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Research Paper

Scarb1 Gene Polymorphism in Type 2 Diabetes Mellitus- A Review

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ABSTRACT:-The SR-BI is a key component on the cholesterol metabolism. Polymorphisms in the SCARBI gene are related with variations on plasma lipoprotein profile and other risk factors for type 2 diabetes mellitus.
Type 2 diabetes mellitus is characterized by changes in the concentration of plasma lipids, modifications in lipoprotein size and composition, which may be important modulators of the SR-BIexpression.T2DM patients down-regulates SR-BI mRNA expression. Interestingly,decreased SR-BIexpression resulted in markedly increased plasma LDL concentrations in T2DM subjects, and the over expression of SR- BIIisoform is responsible for the markedly in- creased plasma LDL-c concentrations. The polymorphism (rs838895) did not modify the mRNA level of SR-BIin leucocytes. Hyperglycemia may affect reverse cholesterol transport by controlling SR- BI expression in diabetic patients. LDL cholesterol levels are associated with low SR-BImRNA expression in T2DM.
Type 2 diabetes mellitus causes a low HDL-c concentration which is also one of the cause for insulin resistance syndrome, a common metabolic disorder and SRB1 gene variation causes heart disease and cardio vascular problems due to Changes in concentration of Hdl-c.

KEYWORDS:- Diabetes mellitus, SCARB1 gene, HDL-c, Lipoprotein, CETP gene.

I. INTRODUCTION

Type 2 diabetes mellitus (T2DM) has originated as one of the most common chronic diseases worldwide. Decreased plasma high-density lipoprotein cholesterol (HDL- c) is one of the most common lipid disorders in diabetic mellitus [1-3]. However, low HDL-c concentrations have also one of the causes for insulin resistance syndrome, a common metabolic disorder colligatedto a type 2 diabetes mellitus. Scavenger receptor class B, type I (SR-BI), a major HDL receptor [4,5] plays an important role in reverse cholesterol transport, a pathway for the clearance of excess cholesterol in the body. In this process, excess cellular cholesterol is packaged into HDL from where it is subsequently stored in the liver and excreted as bile. SR-Intermediates the uptake and secretion of bile of HDL-c by the liver [6,7].

The full length gene encoding SR-BI(gene symbol SCARB1) is composed of 13 exons that are alternatively spliced to produce two major transcripts: the full length SR-BIand the splice variant SR-BII, in which exon 12 is skipped. SR-BIand SR-BIIsplice forms, whereas, SR-BIIis reported to be a minor splice variant in human liver and has shown to be less efficient at reverse cholesterol transport [8-10]. Alternative splicing of the SR-B1 gene transcription generates two isoforms (types I and II) with identical extracellular regions, but distinct C-terminal cytoplasmic tails.

Genes located in chromosomal regions showing inheritance to type 2 diabetes in family based studies are rational candidates for more detailed investigation. SCARB1 lies in a region on chromosome 12q24 that has been linked to type-2 diabetes [11,12-17]. Acton *et al.* [18] were the first to identify single nucleotide polymorphisms (SNPs) of the SCARB1in a white European population and associated some of these common variants with plasma lipid levels and body mass index. Type 2 diabetes mellitus is marked by decrease plasma

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HDL-c concentrations, increase triglycerides, high small dense LDL, an increase in oxidized lipoproteins, as well as by other insulin-resistance related parameters that may change the expression of the SR-BIgene [19,20]

DiminishSCARB1 expression resulted in markedly increased plasma LDL-c concentrations in T2DM subjects. Studies in vitrohave evidenced that LDL-c can serve as a substrate for selective uptake by SR-BI. However, lipid transfer mediated by SR-BIfrom LDL-c particles appeared to be less effective when compared with HDL-c [21,22]. In studies in vivo, alterations in hepatic SR-BIexpression have been associated to changes in plasma concentrations of ApoB-containing lipoproteins. Affirmed, high- level expression of SRBIin livers of transgenic mice results in reduced plasma concentrations of LDL-c and ApoB [23,24] as well as decreased VLDL and IDL/LDL particle size [25].

II. PATHOPHYSIOLOGY OF SRB1 GENE

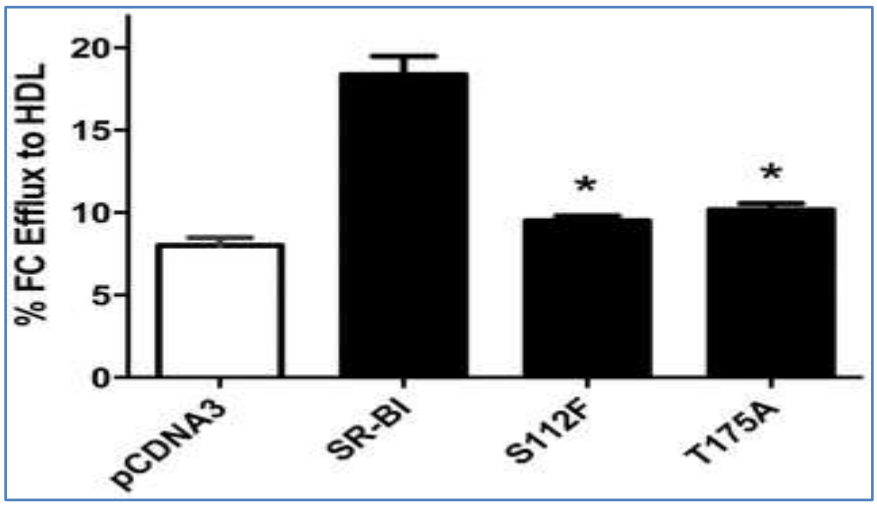
In type 2 diabetic patients Increase in fasting serum glucose, glycated hemoglobin, triglycerides, total cholesterol, low density lipoprotein cholesterol, and decrease in high density lipoprotein cholesterol occurs. SR-BI mRNA expression was lower in T2DM as compared to non-diabetic.Hyperglycemia presents in T2DM patients down-regulates SR-BI mRNA expression.

Genetic variation in the SCARB1 has also been linked with increased risk of coronary artery disease [26], obesity [25], triglycerides [27, 28] and HDL-c [29-33], all aspects of the metabolic syndrome. There is evidence that diabetes status may modify the SCARB1 association with HDL-c [34]. It has been described that elevated triglyceride that occurs in type 2 diabetes may distort the beneficial effects of the SR-BIoverexpression [35]. On the other hand, increasing evidence indicates that SR-BImay play additional roles that might be of particular importance in type 2 diabetes. Thus, the SR-BI, as a scavenger receptor, can also bind oxidized LDL that support to its antiatherogenic properties [34,35].

Type 2 diabetes mellitus causes a low HDL-c concentration which is also one of the cause for insulin resistance syndrome, a common metabolic disorder and SRB1 gene variation causes heart disease and cardio vascular problems due to Changes in concentration of Hdl-c. As a result dysfunction of reverse cholesterol transport in liver occurs dueto which High Hdl-c and lowLdl-c alters results in diabetes mellitus due to obesity which leads to many complications such as macro vascularamputations, retinopathy and neuropathy, nephropathy.

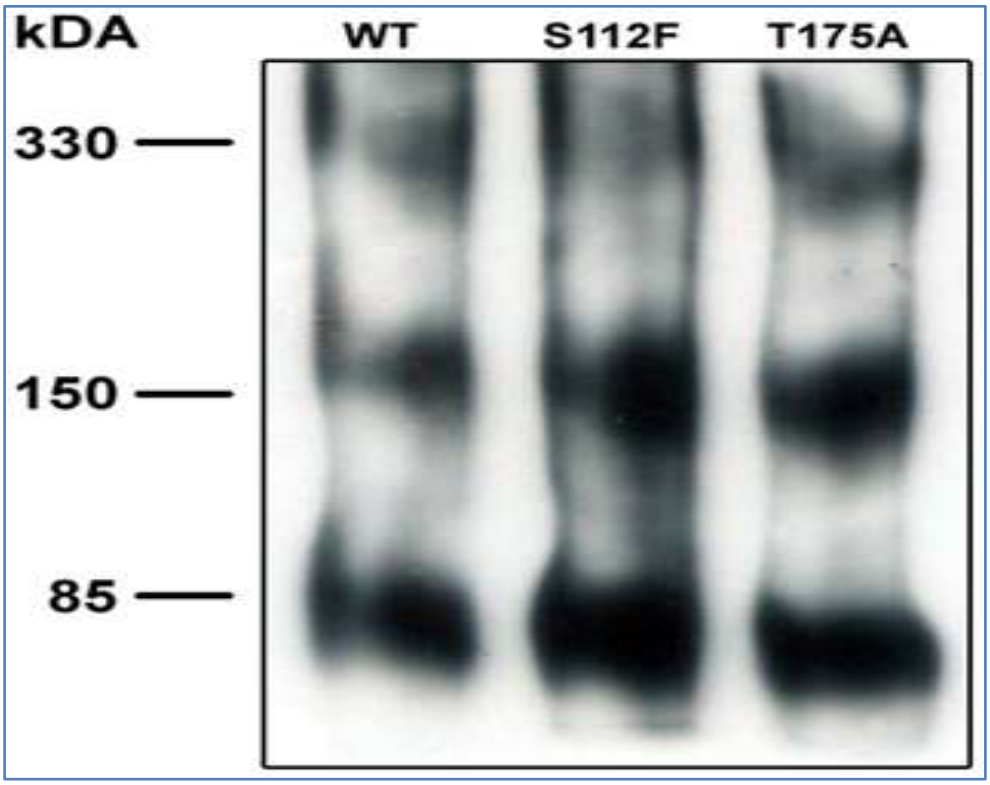
III. MUTATION IN SRB1GENE RECEPTORS CAUSEMODIFICATION IN EFFLUX OF FREE CHOLESTEROL TO HDL-

In addition to its role in selective uptake of HDL-C, SR-BI also plays a role in inducing the transfer of FC from peripheral cells to Receptor particles such as HDL [36]. The ability of wild-type, S112F- and T175A-SR-BI receptors to efflux FC cells to HDL acceptors. Both the S112F- and T175A-SR-BI mutant receptors showsignificant decreases in FC efflux as compared to wild-type SR-BI. As a result [37–40], little to no wild-type- or mutant SR-BI-mediated FC efflux was observed when lipid-free ApoA-I was used as an receptor (data not shown), thus implying that mutant SR-BI receptors affect intracellular membrane pools of FC only in the presence of HDL.



Dysfunctional cholesterol transports of SR-BI mutation are not due to changes in their oligomer status-

SR-BI exists as dimers and higher-order oligomers at the plasma membrane [41,42].Studies suggest that SR-BI oligomerization is required for efficient selective uptake of HDL-CEending support to the notion that SR-BI oligomers form a hydrophobic channel to allow transfer of CE from HDL into the plasma membrane.
These activities depend on lipoprotein binding to its extracellular domain and subsequent lipid exchange at the plasma membrane. Cholesterol ester uptake by liver is later used in the synthesis of steroid hormones and stored as bile for later use.Accordingly, cellular cholesterol levels estrogens and hormones regulate SR-BI expression by both transcriptional and post-Studies in recent years have denoted the cell surface receptor, scavenger receptor (SR)-BI, as playing a key role in the cellular metabolism of HDL.

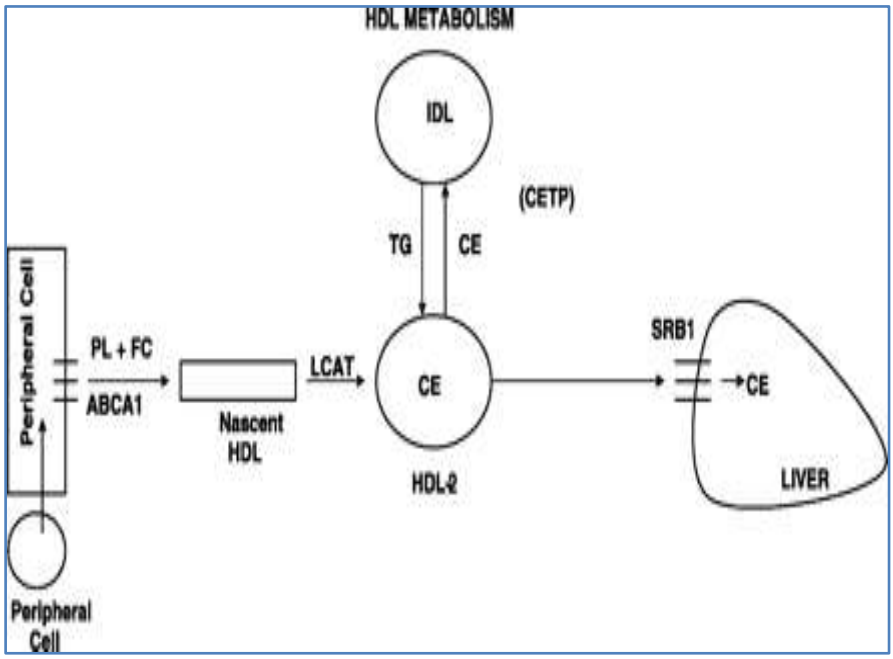


Mutant receptors maintain their ability to form homo-oligomers.

	Desirable	Borderline	High risk
Cholesterol		200-239 mg/dl	240 mg/dl
Triglycerides		150-199 mg/dl	200-499 mg/dl
HDL Cholesterol	60 mg/dl	35-45 mg/dl	
LDL Cholesterol	60-130 mg/dl	130-159 mg/dl	160-189 mg/dl
Cholesterol/HDL ratio	4.0	5.0	6.0

Key point-

- Combined genotypes at exon 8 (silent) and intron 5 were associated with triglyceride levels the TG: HDL-C ratio and HDL cholesterol in women.



Reverse excess cholesterol transfer to liver for later use

IV. CONCLUSION

The aim of this reviewtoexamine the association of polymorphisms in the SR-BIgene with different lipoprotein parameters has suggested that SCARB1 genetic variability plays a significant role in lipoprotein.
Alterations in hepatic SR-BIexpression have been associated to changes in plasma concentrations of ApoB-containing lipoproteins .Although there are no studies in humans examining.

Furthermore, our data also revealed that there is a strong and negative correlation among the expression of SR-BII isoformand LDL-c levels.

To our knowledge, there is novel evidence that hyperglycemia may affect reverse cholesterol transport by controlling SCARB1 expression in diabetic patients. The linear regression analysis revealed that there is a strong and negative correlation between the changes of SCARB1 expression and LDL-c levels. We conclude that the sustained hyperglycemia promotes overexpression of SR-BIIisoform, which is less efficient in reverse cholesterol transport and leads to elevate LDL-c concentrations in T2DM patients.

SR-BI molecules with mutations in the extracellular domain have shown that the binding of HDL and Cholestryl ester transfer to the cell plasma membrane are correlated, although the two steps are independent. Thus, there are SR-BI mutants that bind HDL normally but exhibit defective Cholesterol ester-selective uptake.
SR-BI-mediated flux of lipids between HDL and the cell membrane depends on the proper organization of both the bound ligand and the receptor. In contrast to the effects of mutations of either ApoA-I or SR-BI that can alter both HDL/SR-BI binding and the subsequent lipid transfer alteration of the conformation of ApoA-I in the HDL ligand affects only step.

However, efflux is also dependent on HDL concentration at higher concentrations where binding to SR-BI is saturated; under this condition, the ability of SR-BI to reorganize FC molecular packing in the cell plasma membrane contributes to the change in FC efflux.

Since SR-BII and SR-BI differ only in the C-terminal cytoplasmic tail, this result suggests that the tail is important for high efficiency HDL CE selective uptake as mediated by SR-BI. The C-terminal tail of SR-BI might be responsible for targeting the receptor to a plasma membrane domain or for interactions with cytoplasmic proteins that are necessary for selective uptake. With regard to the first possibility, SR-BI has been found in membrane caveolae a location that might have functional consequences for cholesterol flux .However, both SR-BII and CD36 have also been found in suggesting that caveolar localization per se may not explain the difference in selective uptake efficiency of SR-BI versus SR-BII and rCD36, unless there are uncharacterized differences in localization to lipid domains within caveolar fractions. Another possibility is that the SR-BI C-terminal tail facilitates interactions with other membrane or cytoplasmic proteins that are necessary for efficient HDL CE uptake.

Nonetheless, study confirms previously reported associations between variants in SCARB1 and HDL-C in diabetic kindred and extends these findings to the TG: HDL-C ratio in women with premature coronary disease. Combinations of common SNPs in SCARB1 may be an important determinant of high TG:HDL-C ratio among white women with CAD.

Furthermore, the expression of SCARB1 is known to be regulated by oestrogen. Oestrogen treatment of rats has been shown to down regulate the SR-B1 isoform of SCARB1 and upregulate the splice variant, SR-BII, in the liver Moreover, over expression of SR-B1 in the liver has been shown to result in a pronounced fall in plasma HDL-C. It is possible that the regulation of SCARB1 by oestrogen is influenced by genetic variants in SCARB1, which may have implications for the treatment of postmenopausal women with hormone replacement therapy (HRT).

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