

## REVIEW ARTICLE

# Proprotein Convertase Subtilisin Kexin 9 (PCSK9) Inhibition: A Lipocrinologic Review

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## Abstract

This review describes the endocrine impact of proprotein convertase subtilisin kexin 9 (PCSK9) biology and PCSK9 inhibition. It discusses the relationship of the pituitary, thyroid, parathyroid, pancreatic, adrenal and gonadal hormones with lipid health. It also explores the status of PCSK9, and impact of PCSK9 inhibition, in dyslipidemia associated with endocrinopathy. This review should stimulate interest in the lipocrinologic aspects of PCSK9 inhibitors.

## Introduction

Lipocrinology is the study of the interrelationship between lipids and hormones, in health and disease. Most endocrine illnesses are associated with lipid abnormalities, and the presence of dyslipidemia serves as a flag to screen for endocrinopathy. Endocrinotropic medication and hormone replacement therapy may lead to alterations in lipid profile, while lipid-lowering drugs may have endocrine and metabolic pleiotropic effects.<sup>1</sup>

PCSK9 (proprotein convertase subtilisin kexin 9) belongs to the group proprotein convertases, that includes PC1, PC2, Furin, PC4, PC5, PC7, PACE4, isoenzyme 1 subtilisin kexin and PCSK9. They function as enzyme modulators and regulate the cleavage of precursor proteins, hormones, growth factors, receptors and transmembrane proteins.<sup>2</sup> The PCSK9 is expressed in hepatocytes, where it regulates the cellular uptake and recycling of LDL receptor and promotes LDL receptor degradation. It also increases degradation of VLDL receptor, ApoER2 (apolipoprotein E receptor 2), CD36 and may increase degradation of LRP1 (low-density lipoprotein receptor-related protein 1). PCSK9 is also expressed in the intestine, central nervous system, adrenals, pancreas and mesenchymal cells of the kidney.

The PCSK9i (proprotein convertase subtilisin kexin 9 inhibitors) are a new class of injectable lipid lowering

drugs. They are monoclonal antibodies that prevent the binding of PCSK9 to LDL receptor, and increase the hepatic clearance of LDL cholesterol. This results in significant reduction in LDL cholesterol, even in patients on maximally tolerated doses of statins. Additional therapeutic benefits include increased postprandial clearance of triglycerides and significant improvements in serum triglycerides, effect on triglycerides is minimal apoB and Lp (a). Currently approved drugs, alirocumab and evolocumab are used in the management of FH (familial hypercholesterolemia), in patients with clinically significant ASCVD (atherosclerotic cardiovascular disease) requiring additional LDL lowering on maximally tolerated statin therapy and in cases of statin intolerance. The extensive literature available to demonstrate the efficacy, safety and beneficial outcomes of PCSK9i has been reviewed comprehensively.<sup>2,3</sup> The emphasis, however, has been on lipid-lowering, and the diverse physiological role of PCSK9 and the hormone-modulating effects of these drugs have not yet been completely elucidated. The effect of PCSK9 inhibitors on non-LDL receptor targets, such as mediators of inflammation and immunological processes also needs further evaluation.<sup>3</sup>

This review studies current lipocrinologic aspects of PCSK9 and PCSK9 inhibition. It shares available information regarding the interplay of PCSK9 or PCSK9i with various

endocrine systems. Through this, we highlight an important facet of PCSK9i, which should stimulate interest in lipocrinology in general, and PCSK9 biology in particular.

## Pituitary

Both acromegaly and growth hormone deficiency are associated with dyslipidemia.<sup>4</sup> Growth hormone therapy is known to improve lipid health.<sup>5</sup> GH replacement decreases total cholesterol and LDL cholesterol, beyond the effects noted with statin therapy. There is no significant change in triglycerides; however, the influence of GH replacement on HDL is debatable.

GH exerts its lipo-modulatory effect by increasing the expression of hepatic LDL receptors, and accelerates LDL clearance.<sup>6</sup> Therefore, the beneficial effects of GH are not observed in homozygous familial hypercholesterolemia, where LDL receptors are totally absent. However, the lipid-lowering effect of GH is maintained in persons with heterozygous familial hypercholesterolemia.<sup>7</sup>

It is doubtful if endogenous growth hormone levels will have an impact on the efficacy and tolerability of PCSK9i. Clinicians should aim to normalize growth hormone/insulin-like growth factor 1 (IGF 1) levels prior to, or simultaneously with, initiation of PCSK9i therapy in a patient with acromegaly or growth hormone deficiency and dyslipidemia.

## Thyroid

Hypothyroidism, both overt and subclinical, is associated with elevated total cholesterol and LDL cholesterol levels.<sup>8,9</sup> This is mediated by a decrease in LDL receptor levels in the liver, which in turn decrease LDL clearance. Thyroid hormone has direct stimulatory effects on the LDL receptor promoter. It

also increases LDL receptor expression indirectly, by increasing Sterol regulatory element-binding protein 2 (SREBP-2) levels. Hypothyroidism is associated with an increase in PCSK9 levels, which accelerate LDL receptor catabolism and decrease hepatic LDL receptor levels further.<sup>10,11</sup> The effect of hypothyroidism on LDL cholesterol seems to be mediated by increased TSH, as recombinant TSH administration resulted in enhanced expression of SREBP1c, SREBP2 and PCSK9.<sup>11</sup>

In contrast to GH replacement, thyroid hormone administration is able to reduce LDL levels even if LDL receptors are absent. This is mediated by increasing the breakdown of cholesterol into bile acids, and increasing their excretion. The intestinal absorption of cholesterol and Apo lipoprotein B production are also reduced.<sup>10</sup> PCSK9 levels are increased in hypothyroidism, and this may further reduce LDL receptor activity by accelerating their catabolism. Therefore, there is a robust physiologic explanation to support the use of PCSK9i in hypothyroidism. However, existing guidelines recommend targeting euthyroxinemia in hypothyroid persons with dyslipidemia,<sup>12</sup> prior to considering any lipid-lowering therapy, including PCSK9i.

### Glucose Metabolism

The commonest endocrinopathy associated with dyslipidemia is diabetes.<sup>13,14</sup> While diabetes and dyslipidemia share a common link in metabolic syndrome, there are other gluco-lipocrine associations as well. Statin therapy may lead to dysglycemia, and may not be well tolerated by some. The high risk of ASCVD noted in association with diabetic dyslipidemia implies that greater emphasis must be laid on lipid management. In this context, one must be aware of the effect of PCSK9i on glucose regulation.

In fact, the PCSK9 receptor is a stage where multiple players, including insulin, statins and PCSK9 inhibitors act together to improve CV health.<sup>15</sup> Insulin signaling in the liver regulates LDL receptor levels. Insulin receptor knockout mice had increased expression of PCSK9 and decreased LDL receptor levels. The effect of insulin on PCSK9 seems to be mediated by mTORC1 pathway, which activates of PKC $\delta$  and suppresses HNF4 $\alpha$  and

HNF1 $\alpha$ . Insulin, thus, decreases PCSK9 expression and increases hepatic LDL receptor protein levels with decrease in circulating LDL cholesterol levels.<sup>16</sup> Insulin also stimulates Akt kinase which further stimulates mTORC. mTORC1 pathway, therefore, seems to be the link between diabetes and lipid metabolism. PCSK9 gene expression is known to be suppressed by glucagon and berberine. This fact, too, supports the role of insulin in PCSK9 and lipid metabolism. Plasma concentration of PCSK9 was associated with cardiovascular events in individuals with type 2 diabetes, though not consistently.<sup>17</sup>

It is postulated that inhibition of PCSK9 may predispose to development of diabetes new data dispels it. In some ways, this is similar to the diabetogenic potential of statin therapy. In mouse pancreatic islet  $\beta$ -cells, PCSK9 inhibition was associated with hypoinsulinemia and hyperglycemia and islets cells demonstrated increased apoptosis and inflammation.<sup>18</sup> Paradoxically, FH is associated with a lower risk of diabetes.<sup>19</sup> However, alirocumab was not associated with increased transition to new-onset diabetes in the pooled analysis of 10 phase 3 ODYSSEY trials, over a period of 6-18 months, compared to placebo or ezetimibe.<sup>20</sup> In another meta-analysis of 18 randomized controlled trials including 26,123 non-diabetic participants, the use of two PCSK9 monoclonal antibodies, alirocumab and evolocumab, was not associated with increased risk of new-onset diabetes.<sup>21</sup> There was small but significant increase in fasting blood glucose and HbA1c compared to placebo.<sup>22</sup> The FOURIER trial has clarified that the PCSK9i evolocumab lowers cardiovascular risk, both in persons with and without type 2 diabetes, which is a reassuring finding.<sup>23,24</sup>

### Gonadal Hormones

Circulating PCSK9 levels exhibit a gender gradient, as well as an age gradient with women. PCSK9 is present in higher concentrations in men than in women. Levels also increase in pregnancy, and after menopause.<sup>25</sup>

Serum testosterone levels do not correlate with PCSK9 concentrations in blood in men. Administration of exogenous testosterone does not influence PCSK9, but testosterone ablation therapy has reported variable

effects on PCSK9 levels.<sup>25</sup> It is doubtful, therefore, that PCSK9i therapy will be influenced by testosterone levels in men.

In women, estradiol levels correlate inversely with circulating PCSK9 concentrations. Estrogen treatment leads to decrease in LDL cholesterol, by increasing hepatic LDL receptors and increasing LDL clearance. An additional mechanism is the reduction of PCSK9 levels, which further decreases degradation of LDL receptors, and enhances their ability to degrade LDL.<sup>26,27</sup> Oral estrogen also reduces Lp (a) concentration. Practicing clinicians should be aware of this interaction while treating perimenopausal and menopausal women for dyslipidemia. A history of past, concurrent or planned use of estrogen-based hormone replacement therapy must be enquired into, and updated at each clinical contact. However, there are no recommendations to avoid concurrent estrogen and PCSK9i therapy. Additionally, Lp (a) is independently associated with increased CV risk in post-menopausal women. While statins reduce LDL cholesterol levels in postmenopausal levels, they do not result in significant reduction in Lp (a). PCSK9 inhibitors lead to significant reduction in Lp (a) by up to 44% and their role in high CVD risk postmenopausal women merits further study.<sup>28</sup>

PCSK9 inhibition is postulated to reduce proliferation of prostate cancer, though this effect does not seem to be hormonally mediated.<sup>29</sup> Evolocumab has also been shown not to impair gonadal hormone synthesis.<sup>30</sup>

### Calcification Disorders

Calcific aortic valve disease (CAVD) is a commonly encountered cardiovascular disease in geriatric practice. Though not directly related to parathyroid disorders, CAVD does represent an example of ectopic calcification. PCSK9i may delay the progression of CAVD by reducing lipoprotein (a) levels.<sup>31</sup> Thus, these drugs may emerge as potential candidates for the medical treatment of CAVD.

### Adrenal

PCSK9 is more effective in lowering LDL receptors in the liver than in the adrenals.<sup>32</sup> This is possibly due to impaired PCSK9 retention in the

gland. Annexin A2 (AnxA2) is an endogenous binding partner and functional inhibitor of PCSK9, which acts as a regulator of LDLR degradation, mostly in extrahepatic tissues such as the adrenals.<sup>33</sup> Adrenal function can be maintained even in the face of complete PCSK9 deficiency.<sup>34</sup> Evolocumab has also been shown not to impair adrenal hormone levels.<sup>30</sup>

## Summary

This review describes various lipocrinologic aspects of PCSK9 and PCSK9 inhibition. This is an important facet of PCSK9 biology, and should encourage rational use of PCSK9 inhibitors.

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