Editorial

Statins and risk of diabetes mellitus

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Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which reduces HMG-CoA to mevalonate, the precursor of cholesterol via squalene. Inhibition of HMG-CoA reductase results in a decrease in cholesterol production.

Since 1987, when the United States Federal Drug Administration (FDA) approved lovastatin for clinical use,[1] statins have been widely used for secondary prevention of cardiovascular disease, particularly coronary heart disease (CHD), which is associated with high levels of low-density lipoprotein (LDL) cholesterol. Statins are also used in type 2 diabetes mellitus, since this carries a high risk of CHD.

Statins have several adverse effects, to which must now be added new onset diabetes. In 2012 the FDA issued a warning about the risk of newly developed diabetes mellitus in older persons, such that statin labels now include information on glycemic effects, including diabetes and increases in hemoglobin A1c or fasting plasma glucose.[2]

According to the results of a recent meta-analysis involving 13,966 40+-year patients newly treated with statins between 1 January 1977 and 31 March 2011, a moderate but significant increase was found in the risk of new onset diabetes within the first two years of using regular higher potency statins (rosuvastatin >10 mg, atorvastatin >20 mg, and simvastatin >40 mg), compared with lower potency drugs. Therefore these investigators caution clinicians regarding the use of higher potency statins in secondary prevention of cardiovascular disease.[2]

The use of a new drug carries a "built-in time-bomb", because nothing is known about its side effects, except for those revealed by animal tests and limited clinical trials. Even a multicenter clinical trial cannot be expected to reveal all possible adverse reactions associated with a new drug. As an illustration, in patients without diabetes mellitus, more than 345 000 cases were needed to detect an increase in fasting blood glucose of 3 mg/dL as a result of statin use.[3]

Here is a verbatim quote from Shah and Goldfine: "For any prescription drug, the potential benefits to health must be balanced against potential risks. Understanding these potential risks can help physicians and patients make informed decisions on whether to use a medication." Since the risk of statin-induced diabetes mellitus is important and unknown in the population of persons at lower risk of heart disease, it is considered prudent not to prescribe statins, except when diet and exercise cannot achieve LDL goals.[3]

The mechanism by which statins induce diabetes in older persons has been recently uncovered. A Canadian research team has shown that statins increase macrophage IL-1β secretion, ndicating activation of the nucleotide-binding and oligomerization domain (NOD)-like receptor pyrin domain 3 (NLRP3) inflammasome (caspase-1 inflammasome), which promotes insulin resistance, a precursor of type 2 diabetes. These investigators are of the opinion that the risk of statin-induced insulin

resistance may be reduced by inhibiting the NLRP3/caspase-1 inflammasome, particularly in obese, hyperlipidemic patients who are often at risk for developing diabetes, but have to use statins.[4]

In conclusion, although the risk of new diabetes mellitus with statin therapy may be considered to be minimal, the use of statins should only be prescribed by physicians for patients at risk for cardiovascular disease. However, when these patients are also at risk for diabetes mellitus, their blood glucose level should be monitored.[3] On the other hand, since statins may trigger new onset diabetes, presumably in predisposed persons, and since diabetes carries a risk of cardiovascular disease, even statins with the least side effects should not be used routinely for primary prevention, least of all as over-the-counter drugs. *Primum non nocere.*

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