PCSK9 and carbohydrate metabolism: A double-edged sword

Theodosios D Filippatos, Sebastian Filippas-Ntekouan, Eleni Pappa, Thalia Panagiotopoulou, Vasilios Tsimihodimos, Moses S Elisaf

Department of Internal Medicine, School of Medicine, University of Ioannina, 45110 Ioannina, Greece

Author contributions: Filippatos TD wrote the manuscript; Filippas-Ntekouan S and Panagiotopoulou T searched the bibliography; Pappa E, Tsimihodimos V and Elisaf MS made appropriate comments and checked the final version of the manuscript.

Conflict-of-interest statement: This review was written independently. Professor Elisaf MS reports personal fees from ASTRA ZENECA, grants and personal fees from MSD, personal fees from PFIZER, ABBOTT, SANOFI, BOEHRINGER INGELHEIM, ELI LILLY, GSK. The authors have given talks and attended conferences sponsored by various pharmaceutical companies, including Bristol-Myers Squibb, Pfizer, Lilly, Abbott, Amgen, AstraZeneca, Novartis, Vianex, Teva and MSD.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Abstract

Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays a paramount role in the degradation of low-density lipoprotein (LDL) receptors (LDLR) on the hepatic cells surface and subsequently affects LDL particles catabolism and LDL cholesterol (LDL-c) levels. The anti-PCSK9 monoclonal antibodies lead to substantial decrease of LDL-c concentration. PCSK9 (which is also expressed in pancreatic delta-cells) can decrease LDLR and subsequently decrease cholesterol accumulation in pancreatic beta-cells, which impairs glucose metabolism and reduces insulin secretion. Thus, a possible adverse effect of PCSK9 inhibitors on carbohydrate metabolism may be expected by this mechanism, which has been supported by the mendelian studies results. On the other hand, clinical data have suggested a detrimental association of PCSK9 with glucose metabolism. So, the inhibition of PCSK9 may be seen as a double-edged sword regarding carbohydrate metabolism. Completed clinical trials have not shown a detrimental effect of PCSK9 inhibitors on diabetes risk, but their short-term duration does not allow definite conclusions.

Key words: Proprotein convertase subtilisin/kexin type 9; Diabetes; Carbohydrate metabolism; Low-density lipoprotein; Proprotein convertase subtilisin/kexin type 9 inhibitors

© The Author(s) 2017. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Proprotein convertase subtilisin/kexin type 9 (PCSK9) may play a beneficial role in carbohydrate metabolism because it can decrease low-density lipoprotein receptor and subsequently decrease cholesterol
accumulation in pancreatic beta-cells, which impairs glucose metabolism and reduces insulin secretion. In contrast, clinical data have suggested a detrimental association of PCSK9 with glucose metabolism. These conflicting mechanisms may lead to a neutral effect on carbohydrate variables and explain the results of short-term clinical trials with PCSK9 inhibitors, which have not shown an increased diabetes risk.

Filippatos TD, Filippas-Ntekouan S, Pappa E, Panagiotopoulou T, Tsimihodimos V, Elisaf MS. PCSK9 and carbohydrate metabolism: A double-edged sword. World J Diabetes 2017; 8(7): 311-316 Available from: URL: http://www.wjgnet.com/1948-9358/full/v8/i7/311.htm DOI: http://dx.doi.org/10.4239/wjd.v8.i7.311

INTRODUCTION

Statins can dose dependently increase the incidence of new-onset diabetes in patients mainly with underlying abnormalities of carbohydrate metabolism. This effect is at least partially an "on target" effect related to the statin-induced inhibition of 5-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. These observations have led ongoing research to focus on the possible association of newer hypolipidemic drugs with incident diabetes. Proprotein convertase subtilisin/kexin type 9 (PCSK9) has been identified as a key protein in lipid and lipoprotein metabolism, which plays a paramount role in the degradation of low-density lipoprotein (LDL) receptors (LDLR) on the hepatic cells surface and subsequently affects LDL particles catabolism and LDL cholesterol (LDL-c) levels (Figure 1). The anti-PCSK9 monoclonal antibodies bind circulating PCSK9, thus preventing PCSK9-induced degradation of LDLR. The administration of these drugs on top of conventional lipid lowering treatment substantially decreases LDL-c concentration by approximately 50% in various groups of high-risk patients, while the treatment is well tolerated. Even though significant differences in the incidence of most adverse events were not observed between PCSK9 inhibitors-treated and placebo-treated patients, an increased incidence of neurocognitive events was observed, which needs further evaluation.

It has been shown that PCSK9 can decrease LDLR and subsequently decrease cholesterol concentrations in pancreatic beta-cells; thus, it may beneficially affect beta cell function, since the accumulation of cholesterol in beta-cells impairs glucose metabolism, reduces insulin secretion and can be associated with a diabetic phenotype. Based on this concept, a crucial question emerges whether PCSK9 inhibitors can increase diabetes risk by inhibiting this beneficial effect (Table 1). This question is particularly relevant, because the results of genetic studies have shown contradictory results. Thus, even though no increased risk of diabetes or other changes in glucose homeostasis were found in individuals with PCSK9 loss-of-function variants, carriage of the loss-of-function PCSK9 p.R46L mutation was associated with insulin resistance and increased homeostasis model assessment-insulin resistance (HOMA-IR) index in those with apolipoprotein E4/E4 genotype. However, another study did not confirm these results and showed that the p.R46L mutation was not associated with markers of glucose homeostasis, while p.R46L carriers did not experience an increased risk of new-onset diabetes mellitus. Additionally, experimental data from animal models have also provided conflicting results. One study showed that PCSK9 deficiency does not alter insulin secretion and glucose tolerance in mice, while another study showed that PCSK9 deficient mice (PCSK9+/−) exhibit hyperglycemia, impaired glucose tolerance associated with hypoinsulinemia and pancreatic islet abnormalities (malformation, apoptosis and inflammation). Interestingly, PCSK9, whereas it is not expressed in α- and β-cells, is co-localized specifically with somatostatin in human pancreatic delta-cells, a finding which may be implicated in the previously mentioned results. These findings support the previously mentioned statement concerning the detrimental role of LDLR-associated cholesterol accumulation in pancreatic beta-cells on insulin secretion and carbohydrate homeostasis. Accordingly, three recently published genetic studies showed that PCSK9 variants-associated genetically predicted reduction of LDL-c was related with an increased risk for type 2 diabetes (Table 2). Overall, these observations point to a possible adverse effect of PCSK9 inhibitors on carbohydrate metabolism.

On the other hand, available clinical data have suggested a detrimental association of PCSK9 with glucose metabolism (Table 1). Thus, in children a significant correlation of PCSK9 levels with glucose, insulin, and HOMA-IR levels was observed, while an increase in PCSK9 levels by 1%-2% was associated with 10% higher fasting insulin levels in both sexes. It has been reported that hepatic PCSK9 expression is regulated by insulin via the sterol regulatory element-binding protein I-C (SREBP-1C); thus PCSK9 is secreted in an insulin-dependent fashion, underlying an association between PCSK9 and carbohydrate metabolism. Additionally, in abdominally obese men PCSK9 levels were associated with dyslipidemia (with small dense LDL particles and increased apolipoprotein CIII levels) but also with insulin resistance (increased HOMA-IR).

The results of the clinical trials, however, do not support any significant effect of these drugs on carbohydrate metabolism (Table 1). In fact, a recently published analysis of 10 phase 3 clinical trials with alirocumab showed that the hazard ratio for diabetes-related treatment adverse effects among 3448 non-diabetic individuals was 0.64 (95%CI: 0.36-1.14) in alirocumab-treated patients vs placebo-treated and 0.55 (95%CI: 0.22-1.41) vs ezetimibe-treated patients. In prediabetic individuals, the hazard rate
The ratio associated with transition of prediabetes to new-onset diabetes for alirocumab was 0.90 (95% CI: 0.63-1.29) vs placebo and 1.10 (95% CI: 0.57-2.12) vs ezetimibe. Furthermore, no change in plasma glucose and glycated hemoglobin (HbA1c) levels was observed between treated groups in non-diabetic individuals of these results\(^2\). Additionally, a post hoc analysis of the DESCARTES showed that the administration of evolocumab (420 mg monthly) was not associated with any changes in parameters of carbohydrate metabolism in patients with pre-existing dysglycemia or metabolic syndrome\(^3\). Finally, the available data suggest similar effects of these drugs on the levels of serum lipid parameters in diabetic vs non-diabetic individuals\(^4\). However, the relatively small number of patients, the short-follow up, the design of the studies (administration on top of statin therapy) may reduce the significance of these observations.

| Ref. | Type | Main findings |
|------|------|---------------|
| Mbikay et al\(^1\)| Experimental (mice) | PCSK9-null male mice over 4 mo of age carried more LDLR and less insulin in their pancreas; islets exhibited signs of malformation, apoptosis and inflammation |
| Awan et al\(^1\) | Genetic study | Carriage of the loss-of-function PCSK9 p.R46L mutation was associated with insulin resistance in subjects with apolipoprotein E3/E2 genotype |
| Langhi et al\(^2\) | Experimental (mice) | PCSK9 deficiency does not alter insulin secretion and glucose tolerance |
| Baass et al\(^2\) | Clinical study (children) | Significant correlation of PCSK9 levels with glucose, insulin and HOMA-IR levels; an increase in PCSK9 levels by 1%-2% was associated with 10% higher fasting insulin levels in both sexes |
| Arsenault et al\(^2\) | Clinical study (abdominally obese men) | PCSK9 levels are associated with dyslipidemia and with increased HOMA-IR |
| Langhi et al\(^1\) | Experimental (mice) | PCSK9 deficiency does not alter insulin secretion and glucose tolerance |
| Baass et al\(^2\) | Clinical study (children) | Significant correlation of PCSK9 levels with glucose, insulin and HOMA-IR levels; an increase in PCSK9 levels by 1%-2% was associated with 10% higher fasting insulin levels in both sexes |
| Arsenault et al\(^2\) | Clinical study (abdominally obese men) | PCSK9 levels are associated with dyslipidemia and with increased HOMA-IR |
| Colhoun et al\(^2\) | Analysis of 10 phase 3 clinical trials with alirocumab (3448 non-diabetic individuals) | Hazard ratio for diabetes-related treatment adverse effects 0.64 (95% CI: 0.36-1.14) in alirocumab-treated patients vs placebo-treated and 0.55 (95% CI: 0.22-1.41) vs ezetimibe-treated patients |
| Blom et al\(^2\) | Post hoc analysis of the DESCARTES trial (evolocumab) | No changes in parameters of carbohydrate metabolism in patients with pre-existing dysglycemia or metabolic syndrome |

PCSK9: Proprotein convertase subtilisin/kexin type 9; LDLR: Low-density lipoprotein receptors; HOMA-IR: Homeostasis model assessment-insulin resistance; LDL-c: Low-density lipoprotein cholesterol.

### Table 2 Proprotein convertase subtilisin/kexin type 9 inhibitors and diabetes mellitus: Results of the mendelian randomization studies

| PCSK9 variants | Decrease in serum LDL cholesterol | Odds ratio for type 2 diabetes mellitus |
|----------------|---------------------------------|--------------------------------------|
| rs 11591147\(^4\) | 1 mmol/L (38.4 mg/dL) | 1.19 (95% CI: 1.02-1.38) |
| rs 1583680, rs 11591147, rs 2479109, rs 11206510\(^3\) | 1 mmol/L (38.4 mg/dL) | 1.29 (95% CI: 1.11-1.50) |
| Genetic score\(^2\) | 10 mg/dL | 1.11 (95% CI: 1.04-1.19) |

\(^1\)Associations with fasting glucose, body weight and waist-to-hip ratio were also noticed; \(^2\)The increased risk of diabetes was observed only in individuals with impaired fasting glucose levels. PCSK9: Proprotein convertase subtilisin/kexin type 9; LDL: Low-density lipoprotein; CI: Confidence interval.
Thus, the effects of PCSK9 and accordingly of PCSK9 inhibitors on carbohydrate metabolism may be seen under different points of view (Figure 2). The potential detrimental consequences of PCSK9 inhibitors on pancreatic cells leading to reduced insulin secretion due to a direct effect on pancreatic cells or to increased intracellular cholesterol levels may be counterbalanced by their direct beneficial effects on carbohydrate homeostasis.

Figure 1  The effect of proprotein convertase subtilisin/kexin type 9 (A) and proprotein convertase subtilisin/kexin type 9 inhibition (B) on liver cells low-density lipoprotein receptors expression and serum low-density lipoprotein-cholesterol levels. PCSK9: Proprotein convertase subtilisin/kexin type 9; LDL: Low-density lipoprotein; LDLR: Low-density lipoprotein receptors.

Figure 2  The role of proprotein convertase subtilisin/kexin type 9 on carbohydrate homeostasis. Accordingly, PCSK9 inhibitors may be associated with a neutral effect on carbohydrate homeostasis at least in the short term. PCSK9: Proprotein convertase subtilisin/kexin type 9; LDL: Low-density lipoprotein; LDLR: LDL receptors; HbA1c: Glycated hemoglobin; SREBP-1C: Sterol regulatory element-binding protein I-C; HOMA-IR: Homeostasis model assessment-insulin resistance.
homeostasis. Alternatively, the relatively short duration of the above mentioned clinical trials is not adequate for any detrimental effect of PCSK9 inhibition to be evident. It should be also mentioned that in the clinical trials the addition of PCSK9 inhibitors to statins may have partially masked their effects on glucose metabolism if there are shared mechanisms of action between these two drug classes. Finally, a generally non-significant effect of PCSK9 inhibition on glucose metabolism cannot be excluded. Thus, the results of both Fourier (Clinical Trials.gov Identifier: NCT01663402) outcome trials may better delineate the role of PCSK9 inhibitors on the parameters of glucose homeostasis and their long-term effect on the incidence of new-onset diabetes mellitus.

**REFERENCES**

1. **Ridker PM**, Danielson E, Fonseca FA, Genest J, Goto AM, Kastelein JJ, Koengen W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willersson JT, Glynn RJ. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008; 359: 2195-2207 [PMID: 18997196 DOI: 10.1056/NEJMa0807646]

2. **Sattar N**, Preis D, Murray HM, Welsh P, Buckley BM, de Craen AJ, Seshasai SR, McMurray JJF, Freeman DJ, Jukema JW, Macfarlane PW, Packard CJ, Stott DJ, Westendorp RG, Shepherd J, Davis BR, Press SL, Marchioli R, Mafatti RM, Maggioni AP, Tavazzi L, Togninis G, Kjekshus J, Pedersen TR, Cook TJ, Goto AM, Clearfield MB, Downs JR, Nakamura H, Ohashi Y, Mizuno K, Ray KF, Ford I. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010; 375: 735-742 [PMID: 20167359 DOI: 10.1016/S0140-6736(09)61965-6]

3. **Preiss D**, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, DeMicco DA, Barter P, Cannon CP, Sabatine MS, Braunwald E, Kastelein JJ, de Lemos JA, Blazing MA, Pedersen TR, Tikkanen MJ, Sattar N, Ray KK. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA* 2011; 305: 2565-2564 [PMID: 21693744 DOI: 10.1001/jama.2011.8180]

4. **Swerdlow DI**, Preis D, Kuchenbaecker KB, Holmes MV, Engmann JE, Shah T, Sofat R, Stender S, Johnson PC, Scott RA, Leusink M, Verweij N, Sharp SJ, Guo Y, Gianbartolomei C, Chung C, Peasey A, Amuzu I, Li K, Palmes J, Howard P, Cooper JA, Drenos F, Li YR, Lowe G, Gallagher J, Stewart MC, Tzoulaki I, Buxbaum SG, van der A DL, Forouhi NG, Orland-Miot MC, van der Schouw YT, Schnabel RB, Hubacek JA, Kuhnova R, Boviciene M, Tamosiunas A, Pajak A, Topor-Madray R, Stepaniak U, Malyutina S, Baldassarre D, Tenesa B, Tremoli E, de Faire U, Veqla F, Ford I, Jukema JW, Westendorp RG, de Borst GJ, de Jong PA, Algra A, Spijkerman AM, van Iperen E, Hovingh GK, Demuth I, Norman K, Steinhagen-Thiessen E, Buskens E, Koster A, van Guerau S, Sacerdote C, Wareham NJ, Langenberg C, Scott RA, Wareham NJ. Association Between Low-Density Lipoprotein Cholesterol-Lowering Genetic Variants and Risk of Type 2 Diabetes: A Meta-analysis. *JAMA* 2011; 305: 701-706 [PMID: 20026049 DOI: 10.1001/jama.2010.1381]

5. **Bonnefond A**, Yengo L, Le May C, Fumeron F, Marre M, Balkau B, Charpentier G, Franc S, Frouzel P, Caruso B. The loss-of-function PCSK9 p.R46L genetic variant does not alter glucose homeostasis. *Diabetologia* 2015; 58: 2051-2055 [PMID: 26049403 DOI: 10.1007/s00125-015-3659-8]

6. **Langhi C**, Le May C, Gmyr V, Vandewalle B, Kerr-Conte J, Keenmpt P, Pattou F, Costet P, Caruso B. PCSK9 is expressed in pancreatic delta-cells and does not alter insulin secretion. *Biochem Biophys Res Commun* 2009; 390: 1288-1293 [PMID: 19788649 DOI: 10.1016/j.bbrc.2009.10.138]

7. **Mbkay M**, Sirois F, Mayne J, Wang GS, Chen A, Dewpura T, Prat A, Seidah NG, Chretien M, Scott FW. PCSK9-deficient mice exhibit impaired glucose tolerance and pancreatic islet abnormalities. *FEBS Lett* 2010; 584: 701-706 [PMID: 20262609 DOI: 10.1016/j.febslet.2009.12.018]

8. **Lotta LA**, Sharp SJ, Burgess S, Perry JR, Stewart ID, Wijesundera HC, Goto AM, Kastelein JJ, Ani Z, Ardanaz E, Aróbia L, Balkau B, Lourdes P, Pericou W, Franke L, Sacco RS, Kassis S, Jansen JP, Tschernegg R, van der Schouw YT, Friel F, Tosto G, Chretien M, Scott FW, Sattar N, Langenberg C, Scott RA, Wareham NJ. Association Between Low-Density Lipoprotein Cholesterol-Lowering Genetic Variants and Risk of Type 2 Diabetes: A Meta-analysis. *JAMA* 2011; 316: 1383-1391 [PMID: 22770160 DOI: 10.1001/jama.2011.14568]

9. **Schmidt AF**, Swerdlow DI, Holmes MV, Patel RS, Fairhurst-Hunter Z, LLamy DM, Hartwig FP, Horta BL, Hennpke P, Eskin A, Moldovan M, van Iperen E, Hovingh GK, Demuth I, Norman K, Steinhagen-Thiessen E, Buskens E, Koster A, van Guerau S, Sacerdote C, Wareham NJ, Langenberg C, Scott R, Luan J, Bobak M, Malyutina S, Pajak A, Kubinova R, Tamosiunas A, Pikhart H, Husmeier LL, Graruap N, Pedersen O, Hansen T, Linneberg A, Simonsen KS, Cooper J, Humphries SE, Brilliant M, Kitchner T, Hakonarson H, Carrell DS, McCarty CA, Kirchner HL, Larson EB, Crosslin DR, de Andrade M, Roden DM, Denny JC, Carty C, Hancock S, Attia J, Holliday E, O’Donnell M, Yusuf S, Chong M

**Filippatos TD et al.** PCSK9 and carbohydrate metabolism

**WJD | www.wjgnet.com**

**July 15, 2017 | Volume 8 | Issue 7**
Pare G, van der Harst P, Said MA, Eppinga RN, Verweij N, Snieder H, Christen T, Mook-Kanamori DO, Gustafsson S, Lind L, Ingelsson E, Pazoki R, Franco O, Hofman A, Uitterlinden A, Dehghan A, Teumer A, Baumeister S, Dör M, Lerch MM, Völker U, Völzke H, Ward J, Poll JP, Smith DJ, Meade T, Muiland-van der Zee AH, Baranova EV, Young R, Ford I, Campbell A, Padmanabhan S, Bots ML, Grobbee DE, Frugue P, Thuillier D, Balkau B, Bonnefond A, Cariou B, Smart M, Baos Y, Kumari M, Mahajan A, Ridker PM, Chasman DI, Reiner AP, Lange LA, Ritchie MD, Asselbergs FW, Casas JP, Keating BJ, Preiss D, Hingorani AD, Sattar N. PCSK9 genetic variants and risk of type 2 diabetes: a mendelian randomisation study. *Lancet Diabetes Endocrinol* 2017; 5: 97-105 [PMID: 27908689 DOI: 10.1016/S2213-8587(16)30396-5]

17 Ference BA, Robinson JG, Brook RD, Catapano AL, Chapman MJ, Neff DR, Voros S, Giugliano RP, Davey Smith G, Fazio S, Sabatine MS. Variation in PCSK9 and HMGCR and Risk of Cardiovascular Disease and Diabetes. *N Engl J Med* 2016; 375: 2144-2153 [PMID: 27959767 DOI: 10.1056/NEJMa1604304]

18 Baass A, Dubuc G, Tremblay M, Delvin EE, O'Loughlin J, Levy E, Davignon J, Lambert M. Plasma PCSK9 is associated with age, sex, and multiple metabolic markers in a population-based sample of children and adolescents. *Clin Chem* 2009; 55: 1637-1645 [PMID: 19628659 DOI: 10.1373/clinchem.2009.126987]

19 Costet P, Cariou B, Lambert G, Lalarne F, Lardeux B, Jarnoux AL, Grethorst A, Staels B, Krempf M. Hepatic PCSK9 expression is regulated by nutritional status via insulin and sterol regulatory element-binding protein 1c. *J Biol Chem* 2006; 281: 6211-6218 [PMID: 16407292 DOI: 10.1074/jbc.M508582200]

20 Cariou B, Le Bras M, Langhi C, Le May C, Guyomarc'h-Desalaselle B, Krempf M, Costet P. Association between plasma PCSK9 and gamma-glutamyl transferase levels in diabetic patients. *Atherosclerosis* 2010; 211: 700-702 [PMID: 20452593 DOI: 10.1016/j.atherosclerosis.2010.04.015]

21 Arsenault BJ, Pelletier-Beaumont E, Alméras N, Tremblay A, Poirier P, Bergeron J, Després JP. PCSK9 levels in abdominally obese men: association with cardiometabolic risk profile and effects of a one-year lifestyle modification program. *Atherosclerosis* 2014; 236: 321-326 [PMID: 25128757 DOI: 10.1016/j.atherosclerosis.2014.07.010]

22 Colhoun HM, Ginsberg HN, Robinson JG, Leiter LA, Müller-Wieland D, Henry RR, Cariou B, Baccara-Dinet MT, Pordy R, Merlet L, Eckel RH. No effect of PCSK9 inhibitor alirocumab on the incidence of diabetes in a pooled analysis from 10 ODYSSEY Phase 3 studies. *Eur Heart J* 2016; 37: 2981-2989 [PMID: 27460890 DOI: 10.1093/eurheartj/ehw292]

23 Blom DJ, Koren MJ, Roth E, Monsalvo ML, Djedjos CS, Nelson P, Elliott M, Wasserman SM, Ballantyne CM, Holman RR. Evaluation of the efficacy, safety and glycaemic effects of evolocumab (AMG 145) in hypercholesterolaemic patients stratified by glycaemic status and metabolic syndrome. *Diabetes Obes Metab* 2014; 16: 98-107 [PMID: 27619750 DOI: 10.1111/dom.12788]

24 Sattar N, Preiss D, Robinson JG, Djedjos CS, Elliott M, Somarathne R, Wasserman SM, Raal FJ. Lipid-lowering efficacy of the PCSK9 inhibitor evolocumab (AMG 145) in patients with type 2 diabetes: a meta-analysis of individual patient data. *Lancet Diabetes Endocrinol* 2016; 4: 403-410 [PMID: 26868195 DOI: 10.1016/S2213-8587(16)0003-6]
