, ALT, and AST/ALT ratio, gender-specific cut-off values were used to define the corresponding quartiles. Supplementary Table S1 lists the cut-off values of the quartiles of AST, ALT, AST/ALT ratio, and changes in body weight. HR and 95% CI for NODM were calculated on the basis of Cox proportional hazards analysis. The association of change in weight over 1 year after randomization and NODM risk was analyzed similarly while excluding patients with any previous event during year 1.

Results

Of 7,595 patients, 659 developed NODM over a median of 4.9 years of follow-up. A total of 308 patients (8.1%) developed NODM in the 10-mg atorvastatin group and 351 patients (9.2%) developed NODM in the 80-mg atorvastatin group. Although the 80-mg group had a slightly greater NODM incidence than the 10-mg group, the difference did not research statistical significance. Table 1 lists the number