Mantovani *et al. Metab Target Organ Damage* 2023;3:18
DOI: 10.20517/mtod.2023.24

Metabolism and Target Organ Damage

Commentary

Open Access

Check for updates

PNPLA3 rs738409 polymorphism and kidney dysfunction: an association beyond nonalcoholic fatty liver disease?

Alessandro Mantovani[1], **Giovanni Targher**[1,2]

[1]Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona 37126, Italy.
[2]IRCCS Sacro Cuore-Don Calabria Hospital, Negrar di Valpolicella 37024, Italy.

Correspondence to: Prof. Alessandro Mantovani, Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Piazzale Stefani, 1, Verona 37126, Italy. E-mail: alessandro.mantovani@univr.it

How to cite this article: Mantovani A, Targher G. *PNPLA3* rs738409 polymorphism and kidney dysfunction: an association beyond nonalcoholic fatty liver disease? *Metab Target Organ Damage* 2023;3:18. https://dx.doi.org/10.20517/mtod.2023.24

Received: 13 Jul 2023 **First Decision:** 25 Sep 2023 **Revised:** 25 Sep 2023 **Accepted:** 17 Oct 2023 **Published:** 19 Oct 2023

Academic Editor: Juan Pablo Arab **Copy Editor:** Dan Zhang **Production Editor:** Dan Zhang

Abstract

This commentary is primarily devoted to a recent observational study by Mantovani and colleagues (Aliment Pharmacol Ther. 2023; 57: 1093-102) examining the adverse effect of the patatin-like phospholipase domain-containing protein-3 (*PNPLA3*) rs738409 G allele on the kidney function in a cohort of 1,144 middle-aged Italian individuals with metabolic dysfunction. In this study, the authors found that the *PNPLA3* rs738409 G allele was significantly associated with lower levels of estimated glomerular filtrate rate (eGFR), even after adjusting for not only common anthropometric and cardiometabolic risk factors but also ethnicity, serum liver enzymes, use of drugs against dyslipidemia and chronic kidney disease polygenic risk score. Additionally, in a subgroup of 144 patients followed for a median of 17 months, the authors also found that the *PNPLA3* rs738409 G allele was independently associated with a faster eGFR decline. Commenting on the cohort study by Mantovani *et al*., we also summarized the rapidly expanding evidence linking the *PNPLA3* rs738409 variant with the risk of kidney disease. Furthermore, we discussed the potential research implications of these findings.

Keywords: Nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, glomerular filtration rate, kidney function, chronic kidney disease, *PNPLA3* rs738409

The *PNPLA3* gene, also known as adiponutrin, encodes for a protein of 481 amino acids mainly located in

lipid droplets of hepatocytes and hepatic stellate cells[1,2]. The PNPLA3 protein exerts a hydrolase activity on triglycerides and a transacylase activity on polyunsaturated fatty acids in phospholipids[1,2]. The rs738409 C > G single nucleotide polymorphism in the *PNPLA3* gene leads to an Ile148Met substitution (i.e., 148 isoleucine to methionine protein variant)[1,2], causing a loss of function in the enzymatic activity of the *PNPLA3* protein. Such loss of function in the PNPLA3 protein leads to an accumulation of lipid droplets in hepatocytes and hepatic stellate cells mainly due to a reduction in very-low-density lipoprotein (VLDL) secretion and a lack of proteasomal degradation, thus inducing liver damage and fibrosis over time[1,2]. It is universally acknowledged that the most extensive proportion of heritability in hepatic fat content among adults from the general population, increased proneness to developing nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis, cirrhosis, and primary liver cancer is accounted for by the *PNPLA3* rs738409 polymorphism[2-4].

As summarized in Table 1 many observational studies performed both in adults and adolescents[5-14], although not all[15-17], have reported that carriers of the *PNPLA3* rs738409 G allele have an increased risk of developing NAFLD and its more advanced forms, but also an increased risk of decreased eGFR and chronic kidney disease (CKD stage ≥ 3), regardless of the presence or absence of type 2 diabetes mellitus (T2DM) and hepatic steatosis. For instance, a cross-sectional analysis conducted in 227 Chinese adults with biopsy-proven NAFLD has shown that the *PNPLA3* rs738409 G allele was significantly associated with an increased prevalence of CKD, abnormal albuminuria, and higher levels of urinary neutrophil gelatinase-associated lipocalin (i.e., a biomarker of kidney tubule damage), irrespective of sex, adiposity measures, hepatic and cardiometabolic risk factors[10].

In a clinical and experimental study of 157 Italian postmenopausal women with T2DM, Mantovani *et al.* showed that homozygous carriers of the *PNPLA3* rs738409 G allele had lower eGFR levels and a higher prevalence of CKD than those carrying the *PNPLA3* rs738409 C allele[11]. In a large cross-sectional study of 1,022 Chinese patients with chronic hepatitis virus C infection (22% of whom had coexisting CKD), Liu *et al.* reported that the *PNPLA3* rs738409 G allele was significantly associated with an increased risk of prevalent CKD, after controlling for BMI, HOMA-estimated insulin resistance, hypertension, plasma lipids, C-reactive protein levels, and hepatic steatosis[14]. Conversely, there is very little information about a possible association between the *PNPLA3* rs738409 G allele and the presence of abnormal albuminuria[6,8].

To date, there are no clinical studies examining the risk of developing renal dysfunction in carriers of the *PNPLA3* rs738409 G allele among individuals with metabolic dysfunction and normal or near-normal kidney function. Mantovani *et al.* examined the nexus linking the rs738409 G allele of the *PNPLA3* gene and renal function in a cohort of 1,144 Italian adults with dysmetabolic features belonging to the Liver-Bible-2022 cohort (that enrolled volunteers with either fully preserved or nearly normal renal function at baseline who were submitted to extensive screening for hepatic and cardio-metabolic conditions)[13]. In this cohort, the authors reported that the *PNPLA3* rs738409 G allele was significantly associated with lower eGFR levels after controlling for sex, ethnicity, adiposity measures, cardiometabolic risk factors, serum liver enzymes, lipid-lowering medication use, albuminuria and a CKD polygenic risk score (PRS)[13]. It should be noted that the statistical significance of this association remained unaltered even after controlling for Fibroscan®-assessed controlled attenuation parameter (CAP) or liver stiffness measurement (LSM)[13]. Notably, in a subset of 144 individuals followed for a median period of 17 months, the authors also found that the *PNPLA3* rs738409 G allele was independently associated with a faster decline in eGFR (delta eGFR: -3.57 mL/min/1.73 m^2 per allele, 95% confidence interval: -6.94 to -0.21; $P = 0.037$)[13].

Table 1. Principal observational studies examining the association between the *PNPLA3* rs738409 G allele (or other NAFLD-associated genetic risk variants) and the risk of kidney dysfunction

Author, year	Study characteristics	NAFLD diagnosis	Genetic polymorphism	eGFR equation	Covariate adjustments	Main findings
Oniki *et al.*[5] 2015	Cross-sectional analysis: 740 Japanese and retrospective longitudinal study of 393 Japanese (follow-up 5.5 years)	Ultrasound	*PNPLA3* rs738409 G allele	MDRD equation	Age, sex, BMI, T2DM, hypertension, dyslipidemia, and hepatic steatosis	*PNPLA3* rs738409 G allele was linked with lower eGFR levels
Musso *et al.*[6] 2015	Cross-sectional analysis: 202 Italians who were free of obesity and T2DM	LB	*PNPLA3* rs738409 G allele	CKD-epidemiology collaboration equation	Age, sex, BMI, and MetS	*PNPLA3* rs738409 G allele was linked with higher risks of microalbuminuria and CKD
Mantovani *et al.*[7] 2019	Cross-sectional study: 101 Italian postmenopausal women with T2DM	FLI ≥ 60 (ultrasound in a subset of patients)	*PNPLA3* rs738409 G allele	CKD-epidemiology collaboration equation	Age, T2DM duration, HbA1c, IR, systolic BP, hypertension treatment, and FLI ≥ 60	*PNPLA3* rs738409 G allele was associated with lower eGFR and a higher prevalence of CKD
Targher *et al.*[8] 2019	Cross-sectional analysis: 142 NAFLD cases in Italian adolescents/children	LB	*PNPLA3* rs738409 G allele	Bedside schwartz equation	Age, sex, systolic BP, adiposity, IR, NASH, and stage of hepatic fibrosis	*PNPLA3* rs738409 G allele was linked with reduced renal function and proteinuria
Marzuillo *et al.*[9] 2019	Cross-sectional study: 591 Italian obese children	Ultrasound	*PNPLA3* rs738409 G allele	Bedside schwartz equation	Sex, duration of obesity, ALT, IR, and lipids	*PNPLA3* rs738409 G allele was linked with lower eGFR levels
Di Costanzo *et al.*[17] 2019	Cross-sectional study: 230 Italian overweight or obese children	MRI	*PNPLA3* rs738409 G allele	Bedside schwartz equation	Age, sex, pubertal status, WC, diastolic BP, and liver steatosis	No significant difference was observed among *PNPLA3* rs738409 alleles
Sun *et al.*[10] 2020	Cross-sectional study: 227 Chinese patients with NAFLD	LB	*PNPLA3* rs738409 G allele	CKD-Epidemiology collaboration equation	Age, sex, BMI, WC, hyperuricemia, IR, hypertension, T2DM, and hepatic fibrosis assessed histologically	*PNPLA3* rs738409 G allele was linked with an increased risk of glomerular and tubular injuries
Mantovani *et al.*[11] 2020	Cross-sectional analysis: 157 Italian postmenopausal women with T2D	Ultrasound and VCTE	*PNPLA3* rs738409 G allele	CKD-epidemiology collaboration equation	Diabetes duration, HbA1c, hypertension, presence of significant fibrosis (on VCTE), and abnormal albuminuria	*PNPLA3* rs738409 G allele was linked with lower eGFR levels and a higher prevalence of CKD
Koo *et al.*[15] 2020	Cross-sectional study: 396 South Korean individuals with biopsy-proven NAFLD from the Boramae NAFLD study	LB	*PNPLA3* rs738409 G allele; *TM6SF2* rs58542926 T allele; *MBOAT7* rs641738 T allele	CKD-epidemiology collaboration equation	Age, sex, BMI, and MetS	*MBOAT7* rs641738 T allele was linked with a higher prevalence of CKD. Conversely, CKD was not linked with *PNPLA3* rs738409 G or *TM6SF2* rs58542926 T alleles
Baratta *et al.*[16] 2022	Cross-sectional analysis: 538 individuals with NAFLD (in whom data regarding kidney function were available) were recruited on an outpatient basis	Ultrasound	*PNPLA3* rs738409 G allele; *MBOAT7* rs641738 T allele; *TM6SF2* rs58542926 T allele; *GCKR* rs780094 T allele	CKD-epidemiology collaboration equation	BMI, MetS, and liver fibrosis (as assessed by FIB-4 index)	Deterioration of renal function was not associated with any of NAFLD-related polymorphisms
Mantovani *et al.*[12] 2023	Panel data analysis: 46 postmenopausal T2DM women with preserved kidney function at baseline	Ultrasound and VCTE	*PNPLA3* rs738409 G allele	CKD-epidemiology	Annual changes in age, HbA1c, hypertension, albuminuria, and	*PNPLA3* rs738409 G allele was linked with a faster eGFR decline during a 5-

	(in 2017) who underwent follow-up in 2022			collaboration equation	use of specific glucose-lowering agents during follow-up	year follow-up
Mantovani *et al.*[13] 2023	Cross-sectional study and longitudinal study: 1,144 adults of middle age recruited from the cohort "Liver-Bible-2022". The effect of the *PNPLA3* rs738409 G allele on kidney function was also examined in a subset of 144 individuals over a median follow-up of 17 months	VCTE with CAP	*PNPLA3* rs738409 G allele	CKD-epidemiology collaboration equation	Age, sex, height, WC, systolic BP, lipids, transaminases, fasting insulin, albuminuria, use of lipid-lowering drugs, ethnicity, and PRS-CKD score	*PNPLA3* rs738409 G allele was linked with eGFR decline in the cross-sectional analysis. In the longitudinal analysis, the *PNPLA3* rs738409 G allele was correlated to faster eGFR decline over time
Liu *et al.*[14] 2023	Cross-sectional study: 1,022 patients with chronic HCV infection, 226 of whom had CKD	VCTE with CAP	*PNPLA3* rs738409 G allele; *TM6SF2* rs58542926 T allele	CKD-epidemiology collaboration equation	BMI, IR, hypertension, lipids, C-reactive protein, and liver steatosis on CAP	*PNPLA3* rs738409 G allele was linked with an increased risk of CKD, while the *TM6SF2* rs58542926 T allele was linked with a reduced risk of CKD

LT: alanine transferase; BMI: body mass index; BP: blood pressure; CAP: controlled attenuation parameter; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; FIB-4: Fibrosis-4; FLI: fatty liver index; GCKR: glucokinase regulatory protein; HOMA-IR: homeostasis model assessment-estimated insulin resistance; IR: insulin resistance; LB: liver biopsy; MBOAT7: membrane-bound O-acyltransferase domain containing 7; MetS: metabolic syndrome; MRI: magnetic resonance imaging; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; PNPLA3: patatin-like phospholipase domain-containing 3; PRS-CKD: polygenic risk score of chronic kidney disease; T2DM: type 2 diabetes; VCTE: vibration-controlled transient elastography; TM6SF2: trans-membrane 6 superfamily member 2; WC: waist circumference.

The study by Mantovani *et al.* is the first large cohort study reporting a nexus linking the *PNPLA3* rs738409 G allele with reduced renal function, irrespective of ethnicity, and the PRS-CKD[13], which includes an evaluation of nearly 41,000 genetic predictors of CKD risk[18]. Collectively, therefore, the results of this study show a detrimental impact of the *PNPLA3* p.I148M variant on eGFR levels in middle-aged individuals with metabolic dysfunction and preserved kidney function, suggesting that the identification of the *PNPLA3* genotype might help to triage subjects who are at greater odds of progressive NAFLD forms and, at the same time, individuals who are at higher risk of CKD. This issue has also been recently recognized in a Delphi-based consensus statement[19]. In addition, as insulin resistance (more than other metabolic traits) appears to exacerbate the PNPLA3-rs738409-G genetic risk for NAFLD[20], it is reasonable to hypothesize that improving insulin resistance might offer additional clinical benefits in this patient population.

What is the net effect of *PNPLA3* rs738409 polymorphism on kidney function? The study by Mantovani *et al.* tried to answer this research question, showing that compared to the wild-type genotype, heterozygous and homozygous carriages of the *PNPLA3* rs738409 G allele had a reduction of -1.24 and -2.48 mL/min/1.73 m^2 in eGFR levels, respectively[13]. In addition, in this specific cohort of Italian adults with metabolic dysfunction, the *PNPLA3* rs738409 G allele explained approximately 8% of the spectrum of eGFR variability dysfunction[13]. However, the presumed mechanisms underlying the nexus linking the *PNPLA3* rs738409 G allele and kidney dysfunction are not fully understood. In a previous experimental study, the same group of investigators reported that the concentrations of mRNA of the PNPL A3 were expressed at the maximal levels both intrahepatically and intrarenally and that renal podocytes had the highest expression of mRNA and protein of the *PNPLA3* gene compared to other renal cells[11]. Other experimental findings suggest that podocytes of renal glomeruli can store fatty substrates, such as retinol esters and lipid droplets, thereby promoting fatty kidney disease[21-23]. However, although these experimental findings are fascinating, they are preliminary data. As recently discussed by Pirola *et al.*, some important research questions remain open: (*i*) Could different

PNPLA3 gene expression patterns in the kidney explain the association between the *PNPLA3* rs738409 G allele and kidney dysfunction[24]? (*ii*) Does current experimental data support a direct adverse effect of the *PNPLA3* rs738409 G allele on kidney function? (*iii*) Does the adverse effect of the *PNPLA3* rs738409 G allele on kidney function occur, at least partially owing to this genetic polymorphism affecting the liver? Growing evidence indicates a significant link between NAFLD and the risk of both prevalent and incident CKD, irrespective of common metabolic risk factors, such as diabesity[22,25-28]. Hence, additional pathogenic investigation is required to better understand the long-term effect(s) of the *PNPLA3* rs738409 G allele on the risk of kidney dysfunction.

The results of the cohort study by Mantovani *et al.* should be interpreted with caution, considering the possible inherent limitations of the study[13]. First, while the cross-sectional analysis was performed on the entire cohort of individuals (n = 1,144), prospective assessment was restricted only to a subset of individuals. Moreover, renal function was not assessed with direct measurements but with a validated creatinine-based equation estimating eGFR, as usually done in routine clinical practice. Finally, the Liver-Bible-2022 cohort enrolled Italian individuals without pre-existing T2DM and with normal or near-normal kidney function. As a result, the findings of this study could not apply to the general adult population, other ethnic groups, or other selected patient populations.

In conclusion, the findings of the recent observational study by Mantovani *et al.* support a detrimental effect of the *PNPLA3* p.I148M variant on eGFR levels in a large cohort of Caucasian middle-aged individuals with metabolic dysfunction[13]. This association was independent of established renal risk factors, presence /severity of NAFLD (as assessed by hepatic transient elastography), ethnicity, and genetic predisposition to CKD. Given the possible translational importance for personalized medicine approaches of the relationship linking the polymorphism p.I148M of the *PNPLA3* gene to a faster decline of renal function, additional studies are required to exhaustively clarify the effect of this genetic polymorphism on the risk of CKD. Future research is also needed to examine whether *PNPLA3* p.I148M silencing might protect against kidney damage progression in carriers.

DECLARATIONS

Author's contribution

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Mantovani A, Targher G.

Performed data acquisition, as well as providing administrative, technical, and material support: Mantovani A, Targher G.

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Pingitore P, Romeo S. The role of PNPLA3 in health and disease. *Biochim Biophys Acta Mol Cell Biol Lipids* 2019;1864:900-6. DOI PubMed
2. Eslam M, Valenti L, Romeo S. Genetics and epigenetics of NAFLD and NASH: clinical impact. *J Hepatol* 2018;68:268-79. DOI PubMed
3. Romeo S, Kozlitina J, Xing C, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet* 2008;40:1461-5. DOI PubMed PMC
4. Anstee QM, Darlay R, Cockell S, et al; EPoS Consortium Investigators. Genome-wide association study of non-alcoholic fatty liver and steatohepatitis in a histologically characterised cohort. *J Hepatol* 2020;73:505-15. DOI
5. Oniki K, Saruwatari J, Izuka T, et al. Influence of the PNPLA3 rs738409 polymorphism on non-alcoholic fatty liver disease and renal function among normal weight subjects. *PLoS One* 2015;10:e0132640. DOI PubMed PMC
6. Musso G, Cassader M, Gambino R. PNPLA3 rs738409 and TM6SF2 rs58542926 gene variants affect renal disease and function in nonalcoholic fatty liver disease. *Hepatology* 2015;62:658-9. DOI PubMed
7. Mantovani A, Zusi C, Sani E, et al. Association between PNPLA3rs738409 polymorphism decreased kidney function in postmenopausal type 2 diabetic women with or without non-alcoholic fatty liver disease. *Diabetes Metab* 2019;45:480-7. DOI PubMed
8. Targher G, Mantovani A, Alisi A, et al. Relationship between PNPLA3 rs738409 polymorphism and decreased kidney function in children with NAFLD. *Hepatology* 2019;70:142-53. DOI
9. Marzuillo P, Di Sessa A, Guarino S, et al. Nonalcoholic fatty liver disease and eGFR levels could be linked by the PNPLA3 I148M polymorphism in children with obesity. *Pediatr Obes* 2019;14:e12539. DOI
10. Sun DQ, Zheng KI, Xu G, et al. PNPLA3 rs738409 is associated with renal glomerular and tubular injury in NAFLD patients with persistently normal ALT levels. *Liver Int* 2020;40:107-19. DOI
11. Mantovani A, Taliento A, Zusi C, et al. PNPLA3 I148M gene variant and chronic kidney disease in type 2 diabetic patients with NAFLD: clinical and experimental findings. *Liver Int* 2020;40:1130-41. DOI
12. Mantovani A, Zusi C, Csermely A, et al. Association between PNPLA3 rs738409 variant and 5-year estimated glomerular filtration rate decline in post-menopausal women with type 2 diabetes: A panel-data analysis. *Nutr Metab Cardiovasc Dis* 2023;33:1093-7. DOI
13. Mantovani A, Pelusi S, Margarita S, et al. Adverse effect of PNPLA3 p.I148M genetic variant on kidney function in middle-aged individuals with metabolic dysfunction. *Aliment Pharmacol Ther* 2023;57:1093-102. DOI
14. Liu J, Qi W, Wang S, et al. Metabolic disorders induced by PNPLA3 and TM6SF2 gene variants affect chronic kidney disease in patients infected with non-genotype 3 hepatitis C virus. *Lipids Health Dis* 2023;22:91. DOI PubMed PMC
15. Koo BK, An JN, Joo SK, et al. Association between a polymorphism in MBOAT7 and chronic kidney disease in patients with biopsy-confirmed nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2020;18:2837-9.e2. DOI
16. Baratta F, D'Erasmo L, Di Costanzo A, et al. Metabolic syndrome but not fatty liver-associated genetic variants correlates with glomerular renal function decline in patients with non-alcoholic fatty liver disease. *Biomedicines* 2022;10:720. DOI PubMed PMC
17. Di Costanzo A, Pacifico L, D'Erasmo L, et al. Nonalcoholic fatty liver disease (NAFLD), but not its susceptibility gene variants, influences the decrease of kidney function in overweight/obese children. *Int J Mol Sci* 2019;20:4444. DOI PubMed PMC
18. Khan A, Turchin MC, Patki A, et al. Genome-wide polygenic score to predict chronic kidney disease across ancestries. *Nat Med* 2022;28:1412-20. DOI PubMed PMC
19. Sun DQ, Targher G, Byrne CD, et al. An international Delphi consensus statement on metabolic dysfunction-associated fatty liver disease and risk of chronic kidney disease. *Hepatobiliary Surg Nutr* 2023;12:386-403. DOI PubMed PMC
20. Barata L, Feitosa MF, Bielak LF, et al. Insulin resistance exacerbates genetic predisposition to nonalcoholic fatty liver disease in individuals without diabetes. *Hepatol Commun* 2019;3:894-907. DOI PubMed PMC
21. Mallela SK, Patel DM, Ducasa GM, Merscher S, Fornoni A, Al-ali H. Detection and quantification of lipid droplets in differentiated human podocytes. *Methods Mol Biol* 2019;1996:199-206. DOI PubMed PMC
22. Mantovani A, Zusi C, Dalbeni A, Grani G, Buzzetti E. Risk of kidney dysfunction in nafld. *Curr Pharm Des* 2020;26:1045-61. DOI PubMed
23. Wang TY, Wang RF, Bu ZY, et al. Association of metabolic dysfunction-associated fatty liver disease with kidney disease. *Nat Rev Nephrol* 2022;18:259-68. DOI
24. Pirola CJ, Sookoian S. Editorial: NAFLD, chronic kidney disease, and pleiotropy-why is PNPLA3 omnipresent? *Aliment Pharmacol Ther* 2023;57:1180-2. DOI PubMed
25. Lonardo A, Mantovani A, Targher G, Baffy G. Nonalcoholic fatty liver disease and chronic kidney disease: epidemiology,

pathogenesis, and clinical and research implications. *Int J Mol Sci* 2022;23:13320. DOI PubMed PMC

26. Mantovani A, Petracca G, Beatrice G, et al. Non-alcoholic fatty liver disease and risk of incident chronic kidney disease: an updated meta-analysis. *Gut* 2022;71:156-62. DOI
27. Targher G, Byrne CD. Non-alcoholic fatty liver disease: an emerging driving force in chronic kidney disease. *Nat Rev Nephrol* 2017;13:297-310. DOI PubMed
28. Lonardo A, Singal AK, Osna N, Kharbanda KK. Effect of cofactors on NAFLD/NASH and MAFLD. A paradigm illustrating the pathomechanics of organ dysfunction. *Metab Target Organ Damage* 2022;2:12. DOI PubMed PMC