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Editorial Board Member of *World Journal of Diabetes*, Wei-Chung V Yang, PhD, Director, Professor, Center for Translational Medicine, College of Medical Science and Technology, Taipei Medical University, Taipei 110, Taiwan

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World Journal of Diabetes
 Baishideng Publishing Group Inc
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PCSK9 and carbohydrate metabolism: A double-edged sword

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

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

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Correspondence to: Moses S Elisaf, Professor, Department of Internal Medicine, School of Medicine, University of Ioannina, Staurou Niarchou Avenue, 45110 Ioannina, Greece. melisaf54@gmail.com
Telephone: +30-26-51007509
Fax: +30-26-51007016

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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

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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.

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INTRODUCTION

Statins can dose dependently increase the incidence of new-onset diabetes mainly in patients 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^[1-4]. 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)^[5]. 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^[6]. 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^[7].

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^[8]. 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^[9,10], carriage of the loss-of-function PCSK9 p.R46L mutation was associated with insulin resistance [increased homeostasis model assessment-insulin resistance (HOMA-IR) index] in those with apolipoprotein E₃/E₂ genotype^[11]. 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^[12]. 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^[13], 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)^[14]. 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^[13]. 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)^[15-17]. 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^[18]. 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^[19], underlying an association between PCSK9 and carbohydrate metabolism^[20]. 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)^[21].

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^[22]. In prediabetic individuals, the hazard

Table 1 Studies that examined the association of proprotein convertase subtilisin/kexin type 9 with carbohydrate metabolism

Ref.	Type	Main findings
Studies pointing to a positive effect of PCSK9 on carbohydrate metabolism Mbikay <i>et al</i> ^[14]	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 <i>et al</i> ^[11]	Genetic study	Carriage of the loss-of-function PCSK9 p.R46L mutation was associated with insulin resistance in subjects with apolipoprotein E3/E2 genotype
Studies pointing to a negative effect of PCSK9 on carbohydrate metabolism Langhi <i>et al</i> ^[13] Baass <i>et al</i> ^[18]	Experimental (mice) Clinical study (children)	PCSK9 deficiency does not alter insulin secretion and glucose tolerance 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 <i>et al</i> ^[21]	Clinical study (abdominally obese men)	PCSK9 levels are associated with dyslipidemia and with increased HOMA-IR
Studies pointing to a neutral effect of PCSK9 on carbohydrate metabolism Bonnetond <i>et al</i> ^[12]	Genetic study	The p.R46L mutation is not associated with markers of glucose homeostasis; p.R46L carriers did not experience an increased risk of new-onset diabetes mellitus
Colhoun <i>et al</i> ^[22]	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 <i>et al</i> ^[23]	Post hoc analysis of the DESCARTES trial (evolocumab)	No changes in parameters of carbohydrate metabolism in patients with pre-existing dysglycemia or metabolic syndrome
Ongoing trials that may better delineate the role of PCSK9 inhibition on carbohydrate metabolism Fourier trial (ClinicalTrials.gov Identifier: NCT01764633)	Ongoing trial	Primary hypothesis is that additional LDL-c lowering with evolocumab decreases the risk of cardiovascular events in subjects with clinically evident cardiovascular disease
Odyssey trial (ClinicalTrials.gov Identifier: NCT01663402)	Ongoing trial	Primary hypothesis is that additional LDL-c lowering with alirocumab decreases the risk of cardiovascular events in patients who have experienced an acute coronary syndrome event 4 to 52 wk prior to randomization

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 ^[15]	1 mmol/L (38.4 mg/dL)	1.19 (95%CI: 1.02-1.38)
¹ 4 independent variants ^[16] (rs 11583680, rs 11591147, rs 2479109, rs 11206510)	1 mmol/L (38.4 mg/dL)	1.29 (95%CI: 1.11-1.50)
² Genetic score ^[17]	10 mg/dL	1.11 (95%CI: 1.04-1.19)

¹Associations with fasting glucose, body weight and waist-to-hip ratio were also noticed; ²The 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.

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 (HbA_{1c}) levels was observed between treated groups in non-diabetic individuals of these results^[22]. 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^[23]. Finally, the available data suggest similar effects of these drugs on the levels of serum lipid parameters in diabetic vs non-diabetic individuals^[24]. 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.

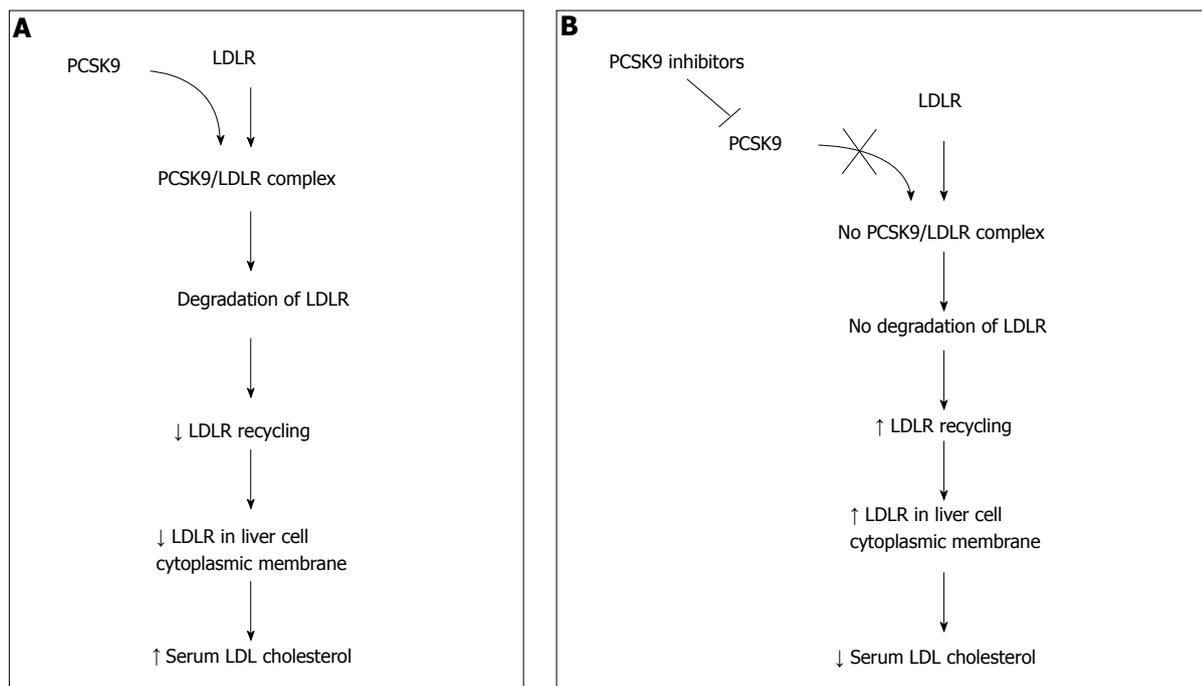


Figure 1 The effect of proprotein convertase subtilisin/kexin type 9 (A) and proprotein convertase subtilisin/kexin type 9 inhibition (B) on liver cells low-density lipoprotein receptors expression and serum low-density lipoprotein-cholesterol levels. PCSK9: Proprotein convertase subtilisin/kexin type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

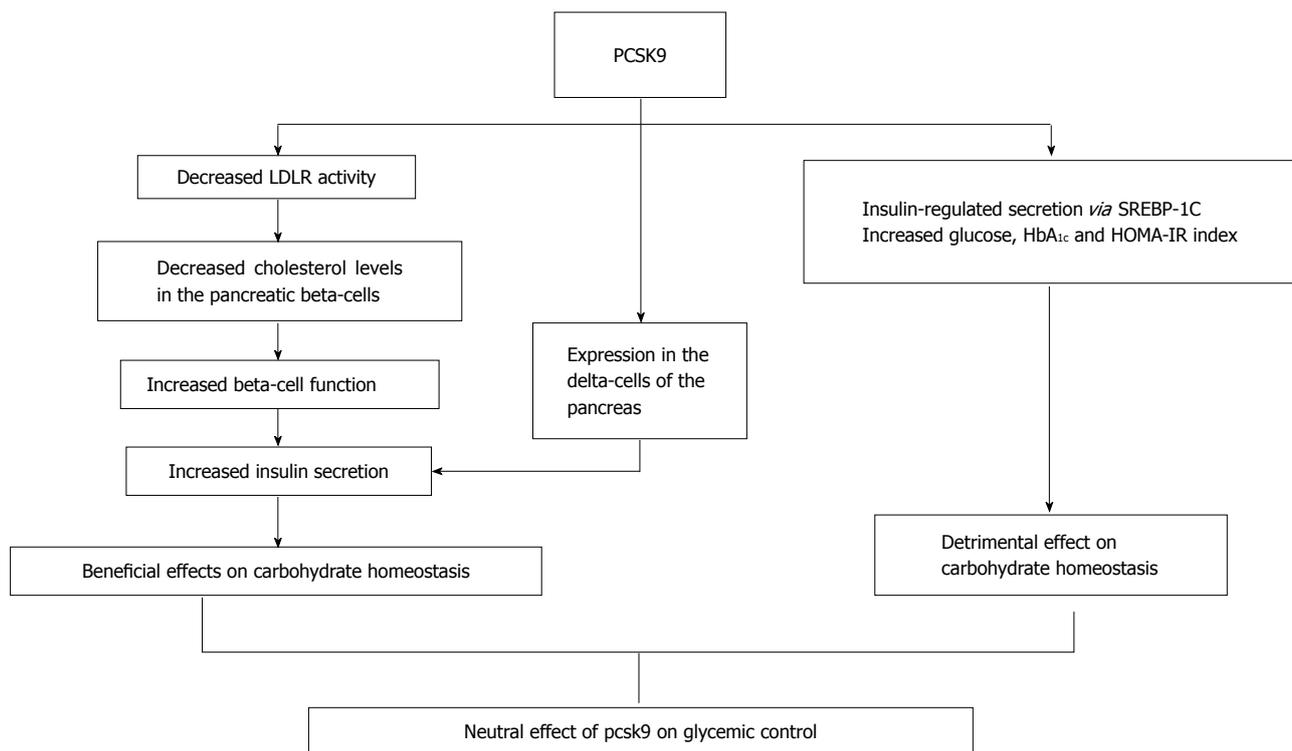


Figure 2 The role of proprotein convertase subtilisin/kexin type 9 on carbohydrate homeostasis. Accordingly, PCSK9 inhibitors may be associated with a neutral effect on carbohydrate homeostasis at least in the short term. PCSK9: Proprotein convertase subtilisin/kexin type 9; LDL: Low-density lipoprotein; LDLR: LDL receptors; HbA1c: Glycated hemoglobin; SREBP-1C: Sterol regulatory element-binding protein 1-C; HOMA-IR: Homeostasis model assessment-insulin resistance.

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. 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 (ClinicalTrials.gov Identifier: NCT01764633) and Odyssey (ClinicalTrials.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.

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