Cardiovasc Drugs Ther (2014) 28:393–394
DOI 10.1007/s10557-014-6551-8

EDITORIAL

Abrogating the Induction of Type 2 Diabetes Mellitus Secondary to Statin Therapy

Editorial to: "PTEN Upregulation May Explain the Development of Insulin Resistance and Type 2 Diabetes with High Dose Statins" by Y. Birnbaum et al.

Sarah M. Planchon

Published online: 3 September 2014

The Western-pattern/Western-style diet, often termed the meat-sweet diet, consists of large amounts of animal products, salty snacks, fried foods, and refined carbohydrates, while containing low amounts of whole fruits, vegetables, and whole grains [1]. It has been noted, for over a half-century, that the long-term consumption of Western-style diet has a strong negative impact on individual health. A 1960s study that examined diet variations across global regions with the incidence of disease rates demonstrated that the Western-pattern diet dramatically increased the incidence of cardiovascular disease (CVD) when compared to individuals consuming Mediterranean- or Eastern-pattern diets. These diets are higher in olive oils, plant-based foods and lower in consumption of red meats and processed foods [2]. As the Western-influence starts impacting dietary consumption in different regions of the world we are seeing a global increase in associated health problems, especially CVD [3, 4].

CVD has consistently remained the leading cause of death in the US population since 1980 [5]. One major risk factor for the development of CVD is high serum cholesterol levels. The percentage of the adult US population with high cholesterol reached 25 % between 1999 and 2002 and surpassed 50 % in men over 65 and women over 55 by 2009–2012 [6]. The use of cholesterol-lowering agents has been demonstrated to decrease the incidence of heart disease in a variety of clinical studies [7]. One class of cholesterol-lowering medications commonly prescribed is the Statins, the first of which, lovastatin, was approved by the FDA in 1987. Statins are a class of drugs which reduce serum low-density lipoprotein (LDL)-cholesterol levels by inhibiting 3-hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase [8]. Given numerous clinical studies showing the ability of statins to significantly reduce cardiovascular events, they are often prescribed as a preventative agent for CVD [7]. The introduction of statins as a therapeutic has had a significantly positive effect on the reduction of heart-disease-related deaths and the associated health care costs [9, 10].

The data supporting the beneficial effects of statin has resulted in a tremendous increase in their use in clinical practice. From 1988 to 1994, cholesterol-lowering agents were used in 1.6 and 5.9 % of individuals ages 18–64 and over 65, respectively [11]. Those levels had increased dramatically by 2007–2010 with 10.7 % of individuals between 18–64 and 46.7 % over 65 reporting their use. This represents a 6–8 fold increase in just over 20 years. As with most pharmaceutical agents, the pleiotropic effects of statins may result in deleterious side effects occurring with the beneficial aspects of therapy. One side effect observed with long-term statin treatment has been an increase in the incidence of Type-2 Diabetes Mellitus (T2DM) in the statin users, an effect frequent enough to elicit the introduction of a FDA-mandated warning label on statin products in 2012 [12]. While several studies have linked statin use to an increase in T2DM, the benefits of reduced CVD due to statin-therapy may outweigh the risks for most individuals [13]. Nevertheless, understanding the mechanism underlying this phenomenon could lead to the development of interventions to abrogate the incidence of statin-induced T2DM.

The results presented in the article by Birnbaum et al. significantly move forward the understanding of the mechanism(s) associated with statin-induced T2DM while also suggesting a potential remedy for this problem [14]. This group demonstrates that in mice fed a Western-style diet, the addition

S. M. Planchon (✉)
Cleveland Clinic, Mellen Center, 9500 Euclid Avenue, U-10, Cleveland, OH 44195, USA
e-mail: planchs@ccf.org

of statin treatment increases PTEN protein levels in skeletal muscle, fasting serum insulin, and insulin resistance, and induces glucose tolerance test failure, all strong indicators of the induction of T2DM. In mice that have low levels of PTEN protein, through conditional knock down, the changes in the indicators of T2DM were significantly reduced, although not completely abrogated. To investigate the effect of decreasing PTEN protein levels through pharmaceutical intervention, the authors treated the mice with Cilostazol (CIL), a phosphodiesterase-3 inhibitor, which decreases PTEN protein levels through protein kinase A activation. CIL, trade name Pletal, is an FDA approved medication used to treat the symptoms associated with intermittent claudication. The introduction of CIL decreased the deleterious effects of statin treatment on insulin levels and glucose tolerance test results, while not affecting the beneficial reduction of serum triglyceride levels elicited by the statins. These results indicate that concomitant treatment with statins and CIL, or a similar agent, may abrogate the increased incidence of T2DM which has been observed to result from long term statin treatment alone.

The results presented by Birnbaum et al. provide compelling evidence which should be followed up with further studies to determine whether these murine results will translate to the human system. The group which is likely to be impacted the most by these results is individuals at risk for CVD who also have a strong family history of T2DM. In studies examining the potential relationship between statin usage and the development of T2DM, the increased risk appears to be greatest in individuals with a family history of diabetes or who have risk factors indicating that they are at risk for developing T2DM [15]. Pairing a medication such as CIL with statins has the potential to significantly reduce the incidence of their development of that T2DM secondary to statin therapy while not abrogating the beneficial effects. Further elucidation of the mechanism identified by the Birnbaum group, may uncover additional therapeutic targets which may be more specific or effective than CIL. Future studies will provide an important step towards the development of a therapeutic regimen which has the potential to become a common partner to statin treatment in people with a strong family history or who present with risk factors associated with DM.

References

1. Hu FB. Globalization of food patterns and cardiovascular disease risk. Circulation. 2008;118:1913–4.
2. Willett WC. Diet and health: what should we eat? Science. 1994;264: 532–7.
3. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9·1 million participants. Lancet. 2011;377:557–67.
4. Farzadfar F, Finucane MM, Danaei G, Pelizzari PM, Cowan MJ, Paciorek CJ, et al. National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3·0 million participants. Lancet. 2011;377: 578–86.
5. CDC NCfHS. Health, United States, 2013: With Special Feature on Prescription Drugs. Table 22. Leading causes of death and numbers of deaths, by sex, race, and Hispanic origin: United States, 1980 and 2010 Hyattsville, MD2014. p. 1–498.
6. CDC NCfHS. Health, United States, 2013: With Special Feature on Prescription Drugs. Table 66. Cholesterol among adults aged 20 and over, by selected characteristics: United States, selected years 1988–1994 through 2009–2012 Hyattsville, MD2013. p. 1–498.
7. Lim SY. Role of statins in coronary artery disease. Chonnam Med J. 2013;49(1):1–6.
8. Endo A. Chemistry, biochemistry, and pharmacology of HMG-CoA reductase inhibitors. Klin Wochenschr. 1988;66:421–7.
9. Law MRWNJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. Brit Med J. 2003;326:1–7.
10. Grabowski DC, Lakdawalla DN, Goldman DP, Eber M, Liu LZ, Abdelgawad T, et al. The large social value resulting from use of statins warrants steps to improve adherence and broaden treatment. Health Aff. 2012;31:2276–85.
11. CDC NCfHS. Health, United States, 2013: With Special Feature on Prescription Drugs. Hyattsville, MD2014. p. 1–498.
12. Rocco MB. Statins and diabetes risk: fact, fiction, and clinical implications. Cleve Clinic J Med. 2012;79:883–93.
13. Shah RV, Goldfine AB. Statins and risk of new-onset diabetes mellitus. Circulation. 2012;126:e282–4.
14. Birnbaum Y, Nanhwan M, Perez-Polo JR, Ye Y, Bajaj M. PTEN Upregulation May Explain the Development of Insulin Resistance and Type 2 Diabetes with High Dose Statins. Cardiovasc Drugs Ther 2014;28: this issue.
15. Desai CS, Martin SS, Blumenthal RS. Non-cardiovascular effects associated with statins. BMJ Clin Res Ed. 2014;349:g3743.