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Overview of LOX-1 Gen 3'UTR188C/T Polymorphism in Medan, Indonesia

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A B S T R A C T

Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is categorized under the class E scavenger receptor subgroup. To date, seven distinct polymorphisms have been characterized within the LOX-1 gene, including the 3'UTR188C/T variant. This investigation clinical trial enrolled 35 volunteer subjects (mean age 43 ± 4.6 years, consisting of 27 females and 8 males). Deoxyribonucleic acid (DNA) was extracted from peripheral blood leukocytes employing the standard salting-out methodology. Genotyping of the LOX-1 3'UTR188CT variant was performed using Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP). Digestion with the RsaI restriction enzyme yielded two fragments (184 bp and 23 bp) corresponding to the C allele, and a single intact 207 bp fragment corresponding to the T allele. The restricted DNA fragments were subsequently visualized via ethidium bromide staining. Genotypic analysis of the LOX-1 gene revealed that the CC genotype was present in 15 participants (43%), the CT genotype in 17 participants (49%), and the TT genotype in 3 participants (8%). Out of the 35 subjects, the T allele was detected in 23 individuals (33%), whereas the C allele was highly predominant, appearing in 47 individuals (67%). In conclusion, our investigation demonstrates that the heterozygous CT genotype is the most prevalent variant within this study cohort, and the frequency of the minor T allele is significantly lower than that of the major C allele.

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INTRODUCTION

Nonalcoholic Fatty Liver Disease (NAFLD) stands as the most widespread chronic hepatic disorder on a global scale, affecting an estimated 20–30% of the worldwide population. The pathological continuum of NAFLD spans from simple, benign steatosis to a more aggressive phenotype known as Nonalcoholic Steatohepatitis (NASH), which is marked by necroinflammatory activity and varying severities of architectural fibrosis. The clinical manifestation of NASH is robustly correlated with an escalated risk of progressing to advanced liver cirrhosis, end-stage liver failure, diabetes mellitus, and serious cardiovascular diseases (CVD).

Histological modifications in the liver parenchyma of NAFLD patients mirror the severity of early-stage atherogenesis and impairments in glucose homeostasis, strongly implying that atheroma formation, metabolic diabetes, and parenchymal liver damage are governed by overlapping molecular pathways. Elucidating these interrelated cascades is vital to identify high-risk NASH cohorts vulnerable to severe cardiometabolic and hepatic complications, thereby enabling early personalized therapy and rigorous clinical monitoring.

Substantially high circulating levels of oxidized low-density lipoproteins (oxLDL) are critically involved in elevating the predisposition toward metabolic conditions, including metabolic syndrome, systemic hyperglycemia, hypertriglyceridemia, and cardiovascular disorders. This pathological process is initiated by an enhanced cellular internalization of oxLDL, which subsequently promotes intracellular reactive oxygen species (ROS) synthesis, accelerates cellular apoptosis, and sustains systemic inflammatory cascades. Furthermore, oxLDL is capable of modulating and activating hepatic stellate cells and Kupffer cells inside the hepatic tissues, driving liver-specific inflammation and fibrogenic transformation. In biopsy specimens obtained from patients with NAFLD, elevated concentrations of localized oxLDL are consistently associated with advanced histological severity.

The LOX-1 receptor is structurally identified as a member of the C-type lectin-like receptor superfamily. This type II transmembrane glycoprotein consists of 273 amino acid residues organized into four separate functional domains: an anchoring single transmembrane domain (TM, 26 aa), a concise N-terminal cytoplasmic domain (CYTO, 34 aa), an extracellular coiled-coil segment termed the NECK domain (82 aa), and a functional C-type lectin-like domain (CTLD, 131 aa) positioned at the carboxy-terminus. Stabilized by non-covalent interactions, the disulfide-linked homodimer configuration of the CTLD domain polymerizes into larger, high-order functional oligomeric assemblies.

X-ray crystallographic structural modeling of the human LOX-1 receptor indicates that specific arginine residues are indispensable for ligand interaction, generating a positively charged basic spine across the CTLD dimeric surface. Molecular dynamics (MD) simulations demonstrate that targeted substitutions of these key basic spine residues, particularly Trp150 and Lys167, induce a dramatic decline in the ligand-binding efficiency of LOX-1.

A centralized hydrophobic core tunnel characterizes the middle region of the CTLD, where the quasi-conical structural topography encircling the tunnel entrance contains discrete hydrophilic and hydrophobic regions. Phospholipid molecules interacting with internal tunnel residues, alongside mutations causing architectural blockage of this channel, markedly suppress the binding capacity of the LOX-1 receptor. Concurrently, the NECK domain projects as a dimer constructed from two parallelly twisted alpha-helices, presenting specific residues that dynamically govern the mechanical elasticity of this extracellular zone.

LITERATURE REVIEW

The LOX-1 receptor displays a broad ligand-binding spectrum, recognizing an array of diverse, negatively charged macro-molecules. Beyond oxLDL, which serves as its primary physiological ligand, this receptor effectively interacts with advanced glycation end products (AGEs), molecular chaperones (such as HSP60 and HSP70), activated blood platelets, apoptotic debris, pathogenic microorganisms, and C-reactive protein (CRP). The baseline expression of LOX-1 is not localized exclusively to endothelial cells; it is also highly detectable on the surface of circulating platelets, tissue fibroblasts, and vascular smooth muscle cells. It participates in innate immune surveillance, infectious responses, and the clearance of circulating cellular detritus or senescent cells from the vascular track.

Under healthy baseline physiology, LOX-1 expression is stringently maintained at low baseline levels. Conversely, in various clinical disorders such as macrovascular atherosclerosis, morbid obesity, systemic inflammation, neoplastic cell transformation, and active carcinogenesis, ligand-receptor engagement induces downstream cell signaling that strongly upregulates LOX-1 expression. Hyperactivation of this pathway triggers a severe oxidative stress response that exponentially elevates the vulnerability to atherosclerotic plaque rupture, resulting in tissue infarction and acute atherothrombotic vascular occlusions.

The over-expression of LOX-1 inside atheromatous plaques and the high microenvironmental concentration of oxLDL offer a cohesive molecular foundation explaining oxLDL-mediated endothelial activation, cellular dysfunction, and vascular wall damage. Genetic ablation of the orl1 gene in Ldlr knockout mouse models leads to a remarkable reduction in atherosclerotic lesion volume, markedly suppresses aortic wall inflammation, and attenuates the severity of ischemia/reperfusion injury. Furthermore, LOX-1 expression on immune-competent cells, including macrophages and dendritic cells, actively promotes foam cell transformation and coordinated inflammatory cascades, respectively.

The binding of oxLDL to LOX-1 stimulates membrane-associated NADPH oxidase, precipitating an immediate surge in intracellular reactive oxygen species (ROS) that downstream activates the redox-sensitive NF-kB transcription pathway. This nuclear activation leads to an increased synthesis of pro-inflammatory cytokines and leukocyte adhesion molecules—such as MCP-

1, VCAM-1, ICAM-1, E-selectin, and P-selectin—thereby accelerating monocyte recruitment to the endothelial layer.

METHODOLOGY

A total of 35 volunteer participants (mean age: 43 ± 4.6 years; demographic distribution: 27 females and 8 males) were prospectively enrolled for this study. Genomic deoxyribonucleic acid (DNA) extraction from peripheral blood leukocyte samples was accomplished via the classic salting-out technique. The profiling of the LOX-1 3′UTR188CT genotypic variants was completed using the PCR-RFLP assay method. Following enzymatic digestion with the restriction endonuclease RsaI, a singular 207 bp DNA band indicated the presence of the T allele, whereas two distinct bands of 184 bp and 23 bp confirmed the C allele. The electrophoretic migration and sizing of these DNA fragments were evaluated using ethidium bromide fluorescence under UV light.

Rigid exclusion criteria were established to filter out confounding metabolic backgrounds: individuals presenting with morbid obesity (Body Mass Index [BMI] ≥ 30 kg/m²), clinical diabetes mellitus (fasting plasma glucose levels ≥ 126 mg/dL, or post-prandial glucose levels ≥ 200 mg/dL during a 2-hour oral glucose tolerance test [OGTT], or currently managed on pharmacologic antidiabetic regimens), overt dyslipidemia (fasting serum total cholesterol ≥ 200 mg/dL or plasma triglycerides ≥ 200 mg/dL), documented anomalies in copper metabolism, aberrant serum α1-antitrypsin levels, or clinical thyroid dysfunction were systematically excluded from the study population.

All analytical findings were expressed quantitatively as mean values ± standard error of the mean (SEM). For variables following a verified normal distribution, statistical differences between groups were computed via Analysis of Variance (ANOVA) combined with post-hoc Bonferroni correction; conversely, non-parametric continuous variables were analyzed using the Kruskal-Wallis test supplemented with the post-hoc Dunn test. The Shapiro-Wilk test was applied uniformly to check data normality. Proportional differences among categorical data parameters were evaluated using either the Chi-square analysis or Fisher's Exact test.

Ethical Approval: The present research protocol received formal institutional review and ethical approval from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Muhammadiyah Sumatera Utara (Protocol Reference Number: 029/FKIKUMSU/V/2024).

RESULTS AND DISCUSSION

Out of the 35 subjects screened for the LOX-1 gene polymorphism, 15 individuals (43%) exhibited the heterozygous CT genotype, 17 individuals (49%) carried the homozygous CC genotype, and 3 individuals (8%) presented with the homozygous TT genotype. With respect to the overall allelic frequency within the sample size, the C allele was observed 47 times (67%), whereas the T allele was noted 23 times (33%).

Clinical sub-analysis indicated that patients with confirmed NASH possessed elevated circulating concentrations of insulin and nitrotyrosine, alongside a concurrent drop in serum adiponectin and high-density lipoprotein (HDL) cholesterol compared to the healthy control group.

Across both the patient cohort and healthy controls, individuals carrying the G allele of the LOX-1 IVS4-14 variant demonstrated higher baseline systolic and diastolic blood pressure compared to those with the homozygous AA genotype; nevertheless, no statistically significant variance was observed between the NASH subgroup and the control group. Adhering to the Adult Treatment Panel III diagnostic criteria, the full spectrum of metabolic syndrome was met by 5% of the control subjects and 28% of the patients diagnosed with NASH.

Although liver iron concentration (LIC) and hepatic iron index (HII) parameters remained statistically balanced across all LOX-1 genotypes, the severity of hepatic macrovesicular steatosis was significantly correlated with specific LOX-1 alleles. Crucially, these genetic variations displayed no measurable impact on the severity of necroinflammatory activity or stage of fibrosis among the NASH patient cohort (data not shown).

The current investigation uncovers several novel findings regarding genetic distributions: the overwhelming majority of the genotypic variations detected within this sample population were of the heterozygous CT configuration. Furthermore, the epidemiological frequency of the C allele was substantially more dominant when contrasted with the T allele. The LOX-1 gene is hypothesized to indirectly aggravate the severity of hepatocyte injury in NASH by modulating the balance of pro- and anti-inflammatory adipokines, which are crucial regulators in the pathobiology of progressive liver damage.

Specifically, an increased LOX-1-mediated internal uptake of circulating oxLDL by adipocytes can accelerate the release of pro-inflammatory cytokines (such as resistin) while downregulating the secretion of adiponectin, an anti-inflammatory and antioxidative adipokine. Intriguingly, the postprandial dynamic responses of resistin, adiponectin, and cytokeratin-18 cleavage fragments emphasize the vital role of LOX-1 in regulating acute inflammation and liver injury triggered by high-fat dietary intake. The presence of the G allele induces an unfavorable pro-inflammatory cytokine profile postprandially—characterized by lowered adiponectin levels and spike-like concentrations of resistin—despite these adipokines showing comparable baselines during fasting conditions.

Furthermore, the comprehensive molecular mechanism explaining how the LOX-1 IVS4-14 A→G single nucleotide polymorphism (SNP) influences the turnover of human lipoprotein subfractions after dietary fat consumption warrants further exploration. In our study, the presence of the G allele was explicitly linked with a moderate accumulation of postprandial triglyceride-rich lipoproteins (TRLPs). Given that highly atherogenic remnants typically present as small-sized TRLP particles, this finding could reveal a distinctive pathway connecting the LOX-1 mutation with heightened cardiovascular disease risk.

Multiple mechanisms can explain the link between LOX-1 polymorphism and the retention of small TRLPs. For instance, remnant particles are established functional ligands for the LOX-1 receptor, capable of stimulating vascular smooth muscle cell migration and forcing endothelial cells to generate ROS and pro-inflammatory signaling molecules.

Consequently, two major pathways are plausible: first, a higher binding affinity for oxLDL in the structural conformation of the LOX-1 receptor encoded by the G allele may cause a preferential uptake of oxLDL, thereby delaying the physiological clearance of TRLP remnants. Second, an accelerated hepatic internalization of oxLDL might upregulate the liver's secretion of small VLDL particles, which actively compete against chylomicron remnants for shared clearance pathways after meals. This competition leads to the accumulation of small TRLPs. Further in vitro and in vivo metabolic kinetic trials are required to fully delineate the functional links connecting the LOX-1 A→G mutation to TRLP metabolism.

CONCLUSIONS AND RECOMMENDATIONS

In summary, the largest proportion of genotypic variants identified in this study corresponded to the heterozygous CT genotype. Concurrently, epidemiological distribution data revealed that the prevalence of the minor T allele is notably lower than the major C allele within the investigated population.

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