Abstract

A novel cholesterol-lowering PCSK9 variant is associated with low blood glucose level and lower cardiovascular risk in type 2 diabetes

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Background: Proprotein convertase substilisin-like kexin type 9 (PCSK9) is a negative regulator of low density lipoprotein (LDL) receptors. While PCSK9 inhibitors are effective in lowering LDL-cholesterol, their use has raised concerns regarding the potential risk of type 2 diabetes mellitus (T2DM). Therefore, the present study aims to assess the association of a new PCSK9 variant with glucose and lipid homeostasis.

Methods: Blood samples were collected from T2DM patients and non diabetic individuals (NDI) aged of 35 and above. Plasma fasting glucose, total cholesterol, high density lipoprotein cholesterol, LDL-cholesterol (LDL-c) and triglyceride levels were measured using Cypress reagents (Cypress Diagnostics, Hulshout, Belgium) as well as insulin level by ELISA (ALPCO, Salem, USA). Exon7 of the PCSK9 gene was sequenced by classical Sanger method.

Results: Among the 132 T2DM patients and 39 NDI included, a novel variant of PCSK9 was detected in 2.27% and 2.56% individuals respectively. The lipid profile revealed that the NDI carrying the variant have lower LDL-c (37.4 mg/dl vs 52.7 mg/dl, p=0.03) and triglyceride (23.0 mg/dl vs 49.0 mg/dl, p<0.001) levels than non-carriers NDI. The same trends were observed in T2DM patients. In addition, T2DM patients glucose level tended to be lower in the variant carriers (104 mg/DL) as compared to non-carriers (137 mg/DL) (p=0.06). These patients also showed a higher plasma insulin level (7.23 µIU/mL vs 5.90 µIU/mL, p=0.03) and interestingly, higher Homeostasis model assessment of β-cell function (HOMA2β) (57.4% vs 32.3%, p<0.001).

Conclusion: We identified a new PCSK9 variant associated with low LDL-cholesterol level, a better glucose homeostasis and a lower cardiovascular risk.

Key-words: PCSK9 Loss of function; Type 2 Diabetes; LDL cholesterol; Diabetic complications