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INVITED COMMENTARY

Statins, Glycemia, and Diabetes Mellitus: Another Point of View

Tomáš Štulc · Richard Češka

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Abstract Glycemic effects of statins have recently become a topic of heated debate. On closer inspection, however, the prevailing opinion regarding this issue may prove to be unsubstantiated. We suggest that the harmful effect of statin-induced diabetes is likely overestimated, and the consequences of the glycemic effects of statins may, theoretically, apply to a greater number of patients beyond just those with statin-induced diabetes. Most notably, though, careful consideration of the issue suggests, albeit surprisingly, that the clinical implications of the glycemic effects of statins may actually be rather limited.

Keywords Statins · Glycemia · Diabetes mellitus · Diabetogenic · Cardiovascular risk

Statins decrease cardiovascular risk, and cholesterol lowering with statins has become a cornerstone of cardiovascular disease prevention for a wide range of patients. However, this optimistic scenario has been disrupted by recent findings indicating that statin use may be associated with an increased risk of new-onset diabetes [1, 2]. Given that diabetes is a strong risk factor for cardiovascular disease, the ensuing heated debate regarding the possible adverse consequences of this newly discovered metabolic side effect of statins has not been surprising.

Thus far, the discussion has been concentrated on the magnitude of the diabetogenic effect of statins and possible adverse effects associated with cases of newly diagnosed diabetes. It is clear that patients with predisposing factors, such as insulin resistance or borderline glycemia, are most likely to develop diabetes following statin treatment and are, therefore, seemingly highest risk for adverse consequences resulting from the diabetogenic effect of statins. In recognition of this potential problem, two consensus statements have recently been published, providing guidance for the use of statins in people at risk of developing diabetes [3, 4], and the US FDA has added information concerning the "effect of statins on incident diabetes and increases in HbA_{1C} and/or fasting plasma glucose" to statin safety labels [5].

However, while this prevailing approach may appear intuitive, it could be misleading in a couple of ways: (1) the harmful effect of statin-induced diabetes is likely overestimated, and (2) the consequences of the glycemic effect of statins may apply to a greater number of patients beyond just those with statin-induced diabetes, which could by itself refocus the current debate. Regardless, the important question remains of how all of this translates into clinically meaningful benefits and risks relative to statin treatment. Here again, the issue is more complicated than it may appear, but cautious consideration of all aspects suggests, albeit surprisingly, that the clinical implications of the glycemic effects of statins may actually be rather limited.

Statin-Induced Diabetes and Cardiovascular Risk: the Need for Reappraisal

The current debate was first triggered when the JUPITER trial reported that rosuvastatin (20 mg/daily) increased the incidence of new-onset diabetes by 26 % [1]. Since that time, several additional studies and meta-analyses have confirmed this finding, demonstrating a 9 % increase in the overall risk of developing diabetes [2]. In terms of absolute risk, approximately 0.5 % of participants developed diabetes as a result of statin use in clinical trials, which equates to one extra case of diabetes per 1000 patient-years of statin therapy. The

T. Štulc (✉) · R. Češka
3rd Department of Internal Medicine, 1st Faculty of Medicine, Charles University, U Nemocnice 1, Praha 2 / Prague CZ 128 21, Czech Republic
e-mail: TSTULC@LF1.CUNI.CZ

diabetogenic effect of statins appears to be dose-related [6], and there is no clear evidence of differences between various statins.

Diabetes is associated with a two- to fourfold increase in cardiovascular risk, which raises natural concerns that the diabetogenic action of statins may be associated with adverse cardiovascular effects. Given the low absolute risk of statin-induced diabetes, the overall comparison yields a favorable risk-benefit ratio of nine cardiovascular events avoided per one new case of statin-induced diabetes [2]. This ratio may seemingly reverse in patients who actually develop diabetes and, assuming that statins reduce cardiovascular risk by one third, while statin-induced diabetes increases cardiovascular risk twofold, then the net outcome would be that of harm. Many physicians intuitively adopt this notion and are reluctant to administer statins to patients at greatest risk for developing diabetes. This approach, however, stems from a misinterpretation of data.

In fact, the conclusion that statin-induced diabetes is associated with a several-fold increase in cardiovascular risk is a direct consequence of inappropriately extrapolated epidemiological data obtained from patients with a well-established history of diabetes. Such results have limited application in patients with recent-onset diabetes and mild hyperglycemia. In line with this, recent research has demonstrated that the level of cardiovascular risk depends upon the duration of diabetes [7]. The most appropriate view of this problem would appear to be that, at the time of diagnosis, the degree of cardiovascular risk in patients with diabetes is equal to that of non-diabetic persons, and only gradually leads to a twofold increased risk after a duration of many years [8].

With regard to statin-induced diabetes, there is no reason to assume that a given individual's cardiovascular risk increases several-fold within a few months solely because of mildly increased glycemia, for example, from 6.9 to 7.2 mmol/l. Similarly, there is no reason to believe that exceeding an arbitrary diagnostic threshold confers any additional risk. The diabetogenic effect of statins should therefore not cause any greater concern in patients at risk of diabetes than it would in other patients. This consideration is of great practical importance. Currently, many clinicians believe that the risks of statins outweigh the benefits in patients at highest risk of developing diabetes. However, these same patients are also at high risk of cardiovascular events, and limiting the use of statins in this high-risk patient group, due to the abovementioned misinterpretation, could have profound and detrimental effects.

Statins and Glycemia: More Than Just Diabetes

Statin use is associated with a mild increase in glycemia. As such, statins may cause some patients with borderline glucose levels to exceed the diagnostic threshold and become diabetics. The ongoing debate has thus far been limited to the problem of statin-induced diabetes. Nevertheless, a statin-induced increase in glycemia may have adverse vascular effects in a significantly greater number of other patients, ranging from those with normal glucose levels to patients with established diabetes. It would therefore seem obvious that the problem may be broader than currently perceived, and the association between a statin-induced increase in glucose and cardiovascular risk deserves exploration.

Surprisingly, in comparison to an abundance of evidence for an increased risk of diabetes, there is a paucity of data regarding the influence of statins on glycemic control, especially in patients without diabetes [1, 9, 10]. Statins are probably associated with a mild 0.1–0.3 % increase in HbA_{1C}, which could be more pronounced in patients with diabetes [11–13]. The evidence for this effect is weak, but in support of this, it should be noted that an increased risk of diabetes after statin use could not be caused by anything other than an increase in blood glucose. Obviously, additional data on the issue would be quite helpful, and perhaps, some could be retrieved from earlier phase II and III studies of the lipid-lowering potency of statins.

The relationship between cardiovascular risk and glycemic control has been established by epidemiological studies. The risk starts to rise at glycemia of about 5 mmol/l; the relationship is probably nonlinear, rising with increasing glucose levels [14]. When considering HbA_{1C}, the increase in cardiovascular risk is approximately 20 % per 1 % higher HbA_{1C}, which is similar for individuals with and without diabetes [15, 16]. Based on this data, it can be estimated that a 0.1–0.3 % increase in HbA_{1C} due to statin therapy might increase cardiovascular risk by 2–6 % in a large number of patients with fasting glycemia in the high-normal to diabetic range.

Glycemic Effects of Statins: Worrisome Issue… or Not?

Closer examination of the glycemic effect of statins provides a perspective that is considerably different from the prevailing view. The cardiovascular consequences of this effect are likely less pronounced than generally believed, but may apply to a significantly greater number of patients, and the current focus on patients with statin-induced diabetes may be misleading. However, the question remains of how to fit all of this into the overall context of the cardiovascular effects of statins.

Simply subtracting the risks from the benefits would appear to be the most appropriate approach. A meta-analysis of statin trials demonstrated a 21 % decrease in cardiovascular risk per 1 mmol/l reduction of LDL cholesterol [17], which corresponds to a risk reduction of ~35 % or even greater with high doses of modern statins. This effect is consistent across patient subgroups, including diabetics when compared to non-

diabetics. If we weigh the estimated increase in cardiovascular risk due to glycemic effect of statins against this proven benefit, we should seemingly subtract 2–6 % from the positive results of statin trials. However, we suggest that even this last assumption may not apply and propose another manner in which to put the glycemic effect of statins into context.

Statins reduce cholesterol levels. However, they also influence the vascular system in many other ways—metabolic and others, known and unknown, and impaired glycemic control is just one of them. These factors, both beneficial and harmful, act together on the vascular system, which translates into the overall effect of statins on cardiovascular events. The results of statin trials have therefore already integrated all of these factors, including the glycemic effect. A decrease in cardiovascular risk, as observed in these trials, was achieved with statins "as they are," and this included all of their positive and negative effects. Therefore, it makes little sense to add or subtract anything on behalf of any particular one of them.

More practically, the estimated increase in cardiovascular risk due to the glycemic effect of statins has no implications for clinical practice. It is only an abstract estimate, not an actual risk; therefore, it probably should not influence physicians when they are considering the use of statins in their patients. Of course, the glycemic effects of statins remain an interesting area of research and the magnitude of their effect, the mechanisms behind them, and possible differences between specific statins (if any) are worth elucidating. For the moment, however, practicing physicians can probably forget about them altogether.

Compliance with Ethics Guidelines

Conflict of Interest Tomáš Štulc and Richard Češka declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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