Muscle skeletal receptor tyrosine-protein kinase (MuSK) is associated with low density lipoprotein levels in diabetic patients on statins without prior cardiovascular disease

A PROTEOMIC ANALYSIS OF FACTOR-64 CLINICAL TRIAL SUBJECTS

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BACKGROUND

There is interest in discovering new pathways that can help reduce low density lipoprotein cholesterol (LDL-C), particularly in patients already on statins that haven't achieved LDL-C goal levels.

The purpose of this project was to examine the plasma-based proteomics associated with LDL-C in individuals with diabetes mellitus (DM), with no known cardiovascular disease, and on statin therapy.

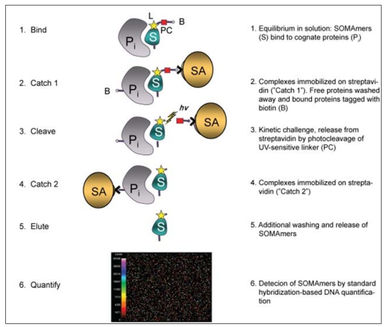
METHODS

Study population:

Subjects, on a statin, enrolled in the FaCTor-64 clinical trial that had a plasma sample collected at the time of enrollment were studied. FaCTor-64 was a randomized clinical trial examining the use of CT angiography to risk stratify DM patients into directed therapy in order to reduce the risk of death and nonfatal coronary outcomes.

Protein analyses:

The SOMAscan© assay was used to determine plasma levels for nearly 4000 proteins. SOMAscan© assay has been developed by SomaLogic, Inc. using their SOMAmer (Slow Off-rate Modified Aptamer) reagents. SOMAmer are sequences of short single-stranded DNA that incorporate a modifications giving the SOMAmer "protein-like" appendages. These chemical modifications allow for tight binding of a target protein and subsequently the quantification of protein levels.



*Source: SOMAmer-based biomarker discovery to diagnostic and clinical applications: a SOMAmer-based, streamlined multiplex proteomic assay. Kraemer S, et al. PLoS One. 2011;6(10):e26332.

Statistical analyses:

After quality control testing (n=4) and the elimination of one subject due to an extreme LDL-C value (>200, n=1), 195 subjects were left for evaluation. Least squares regression was used for all analyses.

RESULTS

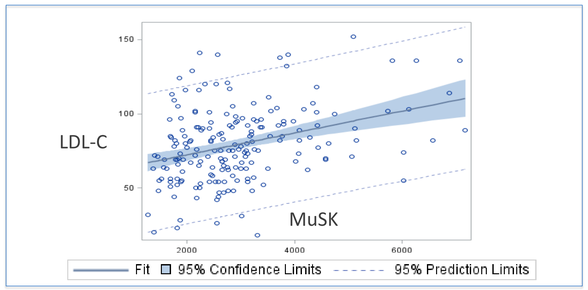
TABLE: DEMOGRAPHICS

Demographics	n=195
Age, mean ± std	60.7 ± 7.9
Male, No (%)	97 (49.8%)
Caucasian, No (%)	188 (96.4%)
BMI, mean ± std	33.6 ± 6.9
Smoking History, No (%)	26 (13.3%)
Type 2 DM, No (%)	175 (89.7%)
Years with DM	12.2 ± 9.6
DM medication, No (%)	
Insulin	30 (15.4%)
Non-Insulin	120 (61.5%)
Both	45 (23.1%)
Hypertension, No (%)	136 (68.7%)
Hyperlipidemia, No (%)	127 (65.1%)
Sleep Apnea, No (%)	51 (26.2%)
Renal Failure, No (%)	15 (7.7%)

TABLE: LEAST-SQUARES REGRESSION RESULTS FOR TOP PROTEIN

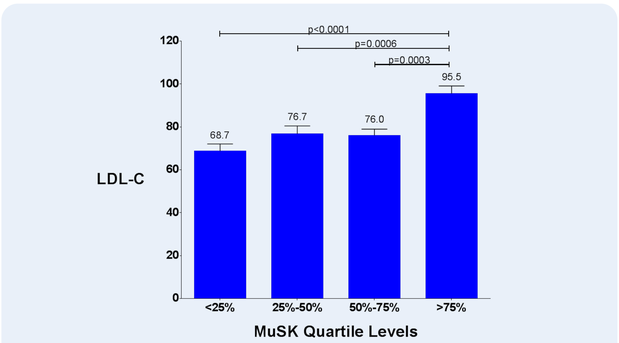
Protein Name	Short Name	Parameter Estimate	pvalue	r-square
Muscle skeletal receptor tyrosine-protein kinase	MuSK	0.006	**9.4×10^{-07}**	0.12
Pregnancy zone protein	PZP	0.022	3.0×10^{-05}	0.08
Low-density lipoprotein receptor-related protein 1B	LRP1B	0.001	3.0×10^{-05}	0.09
Protein S100-A5	S100-A5	0.001	2.0×10^{-04}	0.07
C-reactive protein	CRP	0.000	3.9×10^{-04}	0.06

FIGURE: LEAST-SQUARES REGRESSION FIT PLOT FOR LDL-C AND MUSK



- MuSK (Muscle, skeletal receptor tyrosine-protein kinase), was found to be significantly associated with LDL-C levels (after multiple testing adjustment) with a p=9.4 x 10^{-7}. Significance was maintained after adjustment for sex and age (p=3.4 x 10^{-6}).
- MuSK explained about 12% of the variance in LDL-C.
- Those subjects in the highest quartile of MuSK had substantially higher levels of LDL-C.

FIGURE: LDL-C LEVELS (MEAN ± SE) BY QUARTILES LEVELS OF MUSK



CONCLUSIONS

- **In DM patients on statins, MuSK was associated with increased LDL-C levels.**
- **MuSK is linked to myasthenia gravis, and statin use has been shown to aggravate symptoms in patients with this disease.**
- **We hypothesis that increases in MuSK may be associated with statin-induced myopathy, and in individuals with myopathy the continued compliance to statin use may be compromised. This would explain the increased LDL-C in individuals with higher MuSK levels. This hypothesis deserves further testing.**

Disclosure: SomaScan assay was donated by SomaLogic.