



REVIEW ARTICLE

DIABETOGENIC EFFECT OF STATINS: MOLECULAR MECHANISMS

Nuray Ari

Department of Pharmacology, Faculty of Pharmacy, Ankara University, Ankara, Turkey.

Article Info:



Article History:

Received: 4 April 2021

Reviewed: 9 May 2021

Accepted: 13 June 2021

Published: 15 July 2021

Cite this article:

Ari N. Diabetogenic effect of statins: molecular mechanisms. Universal Journal of Pharmaceutical Research 2021; 6(3):55-58.
<https://doi.org/10.22270/ujpr.v6i3.607>

*Address for Correspondence:

Dr. Nuray ARI, Department of Pharmacology, Faculty of Pharmacy, Ankara University, Ankara Turkey., Tel- +90 05382159596.
E-mail: ari@ankara.edu.tr

Abstract

Statins, HMG CoA inhibitors, are potent hypolipidemic drugs. They are used for the prevention of cardiovascular diseases and some of the most commonly used drugs worldwide. Long term statin therapy can cause a modest increase in new-onset diabetes risk, and there is great interest in the mechanisms for this adverse effect. Main proposed mechanisms are increased insulin resistance and some defects in insulin secretion. Many factors can affect the risk including pre-existing diabetic risk, older age and potency of statin. But clearly, the benefits of these drugs in preventing cardiovascular disease outweigh the potential risk of diabetes. The aim of this review is to give underlying pathomechanisms and clinical relevance of diabetogenic effect of statins.

Keywords: adverse effect, diabetogenicity, mechanism, risk, statins.

INTRODUCTION

Cardiovascular disease (CVD) is an important cause of mortality, and hypercholesterolemia is the major CVD risk factor¹. Statins (HMGCoA) reductase inhibitors were first approved by the FDA in 1987 and they are still the first-choice drugs for their potent hypocholesterolemic properties. Since then statins have become the most prescribed drugs worldwide^{2,3}. They have also pleiotropic effects facilitating cardioprotective properties including benefits on endothelial function, decreasing inflammation and atherosclerotic plaque stabilization⁴⁻⁸. Other pleiotropic mechanisms of statins are improvement of bone diseases and central nervous system diseases⁷. On the other hand, despite well-known clinical benefit of statins on CV prevention, their possible adverse effects cannot be disregarded⁹⁻¹¹. In addition increased in liver enzymes and development of myopathy¹, clinical trials show an increase in new-onset diabetes mellitus (NODM) by statin therapy, especially in the presence of diabetic risk factors, such as insulin resistance with impaired glucose control, obesity, metabolic syndrome, Asian ancestry, woman, elderly people, lower LDL (low density lipoprotein)-C levels, or large LDL-C reduction^{10,12}. Data suggest a 10-22% increased risk of NODM comparing to nonusers. The risk increases with intensive treatment^{13,14}. While this is a drug class effect,

recent data suggest that pravastatin and pitavastatin have no or week effects on glucose homeostasis¹³.

Type 2 diabetes mellitus (T2DM) is a major risk factor for CV outcomes¹⁵. Statins are recommended and prescribed to diabetic patients to prevent CV complications¹⁶. The consensus of their benefits on CV risk reduction is more important than their adverse diabetogenic effect. Currently, on the market there are seven statin drugs: Atorvastatin, pitavastatin, simvastatin, fluvastatin, rosuvastatin, lovastatin and pravastatin. When they are classified, pravastatin and rosuvastatin are hydrophilic; atorvastatin, fluvastatin, lovastatin, pitavastatin and simvastatin are lipophilic statins. NODM risk was observed first in the JUPITER trial in 2008^{17,18}. Then greater attention has been given to this issue, and by the time the risk has been supported by many trials¹⁹⁻²³. In JUPITER study the risk was found to be increased with high statin doses and there were no new NODM cases among patients with no diabetes risk factors at baseline²⁴. After the FDA evaluation, in March 2012, NODM risk warning was inserted to all statin packages²⁵. The risk is limited to people with diabetes risk factors²⁶⁻²⁸. According to data, the risk of diabetes-induced complications, such as microvascular complications are not increased by statins.

The risk of NODM by different statins are arguable. Dormuth *et al.*,²⁹ reported that higher potency statins can cause moderate risk increase compared with lower

potency statins. It appears the risk is in parallel with their HMGCoA reductase inhibition capacity. It was suggested that lipophilic statins are more diabetogenic than the hydrophilic ones^{9,29,31}. But recent clinical data have indicated that there is no difference between them regarding the risk of NODM³². Thus we need more data to determine potential differences among statins. Recent evidence suggests that pravastatin has weak diabetogenic effect³³. In a new cohort study, with moderate-intensity therapy, rosuvastatin was found to be less diabetogenic than pitavastatin³².

Molecular mechanisms

Diabetogenic effect of statins reflect inhibition of HMGCoA reductase. Statins decrease synthesis of mevalonate products causing to impaired pancreatic β -cell function, but the exact mechanism(s) of diabetogenesis are still unclear¹³. It seems some defects on insulin release mechanisms are the major contributors to statin-induced diabetes^{1,34,35}. Several molecular mechanisms have been argued in the literature: Statins can disturb insulin secretion affecting calcium channels in the β -cells; They downregulate GLUT4 (glucose transporter) resulting hyperglycemia; they decrease some downstream products, such as coenzyme Q10, farnesyl and geranylgeranyl pyrophosphates. Depletion of these important products disturbs intracellular signalling. Other mechanisms are inhibition of adipocyte differentiation, modulation of leptin and adiponectin. Genetic links and epigenetic regulations via differential expression of specific micro RNAs have also roles^{1,14,32,36}.

Pancreatic β -Cells and L-type Ca^{2+} channels

In the pancreatic β -cells, voltage gated Ca^{2+} (CaV ; L-type) channels play an important role in insulin release. Dysregulation of these channels impair glucose homeostasis⁷. It is suggested that long-term cholesterol synthesis may disrupt the channel function together with insulin vesicle mobilization³⁷. There is no clear mechanism proposed for this phenomena, however these effects may be due to conformational changes of the membrane and channel subunits^{1,14,23}. On the other hand, statins have beneficial pleiotropic effects on the CV system by activating ATP-dependent potassium channels in the CV tissue. However, opening of these channels in the pancreatic β -cells causes inhibition of insulin secretion and this may lead to NODM³⁸.

Glucose transporters and caveolin

Statins can inhibit both calcium channel and glucose transporter 2 (GLUT2, predominant isoform in β -cells) protein expressions resulting disruption of insulin synthesis and release. GLUT2, K_{ATP} and CaV channel-mediated signalling chain is an important for insulin biosynthesis and release. On the other hand, HMG CoA reductase inhibition disrupts synthesis of isoprenoids, then the expression of GLUT4 is inhibited and causes impairment of glucose uptake. Caveolin-1 is an important protein which is localized in caveolae-rich regions where GLUT4 is translocated by insulin^{1,12}. Khan *et al.*,³⁹ observed that simvastatin treatment in mice, caveolar vesicle docking is inhibited. Takaguri *et al.*,⁴⁰ also reported an alteration of GLUT4 translocation and reduced level after atorvastatin, but not pravastatin. Shortly, statins may

disrupt translocation of GLUT4 in muscle, liver and adipose tissue, leading reduced glucose uptake, increased insulin resistance and hyperglycemia¹⁴.

Insulin Signalling

Statin treatment may disturb insulin transduction cascade and can lead to insulin resistance¹⁴. Statins may alters phosphorylation steps and small G proteins¹. RhoA and Rab4, small G proteins, have roles in the insulin signal cascade. Rab4 is a critical protein for glucose transport. It has been reported that GLUT4 expression was reduced because of decreased Rab4 function in adipocytes after atorvastatin⁴⁰.

Ubiquinone, adiponectin and leptin

Evidence indicate the role of ubiquinone (CoQ10), adiponectin and leptin on glucose metabolism. Statins may affect glucose homeostasis via CoQ10, adiponectin and leptin¹². CoQ10 have a role in the regulation of mitochondrial function, which is important for pancreatic β -cells. Statins may induce myopathy by reducing CoQ10 production, however it is not well known yet whether there is a link between risk of insulin resistance or increased risk of NOMD. In adipocytes CoQ10 can reverse the reduction of GLUT4 induced by simvastatin⁴¹. Experimental data indicate that CoQ10 improves pancreatic β -cell function, insulin sensitivity and mitochondrial function⁴².

Reduced adiponectin levels may associate with obesity, insulin resistance and diabetes. Some results indicate that adiponectin can decrease insulin resistance^{12,35}. Statin trials have been shown a decrease, increase, or no change in adiponectin levels³⁵. Hydrophilic statins have generally been shown to increase adiponectin levels. Pitavastatin in some studies, improves insulin sensitivity and it has consistently been shown to increase adiponectin levels^{12,35}. Leptin, satiety factor, has been shown to be decreased by atorvastatin, rosuvastatin and simvastatin, but not by pravastatin or pitavastatin, in clinical studies^{35,43}. Statins may increase food intake and weight gain in the long term. This may associate with decreases in leptin expression, but the results are still conflicting⁴³.

Inflammation

Inflammation can promote insulin resistance and/or diabetes⁴⁴. Statins generally exert anti-inflammatory effects mainly by their pleiotropic effects. Statin use reduces C-reactive protein and may decrease the risk of myocardial infarction¹². They also reduce many inflammatory events, such as changing cytokine profiles. They reduce tumor necrosis factor (TNF) and interleukin (IL)-6 (pro-inflammatory cytokines). But, conversly, they can increase IL-1 β (pro-inflammatory cytokine), by reducing prenylation of proteins. According to the "inflammatory hypothesis of statins" they exert pro-inflammatory effects in dysmetabolic states by activating of some inflammasomes leading IL-mediated insulin resistance. This concept requires more study³⁴.

Genetic link

HMG CoA reductase single nucleotide polymorphisms (SNPs) can lead a small increase in the risk of NODM^{33,35,45}. A study (Mendelian) showed this association between genetic variation in the HMG CoA reductase gene (rs17238484 and rs12916 alleles) and

increased risk of NODM by statin treatment^{12,33}. On the other hand, epigenetic changes can explain NODM risk such as, miRNA regulation, and DNA methylation (DNAm), particularly at genes for lipid or insulin regulation⁴⁶. A recent epigenome-wide association study has investigated the association between statin use and changes in DNAm at sites in CpGs genome and found an evidence on DNAm partially mediating statins' effects⁴⁶. Increased hepatic gluconeogenesis is an important mechanism for statin-induced NODM. However, the exact mechanism(s) is not clear. Aging is a strong risk factor for NODM and aging associated molecules may have roles on the development of NODM in statin use. In a recent study, simvastatin has been shown to induce miR-495 (a novel inhibitor of Sirt6) and down regulate Sirt6 expression in mice liver. Hence, this leads gluconeogenesis in the liver. Further, mRNA levels of Pck1, G6pc, and Ppargc1, as a gluconeogenesis genes, was found to increased in the liver of statin treated mice. Thus, it is suggested that Sirt6 activation may be a good strategy to prevent NODM⁴⁷.

CONCLUSIONS

After the JUPITER study, potential mechanisms involving on statin-induced NODM has been searched intensively. It seems a multiple mechanisms are involved in this adverse effect. Potentiating insulin resistance (increased hepatic gluconeogenesis, inhibition of GLUT4 translocation) or decreased insulin release (β -cell dysfunction) have been proposed as major mechanisms^{9,12,45}. There is also genetic link and intense research is going at the molecular level⁴⁸. Statins are associated with a modest increase in the risk (about one per thousand patient-years) and their benefits in preventing CVD outweigh the risk of NODM. It is important that before starting therapy the risk of NODM should be determined^{10,13}. Lifestyle changes and controlled diet are important to reduce the risk. If diabetes develops, it should be managed according to the guidelines^{13,16,35}. Statins are recommended diabetic patients since they benefit from therapy regarding to CV risk⁴⁹. It is not recommended to stop the statin therapy in patients with NOD since statins have important effect in reducing CV risk^{15,50}. On the other hand, statins may have fewer benefits in elderly people because of they have a short life expectancy and comorbidities. Thus, the benefits and disadvantages of statins should be evaluated carefully in elderly individuals⁴⁹.

ACKNOWLEDGEMENTS

Author extends her thanks and appreciation to the Ankara University, Ankara Turkey to provide necessary facilities for this work.

AUTHOR'S CONTRIBUTION

Ari N: Writing original draft, review, literature survey, editing, methodology, data curation.

DATA AVAILABILITY

Data will be made available on reasonable request.

CONFLICT OF INTEREST

None to declare.

REFERENCES

1. Brault M, Ray J, Gomez YH, Mantzoros CS, Daskalopoulou SS. Statin treatment and new-onset diabetes: a review of proposed mechanisms. *Metabolism* 2014; 63: 735–745. <https://doi.org/10.1016/j.metabol.2014.02.014>
2. Anyanwagu U, Idris I, Donnelly R. Drug-induced diabetes mellitus: Evidence for statins and other drugs affecting glucose metabolism. *Clin Pharmacol Ther* 2016; 99(4): 390–400. <https://doi.org/10.1002/cpt.274>
3. Ramkumar S, Raghunath A, Raghunath S. Statin therapy: Review of safety and potential side effects. *Acta Cardiol Sin* 2016; 32(6): 631–639. <https://doi.org/10.6515/acs20160611a>
4. Cumaoğlu A, Ozansoy G, Irat AM, Arıcıoğlu A, Karasu C, Ari N. Effect of long term, non cholesterol lowering dose of fluvastatin treatment on oxidative stress in brain and peripheral tissues of streptozotocin-diabetic rats. *Eur J Pharmacol* 2011; 654(1): 80–5. <https://doi.org/10.1016/j.ejphar.2010.11.035>
5. Davignon J. Beneficial cardiovascular pleiotropic effects of statins. *Circulation* 2004; 109(23 Suppl 1): III39–43
6. Kavalipati N, Shah J, Ramakrishan A, Vasawala H. Pleiotropic effects of statins. *Indian J Endocrinol Metab* 2015; 19(5): 554–62. <https://doi.org/10.4103/2230-8210.163106>
7. Muscogiuri G, Sarno G, Gastaldelli A, et al. The good and bad effects of statins on insulin sensitivity and secretion. *Endocr Res* 2014; 39(4): 137–43. <https://doi.org/10.3109/07435800.2014.952018>
8. Oesterle A, Laufs U, Liao JK. Pleiotropic effects of statins on the cardiovascular system. *Circ Res* 2017; 120(1): 229–243. <https://doi.org/10.1161/CIRCRESAHA.116.308537>
9. Núñez-Cortés JM, Amenós AC, Gimilio JFA, et al. Consensus on the statin of choice in patients with impaired glucose metabolism: Results of the DIANA Study. *Am J Cardiovasc Drugs* 2017; 17(2): 135–142. <https://doi.org/10.1007/s40256-016-0197-9>
10. Cybulska B, Kłosiewicz-Latoszek L. How do we know that statins are diabetogenic, and why? Is it an important issue in the clinical practice? *Kardiologia Pol* 2018; 76(8): 1217–1223. <https://doi.org/10.5603/KP.a2018.0150>
11. Pinal-Fernandez I, Casal-Dominguez M, Mammena AL. Statins: pros and cons. *Med Clin (Barc)* 2018; 150(10): 398–402. <https://doi.org/10.1016/j.medcli.2017.11.030>
12. Chan DC, Pang J, Watts GF. Pathogenesis and management of the diabetogenic effect of statins: a role for adiponectin and coenzyme Q10? *Curr Atheroscler Rep* 2015; 17(1): 472. <https://doi.org/10.1007/s11883-014-0472-7>
13. Carmena R, Betteridge DJ. Diabetogenic action of statins: Mechanisms. *Curr Atheroscler Rep* 2019; 21(6): 23. <https://doi.org/10.1007/s11883-019-0780-z>
14. Galicia-Garcia U, Jebari S, Larrea-Sebal A, et al. Statin treatment-induced development of Type 2 diabetes: From clinical evidence to mechanistic insights. *Int J Mol Sci* 2020; 21(13): 4725. <https://doi.org/10.3390/ijms21134725>
15. Ray K. Statin diabetogenicity: guidance for clinicians. *Cardiovasc Diabetol* 2013; 12(Suppl 1): S3.
16. Chogtu B, Magazine R, Bairy KL. Statin use and risk of diabetes mellitus. *World J Diabetes* 2015; 6(2): 352–7. <https://doi.org/10.4239/wjd.v6.i2.352>
17. Ridker PM. The JUPITER Trial. Results, controversies, and implications for prevention. *Circulation: Cardiovascular Quality and Outcomes*. 2009; (2):279–285.

- <https://doi.org/10.1161/CIRCOUTCOMES.109.868299>
18. Ridker PM, Danielson E, Fonseca FA, *et al.* Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008; 359(21):2195-207. <https://doi.org/10.1056/NEJMoa0807646>
 19. Benes LB, Bassi NS, Davidson MH. The risk of hepatotoxicity, new onset diabetes and rhabdomyolysis in the era of high-intensity statin therapy: Does statin type matter? *Progress in Cardiovasc Dis* 2016; 59:145-152. <https://doi.org/10.1016/j.pcad.2016.08.001>
 20. Culver AL, Ockene IS, Balasubramanian R, *et al.* Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. *Arch Intern Med* 2012; 172: 144-152 <https://doi.org/10.1001/archinternmed.2011.625>
 21. Sattar N, Taskinen MR. Statins are diabetogenic--myth or reality? *Atheroscler Suppl* 2012; 13(1):1-10. <https://doi.org/10.1016/j.atherosclerosis.2012.06.001>
 22. Sattar N, Preiss D, Murray HM, *et al.* Statins and risk of incident diabetes: a collaborative metaanalysis of randomised statin trials. *Lancet* 2010; 375:735-42. [https://doi.org/10.1016/S0140-6736\(09\)61965-6](https://doi.org/10.1016/S0140-6736(09)61965-6)
 23. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-associated side effects. *J Am Coll Cardiol* 2016; 24: 67(20):2395-2410. <https://doi.org/10.1016/j.jacc.2016.02.071>
 24. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *Lancet* 2012; 380:565-71. [https://doi.org/10.1016/S0140-6736\(12\)61190-8](https://doi.org/10.1016/S0140-6736(12)61190-8)
 25. U.S. Food and Drug Administration. FDA drug safety communication: important safety label changes to cholesterol-lowering statin drugs. FDA Drug Safety Communication.
 26. Bell DSH, Di Nicolantonio JJ, O'Keefe JH. Is statin-induced diabetes clinically relevant? A comprehensive review of the literature. *Diabetes, Obesity and Metabolism* 2014; 16:689-694. <https://doi.org/10.1111/dom.12254>
 27. Chrysant SG. New onset diabetes mellitus induced by statins: Current evidence. *Postgraduate Medicine* 2017; 129(4): 430-435. <https://doi.org/10.1080/00325481.2017.1292107>
 28. Wallemacq C. Statins and new-onset diabetes: Benefit-risk balance. *Rev Med Suisse* 2019; 15 (659): 1454-1457.
 29. Dormuth CR, Fillion KB, Paterson JM, *et al.* Higher potency statins and the risk of new diabetes: Multicentre, observational study of administrative databases. *BMJ* 2014; 348:g3244. <https://doi.org/10.1136/bmj.g3244>
 30. Agouridis AP, Kostapanos MS, Elisaf MS. Statins and their increased risk of inducing diabetes. *Expert Opin Drug Saf* 2015; 14(12): 1835-44. <https://doi.org/10.1517/14740338.2015.1096343>
 31. Guertin JR, Rahme E, LeLorier J. Use of continuous exposure variables when examining dose-dependent pharmacological effects - Application to the association between exposure to higher statin doses and the incidence of diabetes. *J Popul Ther Clin Pharmacol* 2017; 24(1):5-15. <https://doi.org/10.22374/1710-6222.24.1.1>
 32. Liu WT, Lin C, Tsai MC, *et al.* Effects of pitavastatin, atorvastatin and rosuvastatin on the risk of new-onset diabetes mellitus: A single-center cohort study. *Biomedicine* 2020; 8:499. <https://doi.org/10.3390/biomedicine8110499>
 33. Laakso M, Kuusisto J. Diabetes secondary to treatment with statins. *Curr Diab Rep* 2017; 17(2):10. <https://doi.org/10.1007/s11892-017-0837-8>
 34. Ganda OP. Statin-induced diabetes: incidence, mechanisms, and implications. *F1000 Research* 2016; 5(F1000 Faculty Rev):1499. <https://doi.org/10.12688/f1000research.8629.1>
 35. Robinson JG. Statins and diabetes risk: how real is it and what are the mechanisms? *Curr Opin Lipidol*. 2015; 26(3):228-35. <https://doi.org/10.1097/MOL.0000000000000172>
 36. Paseban M, Butler AE, Sahebkar A. Mechanisms of statin-induced new-onset diabetes. *J Cell Physiol* 2019; 234: 12551-12561. <https://doi.org/10.1002/jcp.28123>
 37. Xia F, Xie L, Mihic A, *et al.* Inhibition of cholesterol biosynthesis impairs insulin secretion and voltage-gated calcium channel function in pancreatic beta-cells. *Endocrinol* 2008; 149: 5136-45. <https://doi.org/10.1210/en.2008-0161>
 38. Sehra D, Sehra S, Sehra ST. Cardiovascular pleiotropic effects of statins and new onset diabetes: is there a common link: do we need to evaluate the role of KATP channels? *Expert Opin Drug Saf* 2017; 7:823-831. <https://doi.org/10.1080/14740338.2017.1338269>
 39. Khan T, Hamilton MP, Mundy ID, Chua SC, Scherer PE. Impact of simvastatin on adipose tissue: Pleiotropic effects *in vivo*. *Endocrinol* 2009; 150: 5262-5272. <https://doi.org/10.1210/en.2009-0603>
 40. Takaguri A, Satoh K, Itagaki M, Tokumitsu Y, Ichihara K. Effects of atorvastatin and pravastatin on signal transduction related to glucose uptake in 3T3L1 adipocytes. *J Pharmacol Sci* 2008; 107(1):80-89. <https://doi.org/10.1254/jphs.jp0072403>
 41. Ganesan S, Ito MK. Coenzyme Q10 ameliorates the reduction in GLUT4 transporter expression induced by simvastatin in 3T3-L1 adipocytes. *Metab Syndr Relat Disord* 2013; 11:251-5. <https://doi.org/10.1089/met.2012.0177>
 42. Schroeder MM, Belloto Jr RJ, Hudson RA, McInerney MF. Effects of antioxidants coenzyme Q10 and lipoic acid on interleukin-1 β -mediated inhibition of glucose-stimulated insulin release from cultured mouse pancreatic islets. *Immunopharmacol Immunotoxicol* 2005; 27:109-22. <https://doi.org/10.1081/iph-51755>
 43. Singh P, Zhang Y, Sharma P, *et al.* Statins decrease leptin expression in human white adipocytes. *Physiol Rep* 2018; 6(2):e13566. <https://doi.org/10.14814/phy2.13566>
 44. Henriksbo BD, Schertzer JD. Is immunity a mechanism contributing to statin-induced diabetes? *Adipocyte* 2015; 4(4):232-8. <https://doi.org/10.1080/21623945.2015.1024394>
 45. Collins PD, Sattar N. Glycaemic effects of non-statin lipid-lowering therapies. *Curr Cardiol Rep* 2016; 18(12): 133. <https://doi.org/10.1007/s11886-016-0795-9>
 46. Ochoa-Rosales C, Portilla-Fernandez E, Nano J, *et al.* Epigenetic link between statin therapy and type 2 diabetes. *Diabetes Care* 2020; 43:875-884. <https://doi.org/10.2337/dc19-1828>
 47. Shi MY, Bang IH, Han CY, Lee DH, Park BH, Bae EJ. Statin suppresses sirtuin 6 through miR-495, increasing FoxO1-dependent hepatic gluconeogenesis. *Theranostics* 2020; 10(25):11416-11427. <https://doi.org/10.7150/thno.49770>
 48. Yandrapalli S, Malik A, Guber K, *et al.* Statins and the potential for higher diabetes mellitus risk. *Expert Rev Clin Pharmacol* 2019; 12(9):825-830. <https://doi.org/10.1080/17512433.2019.1659133>
 49. Horodinschi RN, Stanescu AMA, Bratu OG, *et al.* Treatment with statins in elderly patients. *Medicina (Kaunas, Lithuania)* 2019; 55(11):72. <https://doi.org/10.3390/medicina55110721>
 50. Betteridge DJ, Carmena R. The diabetogenic action of statins-mechanisms and clinical implications. *Nat Rev Endocrinol* 2016; 12(2):99-110. <https://doi.org/10.1038/nrendo.2015.194>