

## 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 subtilisin-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  $\mu$ IU/mL vs 5.90  $\mu$ IU/mL,  $p=0.03$ ) and interestingly, higher *Homeostasis model assessment* of  $\beta$ -cell function (HOMA2 $\beta$ ) (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