Low PCSK-9 Serum Levels Do Not Predict Insulin Resistance in Racially Admixed Population. The ELSA-Brasil

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BACKGROUND

- Proprotein convertase subtilisin/kexin type 9 (PCSK9) is secreted by the liver and acts as an endogenous inhibitor of the LDL receptor. PCSK9 loss-of-function mutations induce lower levels of plasma LDL-cholesterol and reduce ischemic heart disease.

- However, in vivo and epidemiological studies indicate that enhanced LDL receptor function promotes new onset type-2 diabetes in predisposed individuals, possibly by altering beta cell function and/or by increasing insulin resistance.

HYPOTHESIS

- Low levels of PCSK9 are associated with insulin resistance.

METHODS

- We sampled 2092 participants from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) with the diagnosis of prediabetes and free of lipid-lowering agents.
- PCSK9 was measured by ELISA (R&D Systems, Lille, France).
- Lipoprotein particle subclasses and sizes were measured by nuclear magnetic resonance (NMR) spectroscopy (LabCorp, Morrisville, NC).
- Six of the lipoprotein subclass and size parameters were combined to produce the Lipoprotein Insulin Resistance Index (LP-IR) which has been shown to be strongly associated with insulin resistance assessed by Homeostatic Model Assessment, frequently-sampled intravenous glucose tolerance testing, and euglycemic clamps and risk of future diabetes is several large cohort studies.
- We applied a generalized linear model adjusted for variables related to LP-IR such as age, sex, race, fasting glucose, body-mass index and waist circumference.

RESULTS:

2092 subjects with prediabetes
median age=50 years;
51%, women; 61.2%
White; 21.3% Mixed; 13.3% Black; 4.2% Asian,
After adjustment for those covariates the the Lipoprotein Insulin Resistance Index had a
β -coefficients for 1-standard deviation of PCSK9 levels of
β=1.250
(95% Confidence Interval, 0.333 to 2.168).

This association was significant for
women (β=1.884; 0.641 to 3.128), but not for
men (β=0.416; -0.919 to 1.751).
We analyzed separately by race with significant associations only for
Whites (β=1.645; 0.477 to 2.813) and
Asians (β=7.237; 2.473 to 12.001) but not for
Mixed and Black races

CONCLUSIONS In contrast to our initial hypothesis, the
higher the PCSK9 levels, the higher the risk of insulin resistance and risk of new-onset diabetes, in particular among women, White and Asian subjects.