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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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See page 1597 for disclosure information.

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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

Table 3
Univariate and multivariate analyses of predictors of new-onset diabetes mellitus

Characteristics	Univariate Analysis (n = 7,588)		Multivariate Analysis (n = 7,423)	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age (per 5-yr increase)	0.97 (0.93−1.01)	0.14	1.01 (0.95−1.06)	0.81
Fasting glucose level (per 0.6 mmol/L increase)	2.99 (2.76−3.24)	<0.001	2.68 (2.46−2.91)	<0.001
Body mass index (per 3 kg/m^2 increase)	1.28 (1.25−1.32)	<0.001	1.19 (1.14−1.25)	<0.001
White blood cell count (per 0.25 log [10^3/mm^3] unit increase)	1.28 (1.18−1.38)	<0.001	1.16 (1.06−1.26)	0.001
Systolic blood pressure (per 20-mm Hg increase)	1.24 (1.13−1.36)	<0.001	1.07 (0.95−1.21)	0.28
Diastolic blood pressure (per 10-mm Hg increase)	1.20 (1.11−1.31)	<0.001	1.02 (0.92−1.13)	0.74
Total cholesterol (per 0.6 mmol/L increase)	1.16 (1.08−1.25)	<0.001	—	—
LDL cholesterol (per 0.5 mmol/L increase)	1.06 (0.98−1.16)	0.16	—	—
HDL cholesterol (per 0.3 mmol/L increase)	0.73 (0.67−0.80)	<0.001	—	—
Total/HDL cholesterol ratio (per 1-unit increase)	1.50 (1.39−1.63)	<0.001	1.07 (0.95−1.21)	0.25
Triglycerides (per 0.01 log [mmol/L] unit increase)	2.75 (2.30−3.28)	<0.001	1.61 (1.24−2.07)	<0.001
Male gender	0.94 (0.77−1.15)	0.57	1.01 (0.81−1.26)	0.92
Current smokers	1.14 (0.92−1.41)	0.24	0.96 (0.76−1.22)	0.76
Hypertension	1.62 (1.38−1.90)	<0.001	1.21 (1.02−1.43)	0.03
Use of statins during screening	1.07 (0.91−1.25)	0.41	1.02 (0.87−1.21)	0.78
Use of β blockers before or at baseline	1.28 (1.09−1.49)	0.002	1.02 (0.87−1.20)	0.81
Treatment with atorvastatin 80 mg	1.15 (0.99−1.35)	0.07	1.11 (0.95−1.30)	0.18
AST				
Quartile 1	1.00 (Referent)	—	—	—
Quartile 2	0.87 (0.70−1.08)	0.20	—	—
Quartile 3	0.93 (0.76−1.15)	0.50	—	—
Quartile 4	0.87 (0.70−1.07)	0.19	—	—
ALT				
Quartile 1	1.00 (Referent)	—	—	—
Quartile 2	1.12 (0.89−1.42)	0.34	—	—
Quartile 3	1.07 (0.84−1.36)	0.58	—	—
Quartile 4	1.79 (1.45−2.21)	<0.001	—	—
AST/ALT ratio				
Quartile 1	1.00 (Referent)	—	1.00 (Referent)	—
Quartile 2	0.71 (0.59−0.86)	<0.001	0.82 (0.67−1.00)	0.05
Quartile 3	0.55 (0.44−0.67)	<0.001	0.75 (0.60−0.93)	0.01
Quartile 4	0.41 (0.32−0.51)	<0.001	0.75 (0.58−0.96)	0.02

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

of subjects identified as having NODM by each of the different criteria, which did not differ significantly between the 2 treatment groups.

Table 2 lists the baseline clinical characteristics of patients with and without NODM. As expected, patients with NODM had higher fasting blood glucose levels, body mass index, white blood cell count, systolic blood pressure, diastolic blood pressure, total cholesterol, total cholesterol/high-density lipoprotein cholesterol ratio, and triglycerides and lower high-density lipoprotein cholesterol at baseline. They also tended to have hypertension and history of β-blocker usage. Although there was no significant difference in baseline AST levels between patients with and without NODM, patients with NODM had significantly higher ALT levels and lower AST/ALT ratio at baseline.

In multivariate analysis (Table 3), a higher body mass index at baseline was independently associated with a higher risk of NODM, in addition to higher fasting blood glucose level, higher white blood cell count, higher triglyceride level, hypertension, and lower AST/ALT ratio. For baseline body mass index, the adjusted HR was 1.19 (95% CI 1.14 to 1.25) per 3 kg/m^2 increase. As listed in Table 4, there was a significant increase in body weight ($p < 0.01$ in both men and women) over 1 year after randomization. There was also a small, but significant, correlation between change in fasting blood glucose level and change in body weight (Figure 1). The increase in body weight was greater in patients with NODM than those without NODM ($p < 0.001$, Table 4). In gender-specific analysis, such difference was significant in men ($p < 0.001$) but did not reach statistical significance in women ($p = 0.24$). In contrast, although there was a significant decrease in AST/ALT ratio ($p < 0.01$ in both men and women) over 1 year after randomization, the change in AST/ALT ratio did not differ significantly between patients with and without NODM ($p = 0.16$ in men and 0.59 in women).

As listed in Table 5, the association of change in body weight with NODM remained significant after adjusting for other predictors of NODM in multivariate analysis. No significant interaction between change in body weight and gender or treatment group was found ($p > 0.05$). In gender-specific analysis, quartile 4 of body weight change was significantly associated with higher risk of NODM in both men and women, with similar HRs of about 1.9 compared with quartile 1.

Similar results were obtained in a separate analysis, in which we only included patients with normal fasting glucose level (<5.6 mmol/L or <100 mg/dl). As listed in

Table 4
Changes in weight and aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio over 1 year in patients with and without new-onset diabetes mellitus (NODM)

Characteristics	Total		With NODM		Without NODM	
	n	Estimate	n	Estimate	n	Estimate
Weight at baseline (kg)						
Men	6,272	85.7 ± 13.9	538	93.3 ± 16.1	5,734	85.0 ± 13.4
Women	1,318	74.2 ± 14.5	121	82.5 ± 14.8	1,197	73.3 ± 14.2
Weight at year 1 (kg)						
Men	6,186	86.6 ± 14.4	534	95.0 ± 16.9	5,652	85.8 ± 13.9
Women	1,306	74.9 ± 14.9	120	83.6 ± 15.5	1,186	74.1 ± 14.6
Change in weight (kg)						
Men	6,182	0.90 (−0.90 to 2.70)	534	1.59 (−0.22 to 3.50)	5,648	0.90 (−0.90 to 2.61)
Women	1,306	0.90 (−1.00 to 2.50)	120	1.54 (−0.68 to 3.50)	1,186	0.80 (−1.00 to 2.47)
AST/ALT ratio at baseline						
Men	6,275	0.98 (0.83−1.16)	538	0.91 (0.76−1.08)	5,737	1.00 (0.84−1.17)
Women	1,318	1.17 (1.00−1.35)	121	1.04 (0.89−1.22)	1,197	1.18 (1.00−1.36)
AST/ALT ratio at year 1						
Men	6,181	0.93 (0.79−1.12)	532	0.85 (0.72−1.00)	5,649	0.94 (0.79−1.13)
Women	1,299	1.09 (0.93−1.31)	120	1.00 (0.85−1.18)	1,179	1.11 (0.94−1.31)
Change in AST/ALT ratio						
Men	6,180	−0.04 (−0.16 to 0.08)	532	−0.05 (−0.17 to 0.05)	5,648	−0.04 (−0.16 to 0.08)
Women	1,299	−0.05 (−0.19 to 0.10)	120	−0.04 (−0.16 to 0.10)	1,179	−0.05 (−0.20 to 0.10)

Data are expressed as mean ± SD or median (interquartile range).

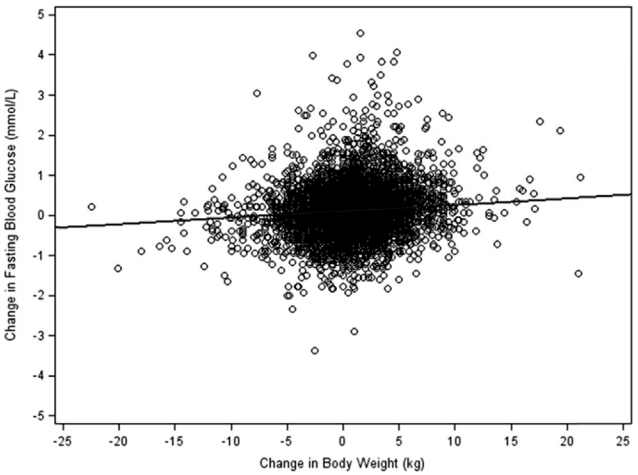

Figure 1. A scatter plot showing the relation between change in fasting blood glucose level and change in body weight (Spearman r = 0.093, p <0.001) over 1 year.

Supplementary Table S2, patients with AST/ALT ratio in quartile 4 had an adjusted HR of 0.49 (95% CI 0.29 to 0.83) for NODM compared with those in quartile 1 (p = 0.008). The association of change in body weight over 1 year with subsequent NODM risk also remained significant (HR 1.62, 95% CI 1.04 to 2.53, for quartile 4 compared with quartile 1), and such association was more prominent in men than women, with no significant gender interaction (p = 0.76; Supplementary Table S3).

Discussion

Our findings indicate that change in body weight over 1 year is an independent predictor of NODM in patients treated with statins. These factors are in addition to features of the metabolic syndrome, specifically, higher fasting blood glucose, body mass index, and triglycerides, and hypertension, which we found to be independent predictors of NODM in TNT and 2 other large statin trials.[9] Other results further confirm that the usual risk factors for type 2 diabetes mellitus seem to be the same as those for NODM in patients who undergo statin therapy, independent of the statin dose.

Our finding that weight gain during the first year of statin treatment is a predictor of subsequent NODM should be of clinical value as extra motivation for these patients to lose weight. Although the overall weight gain over 1 year is small in this study, such weight gain is statistically significant and is consistent with the small risk of NODM associated with statin therapy in the literature.[10] Moreover, the weight gain over 1 year in patients with NODM (1.6 kg) is almost double of that in patients without NODM (0.9 kg). Because patients with change in weight in quartile 4 have about 90% higher NODM risk than those in quartile 1, our study indicates that a small weight loss, which can be achieved readily, can result in substantial reduction of NODM risk in both men and women. Obesity appears to be the main driving force behind the development of diabetes mellitus and metabolic syndrome.[11] Both body mass index at baseline and weight gain thereafter predicted NODM in our study. Indeed, the association between hepatic markers at baseline and the risk of NODM may be mediated or confounded by the effect of obesity. Further studies are needed to unravel the pathophysiological links between obesity and statin-related NODM.

In this study, 8.1% patients in the 10-mg atorvastatin group and 9.2% patients in the 80-mg atorvastatin group developed NODM. The high-dose statin group has about 14% higher risk of developing NODM than the low-dose

Table 5
Association of change in weight over 1 year with new-onset diabetes mellitus

Change in Weight over 1 yr	Univariate Analysis		Multivariate analysis*	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Overall (n = 7,515)				
Quartile 1	1.00 (Referent)	—	1.00 (Referent)	—
Quartile 2	1.16 (0.90−1.50)	0.26	1.33 (1.03−1.73)	0.03
Quartile 3	1.27 (0.99−1.63)	0.06	1.42 (1.10−1.83)	0.007
Quartile 4	1.79 (1.42−2.26)	<0.001	1.88 (1.48−2.39)	<0.001
Men (n = 6,212)				
Quartile 1	1.00 (Referent)	—	1.00 (Referent)	—
Quartile 2	1.18 (0.89−1.58)	0.25	1.34 (1.00−1.79)	0.05
Quartile 3	1.36 (1.03−1.79)	0.03	1.48 (1.12−1.96)	0.006
Quartile 4	1.81 (1.39−2.35)	<0.001	1.89 (1.44−2.47)	<0.001
Women (n = 1,303)				
Quartile 1	1.00 (Referent)	—	1.00 (Referent)	—
Quartile 2	1.09 (0.61−1.93)	0.77	1.31 (0.74−2.35)	0.36
Quartile 3	0.93 (0.52−1.66)	0.80	1.08 (0.59−1.98)	0.80
Quartile 4	1.77 (1.06−2.95)	0.03	1.94 (1.14−3.30)	0.02

* Adjusted for all the variables in the multivariate model as in Table 3.

statin group, although the difference did not reach statistical significance, probably because of small effect size and hence insufficient study power. This is in line with a recent meta-analysis of 5 clinical trials (including the TNT trial) with a total of 32,752 participants showing that intensive statin therapy is associated with an additional 12% increase.[12] Despite their adverse effect on glycemia, statins can lower low-density lipoprotein cholesterol and reduce cardiovascular disease risk.[13,14] These beneficial effects of statins overweigh their slightly adverse effect on glycemia. As the effect of statins on glycemia is small, risk factors for NODM may be the same regardless of the use of statins. As there is no significant interaction between treatment group and body weight change on NODM risk, our study suggests that statin-related NODM could be prevented by the usual lifestyle interventions, especially weight loss.

This study takes advantage of the large sample size, well-defined inclusion and exclusion criteria, and uniform follow-up of the TNT trial. However, the study has some limitations. There are no concurrent control data on NODM obtained from a parallel group comprising patients who did not undergo any statin therapy. Insulin levels were not measured and a family history of diabetes mellitus was not recorded in the TNT trial, so that we cannot assess the role of insulin resistance and family history of diabetes mellitus in the development of NODM. Further studies are also needed to confirm our findings in other clinical trials with statins other than atorvastatin.

Disclosures

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Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2014.02.011.

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