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Letters to the Editor

Is Prolong Use of Statins Associated With Increase in the Risk of Diabetes?

The study by Wang et al. (1) assessed the risk of diabetes associated with statin use in the general population. The authors concluded that statin therapy is associated with an elevated risk for diabetes. However, the study does not indicate the classes or proportion of the different antihypertensive drugs (AHDs) administered in the statin-treated and control populations. This information is imperative because thiazide diuretics and specific beta-blockers exhibit undesirable glycemic effects.

Assessment of the ALLHAT study (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) revealed that the 4-year incidence of new-onset diabetes mellitus was significantly elevated in the chlorthalidone group compared with either the amlodipine or lisinopril group (11.6% vs. 9.8% and 8.1%, respectively; $p < 0.05$) (2). Comparable outcomes were also obtained from the INSIGHT (International Nifedipine GITS Study of Intervention as a Goal in Hypertension Treatment) and ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm) trials (3,4). These effects of diuretic AHDs on glucose metabolism are plausibly due to hypokalemia induced by these drugs.

Hyperglycemia induced by beta-blockers is due to the reduction in peripheral blood flow, followed by the channeling of blood away from locales of glucose uptake, thereby reducing glucose clearance. A systematic review by Elliott and Meyer (5), with 48 randomized groups of 22 clinical trials involving 143,153 participants, revealed that association of AHDs with incident diabetes is the highest for beta-blockers and diuretics (in rank order).

Therefore, the question that remains unrequited in the current study – "Is the adverse glycemic effect of statins observed in the present study getting augmented, as a greater number of subjects in the statin-group are being treated for hypertension with diuretics or beta-blockers?"

Furthermore, a prospective population-based cohort study by Dunder et al. (6) examined the impact of blood glucose elevation on the risk of developing myocardial infarction in individuals between 50 and 60 years of age who were receiving AHDs. They found that the elevated blood glucose and proinsulin levels produced by use of diuretics and beta-blockers were linked to the increased risk of myocardial infarction in these subjects. Therefore, in the current study, if the statin-treated group has a higher number of subjects receiving diuretics and beta-blockers, then the favorable outcome of statins may be further augmented.

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Reply

We thank Dr. Banerjee for his comments regarding our publication on statin therapy and the risk of incident diabetes (1). He highlighted for us the importance of diabetogenic effects of concomitant medications, particularly diuretics and beta-blockers, which have been independently associated with a higher risk of diabetes (2,3).

The effects of diuretics and beta-blockers were essential in our analysis because 73.9% of subjects in our population had hypertension and 8.6% had heart failure. Our approach of matching measurable comorbid risks to establish the study cohort resulted in a similar distribution of demographic characteristics and cardiovascular comorbidities. There was no significant difference in the proportions of diuretic and beta-blocker use among the control group and the statin group (13.1% vs. 13.0%, $p = 0.795$ [diuretics]; 34.5% vs. 34.3%, $p = 0.693$ [beta-blockers]). Statins, diuretics, and beta-blockers were associated with an increase in risk of incident diabetes; hazard ratios (95% confidence intervals) were

1.15 (1.08 to 1.22), 1.53 (1.42 to 1.64), and 1.40 (1.33 to 1.48), respectively. In the multivariate model adjusted for age, sex, comorbid risk, and concomitant diuretics and beta-blockers, statin therapy was independently associated with the risk of diabetes occurrence (hazard ratio: 1.13 [95% confidence interval: 1.07 to 1.20], $p < 0.001$).

Statin therapy has been associated with excessive occurrence of diabetes in subjects with unfavorable metabolic profiles (4,5). Beyond that, it is particularly important to investigate whether the risk would be further amplified by the concomitant treatment targeting those factors to decide the treatment matrix for future patients.

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Slimming the Heart With Bariatric Surgery

We read with interest the paper by Gaborit et al. (1) describing the effects of bariatric surgery on epicardial fat and myocardial triglyceride content (MTGC). One of the authors' main conclusions is that a reduction in epicardial fat may be partially responsible for the decrease in cardiac mortality observed after successful weight-loss surgery because ectopic cardiac fat releases inflammatory mediators and free fatty acids into the vasculature (1). The study also demonstrates a decrease in systemic insulin resistance and improvement in diastolic function after bariatric surgery. We have made similar observations (2–4) and wish to offer a somewhat different interpretation, which should complement the authors' well-designed study. In patients with clinically severe obesity and insulin resistance, we observed a negative association between the plasma levels of long-chain free fatty acids and diastolic function and suggest that excess free fatty acids exert lipotoxic effects on the heart, leading to impairment in intracellular calcium cycling and cardiac function (2). Thus, one may reasonably conclude that the improvement in cardiac function after bariatric surgery is directly related to a decrease in lipotoxicity. However, no considerable change in MTGC was appreciated in the authors' study through the use of magnetic resonance spectroscopy despite a statistically significant decrease in epicardial fat and serum triglyceride levels. One plausible explanation involves the modality used in the measurement of MTGC. The practical method used to determine MTGC is a conventional technique known as voxel positioning in the ventricular septum to avoid contamination from epicardial fat and lessen the degree of artifact from cardiac motion. Nonetheless, the distribution of triglycerides in the human heart is heterogeneous in nature; thus, the conventional approach does not correlate well with overall cardiac steatosis (5).

After successful bariatric surgery, our studies also show a remarkable decrease in increased plasma free fatty acid levels, as well as improved derangements in muscle metabolism and cardiac function (3). Moreover, even as other hallmarks of obesity, such as insulin resistance, free fatty acid levels, body composition, and body mass index, have a tendency to plateau postoperatively, the benefits of successful weight-loss surgery on left ventricular mass are sustained and show a linear decrease over a 2-year period (4).

In short, our earlier work adds to the authors' remarkable study on the effects of weight loss after bariatric surgery on cardiac function. We propose that by targeting the source of excess energy, weight-loss surgery reduces left ventricular mass and improves overall cardiac function by limiting the substrate supply to a metabolically overloaded heart (6). The decrease in epicardial fat volume after weight loss likely plays a key role in decreasing fatty acid fuel to the heart, further reducing lipotoxicity. There is much more to be gained from this fascinating area of research.

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