



THE MOLECULAR PROFILING AND NEWLY DISCOVERED BIOMARKERS FOR NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) AMONG THE ASIAN INDIAN POPULATIONS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT Nonalcoholic fatty liver disease (NAFLD) is a major complain in the world. Patients with NAFLD have an increased risk of liver-related ongoing, lifestyle modification. Present evidence-based lifestyle intervention (EBLSI) is required prevent and managing NAFLD. Several gaps in managing NAFLD discussed AND highlight the evidence-based opportunities to overcome those gaps novel findings up to next level of research to find more about medical values With Molecular aspects for novel identification may help in the prognosis, diagnosis and management in the near future. Need more sample size to know all.

KEYWORDS : Nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVDs), insulin resistance, glucotoxicity and lipotoxicity, R&D.

INTRODUCTION:

Currently, researchers thought T2DM and NAFLD dreadful diseases contributing to cardiovascular mortalities for effective and safe therapies and management techniques [1-3]. Molecular identification have significantly improved the prognosis, diagnosis and management [4-5]. An epidemiological and clinical evidence calls for an integrative strategy in order to consider the recording of all hepatological, diabetological, and cardiovascular aspects of several anti-diabetic and liver-targeted drugs have been found to improve their loss of the NAFLD and the vasculature tissues [3-6]. But then again it won't be possible to provide patients with the best possible care until the multifaceted bidirectional relationship of underlying diseases are better understood including with the mechanisms [4-5-7].

Non-alcoholic fatty liver disease (NAFLD) encompasses a wider range of disorders ranging from mild cases without inflammation, infection and damage to severe issues with inflammatory reactions and infections. In the Hepatocytes damage had a new possibility for the progress to fibrosis [1]. Hepatocellular carcinoma (HCC), liver transplantation without significant alcohol consumption is also responsible for (NAFLD) [1-2]. NAFLD is a prevalent condition that impacts 20–35 % of the world's population. According to higher likelihood ratio we observed that in males compared to female's ratio are increasing now a days. NAFLD is not exclusive into the adults, 15 % of individuals aged 2–20 years old are also susceptible with the liver disease. NAFLD can affect people of all ages and genders [2, 3]. Experts believed that unhealthy lifestyle modifications, genetic factors, aging and are all contributing factors in NAFLD [3-4].

Glucose and fructose consuming levels are quite higher as leading with sedentary lifestyle maintaining a positive energy balance may be resulted within insulin resistance, obesity [2], production of new fats in the liver are keys to the development of NAFLD & CAD/CVD. Particularly, changes in hormone levels among the elder adult population contain changes in the drugs such as glucocorticoids or estrogen as well. Toxins are also including with Bacillus cereus toxin and infections like HIV/AIDS, hepatitis C virus (HCV) may result the NAFLD [3]. These are very crucial points to bear in mind when it comes to understanding and how we were able to prevent the disease [4]. NAFLD has been linked with several heightened risk of cerebrovascular accident (CVA) and cardiac complications such as aortic-valve sclerosis, left ventricular hypertrophy, arrhythmias and CAD/CVD/CABG and the cardiac tissue damages are involved [4-5].

Additionally, it triggers in the progression of conditions unlike overweightness, type 2 diabetes mellitus, other metabolic disorders obesity also associated [3-5]. Above all the potential for NAFLD to lead to HCC conditions with irreversible consequences evidence highlights the fact that NAFLD [4]. As it is a complex, multiple-organ disorders that are very necessitates and need prompt diagnosis and treatment among the younger adult populations [5]. It is coexisting with the NAFLD and diabetes mellitus (DM). Key contributor to the

rise of CAD/CVD/CABG [5-6]. Experts reported that environmental factors and patient genetic variability determine the disease progression and their phenotype and genotypic characters in the both aspects of T2DM and NAFLD in the world and our Asian Indian patients [3-6].

A better comprehension of the complex mechanisms of (T2DM and NAFLD coexistence) would be helpful in addressing cardiovascular problems [6]. One of the biggest clinical and public health challenges Diabetes mellitus (DM) is one of the most common chronic diseases has been related to various liver illnesses such as liver enzyme derangements [5-7], non-alcoholic fatty liver disease, hepatocellular carcinoma, and liver cirrhosis had been increased day by day [6]. In interest with the contribution of liver enzymes to prediction of diabetes and glycemic control [6-7]. In the recent decade, clinical and epidemiological studies and provided a strong evidence that NAFLD is closely linked with CVD/CAD progression along with associated morbidity/co-morbidity and mortality in both patients along with and without NAFLD, NASH, T2DM [8].

Although, several mechanistic approaches are develop to contribute cardiovascular consequences and their essential abnormalities in cardiac biomarkers including with (T2DM and NAFLD patients) [7-8]. In an adipose tissue malfunction (ATM), mitochondrial dysfunction (MCD), microbiota, genetic and epigenetic alterations contributing to insulin resistance, glucotoxicity and lipotoxicity are developed spontaneously [9]. According to very basic and text book knowledge blood sugar levels (BSLs) managed well to decrease the risk of complications related to type 2 diabetes T2DM [10]. In addition to microvascular complications is define as Micro means smaller and Vascular means blood vessels [11]. As high blood sugar injure the small blood vessels of the eyes, kidneys, and nerves were leading into the serious issues including with the blindness, kidney failure, foot ulcers requiring amputation, sexual dysfunction in the human [10-11-12]. Microvascular complications had diabetes for many years, and they had related to elevated levels of blood sugar level over time [13]. Patients with diabetes for a long time before they seek medical care complications may be present at the time of initial diagnosis with very common complication of type 2 diabetes is cardiovascular disease (CVD/CAD) [14]. Heart disease/ Heart Failure also increase a person's risk of heart attack and death. There are so many ways to lower the risk of heart disease (CAD/CVD/CABG) [14-15]. It is including with the lifestyle modifications unlike avoiding smoking, eating a healthy diet, exercising regularly morning and evening in time [16]. Patients need to maintain healthy weight and medications to manage blood pressure (BP) and cholesterol as these are required to minimize and need to maintain in an average ranges [17]. Routine check up is quite helpful to prevent (T2DM and NAFLD patients) in the 3 months, 6 months, 9 months and 12 months and follow up regularly [18].

MATERIAL AND METHODS:

Age, sex, BMI, blood pressure, diabetes status, Covariates included

with their lipids TC, TG, LDL, HDL, glycemic indices are FPG, HbA1C, and their physical activity. According to their Multivariable logistic regression applied and estimated that independent effect of SUA levels and hyperuricemia on NAFLD are quite higher in ranges.

RESULTS:

Table No: 1 (New Biomarkers for Nonalcoholic Fatty Liver Disease among the Asian Indian Populations with Type 2 Diabetes Mellitus).

Sl. No:	New Biomarkers	Clinical Application	Diseases Specific	Remarks
1.	Galectin 3	Prognostication, diagnosis, and therapy options	HF	Biomarkers for risk stratification, diagnosis, and management of HF in the clinics.
2.	Withdrawal of Cardioprotective beta-blockers	Prognostication and diagnosis	CVD	Exacerbated by sepsis or systemic inflammatory response syndrome
3.	BNP and pro-peptide N-terminal pro-peptide BNP (NT-proBNP)	Care for assessment of acute coronary syndrome	MCN	Chronic myocardial wall stretch
4.	Cardiac troponin T and I	Assessment of acute coronary syndrome	CVD	Heart failure and cirrhosis
5.	Galectin-3 inhibitors	Prognostication, diagnosis, and therapy options	LD	Cirrhosis-associated Cardiomyopathy
6.	Mineralocorticoid antagonists	Prognostication and diagnosis	LD	Liver Disease
7.	Beta-adrenoreceptor down-regulation	Prognostication and diagnosis	CAD in ESLD	End Stage Liver Disease
8.	Beta-blockers	Prognostication and diagnosis	LD	Liver Transplantation
9.	N-terminal pro-peptide brain natriuretic peptide	Prognostication and diagnosis	CAD in ESLD	Liver Transplantation
10.	Cardiac troponins,	Models for End Stage Liver Disease	LD	ESLD
11.	Soluble suppression of tumorigenesis-2	Myocardial Energy Expenditure	CVD	Heart failure and cirrhosis
12.	Anti-diuretic hormone [ADH] states	Acute myocardial failure	CVD in LD	Cirrhosis-associated Cardiomyopathy

NB: Coronary Artery Disease (CAD), End Stage Liver Disease (ESD), Cardiovascular Diseases (CVD), Liver Disease (LD), Myocardial necrosis (MCN), Heart Failure (HF).

Among 500 patients, the mean age was 70 years. Eighty-five patients (65%) were males and 35 (30.5%) were females in the younger adult. The mean duration of diabetes is 8.85 ± 5.83 , mean HbA1c is 8.69 ± 2.63 . Mean fasting blood sugar and post-prandial blood sugar were 175.4 ± 95.3 and 251 ± 135.5 , respectively. Hyperuricemia associated with increased NAFLD risk and adjusted OR 2.15, 95% CI 1.27–3.65). A stronger association in individuals with elevated triglycerides Stratified analysis revealed that ($TG \geq 2.25$ mmol/L, OR 7.05, 95% CI 1.73–29.15). A negative correlation is seen among Aspartate transferase (AST), gamma-glutamyl transferase (GGT) and AST/Platelet (PLT) ratio, but not alanine aminotransferase (ALT) significantly.

A negative Pearson correlation between HbA1C and liver enzymes are statistically not significant except in the AST/PLT ratio. The importance of monitoring the liver function tests is clinically

uncontrolled with T2DM patients showed association among the new biomarkers Galectin 3, Withdrawal of Cardioprotective beta-blockers, BNP and pro-peptide N-terminal pro-peptide BNP (NT-proBNP), Cardiac troponin (T and I), Galectin-3 inhibitors, Mineralocorticoid antagonists, Beta-adrenoreceptor down-regulation are very good biomarkers for NAFLD, NASH, T2DM and CVDs All parameters were negatively correlated with HbA1C, but statistically significant correlation is seen only with AST: PLT ratio among the older population. Our results indicated that combination therapy along with SGLT2i and pioglitazone is beneficial for managing MASLD, FIB-4 index and APRI score in the Indian population with T2DM patients with MASLD among the elder's adult populations with ESLD. We have got the better results in these newly developed biomarkers for T2DM in NAFLD, NASH, CVD/CAD and liver failure with their associated diseases were observed.

DISCUSSION:

Non-alcoholic fatty liver disease (NAFLD) is a prevalent liver disorder and strongly associated with metabolic dysfunctions in the world [8-9-10]. So, particularly in elderly populations presents with higher prevalence and severity association between their serum uric acid (SUA) levels and NAFLD in older adult rates are pretty higher in number [10-11]. It is focusing with an independent effect of hyperuricemia on NAFLD risk [12]. We enrolled with more than 700 individuals aged ≥ 65 years those who were underwent community health checkups frequently exposure with the variable and baseline SUA levels were reported. The variable outcomes were the occurrence of NAFLD with T2DM patients [12-13].

NAFLD risk was attenuated after adjusting for metabolic factors [14-18]. Hyperuricemia independently increases NAFLD risk in older adults, particularly in those with elevated triglycerides, suggesting a potential synergistic effect [15]. These findings were highlighted that importance of incorporating SUA assessments into routine metabolic evaluations and their developing targeted interventions to mitigate NAFLD risk as well [14-15]. Several studies also supported that type 2 diabetes mellitus (T2DM) had risk factors of metabolic dysfunction associated steatotic liver disease (MASLD). The use of pioglitazone and sodium-glucose co-transporter 2 inhibitors (SGLT2i) has been considering its beneficial effects in reducing liver dysfunction and their associated diseases [15]. We determine the clinical effectiveness of these drugs is quite improving MASLD and T2DM and CVD/CAD [14-15].

Non-alcoholic fatty liver disease (NAFLD) is also a global cause of liver dysfunction [15]. This spectrum of hepatic disorders can progress to severe major conditions in the non-alcoholic steatohepatitis (NASH) and cirrhosis, due to oxidative stress and the sustained cellular injury (SCI) [15-16]. In addition to the Pharmacological options, glutathione (GSH), a key antioxidant, has shown that a specific promising and their potential effect in reducing oxidative stress, maintaining redox balance, and improving patients liver function according to the present data [16]. GSH therapy in the NAFLD patients will be assessed through GSH as the primary intervention for NAFLD in the human subjects. Laboratory report outcomes such as liver function or important oxidative stress markers are giving better picture clinically liver associated diseases [17]. Randomized clinical trials were eligible, while combination therapy studies were included that GSH's effect could be isolated one than the cohort [18].

Exclusions applied to non-NAFLD in vitro models, and non-GSH antioxidant interventions suggested that improvements in alanine transaminase (ALT) levels and reductions in oxidative stress markers like 8-hydroxy-2-deoxyguanosine (8-OHdG) [19-20]. Expert demonstrated that consistent with smaller sample sizes and inconsistent protocols limited to generalizability. Larger-scale RCTs are required to confirm GSH's efficacy and able to determine optimal dosing; assess the long-term effects [20]. GSH's potential as a novel NAFLD therapeutic strategy while emphasizing that need for further studies to refine its clinical application for early management [20-21]. T1D showed higher level of the liver stiffness values than the healthy controls. A weakly positive relationship of liver stiffness was observed with BMI, duration of diabetes including with glycemic control, and serum GGT. Hence one-fourth of children with diabetes showed sonographic evidence of hepatic steatosis as compared to the elder populations [22]. Larger studies are needed to know the effects of obesity, diabetes duration, and metabolic disorders and their control in the both groups. The prevalence and progression of MAFLD in

children with T1D [23]. For more accurate predictive value for diagnosing dyslipidemia, particularly in East Asian men are also these new biomarkers are more important [24-25]. Thus, our study has the clinically potential for identifying high-risk individuals and determining preventive measures for dyslipidemia in a sex-specific manner [26-30]. These biomarkers are more helpful to early diagnosis and prognosis for NAFLD, NASH, T2DM and CVDs were used including with their associated diseases [30-40]. Regular basis health check up is advisable for these patients [41-42]. Beside the glucotoxicity and lipotoxicity need to avoid in these cases are on the priority [42-45].

Recent Advances And Future Prospective:

Cardiovascular disease (CVD) was remaining the leading cause of mortality globally as novel preventative strategies. Omega-3 fatty acids, known for their anti-inflammatory and lipid-lowering properties, have been widely studied for their cardiovascular diseases [46]. Concurrently, the gut micro biome has emerged as a crucial player in health and disease, including CVD. Recent studies have highlighted the influence of omega-3 fatty acids on gut microbiome composition and diversity, and conversely, the gut micro biome's impact on the metabolism and efficacy of omega-3s [47].

Kudzu (*Pueraria* species) is a perennial plant within the Fabaceae family, native to China, Japan, and India [47-48]. It contains isoflavones, including puerarin, daidzein, daidzin, genistein, and genistin molecules [48]. These isoflavones are found throughout the plant and are important in developing pharmaceutical drugs. This review comprehensively analyzes naturally occurring isoflavones in Kudzu, focusing on advanced and green techniques for their extraction, purification, and identification.

Now the growing demand in the global food and pharmaceutical industries their superior efficiency, scalability, and cost-effectiveness, contemporary eco-friendly extraction methods like ultrasound, microwave, enzyme-assisted, and supercritical fluid extraction are gaining prominence to optimize the extraction process. It is driving innovation within industries, and harnessing natural sources, ultimately boosting global economies. Scientific studies confirm that Kudzu isoflavones have various anti-diabetic, neuroprotective, anti-cancer, antioxidant, alcohol detoxification, for cardiovascular protective effects. Clinical trials and observational observed that impact of omega-3 supplementation on gut microbiome and cardiovascular health are discussed, underscoring existing research gaps. As potential for personalized approaches and future research directions to leverage the gut microbiome to enhance the cardiovascular benefits of omega-3 fatty acids are also considered in both of groups. It should be involved with increased in number of patients with varying degrees and stages of liver dysfunction for more comprehensive understanding of how GSH impacts liver health across the spectrum of NAFLD. Additionally, to establish the gold standard as a reliable therapeutic option, future studies should prioritize well-designed, high-quality RCTs with standardized protocols need to ensure consistency in treatment approaches and facilitate robust comparisons across the different populations and ethnicities are also quite important. More number of sample sizes is required in these study designed, RCT and clinical study.

Nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM) both diseases are associated with a multifactorial/complicated aetiology associated with several conditions. It is coexisting with very strong major distinct connection with cardiovascular diseases (CVD/CAD) and liver diseases (LDs). A major ideal understanding and its interaction between NAFLD patients with T2DM, patients with CVDs. Both diseases are required several attention to control the progression of the disease. Although, prevalence rate with several clinical conditions were varied worldwide. In epidemiology and molecular mechanisms behind the relationship between (NAFLD & T2DM) and NAFLD related cardiovascular diseases and their appropriate consequences. Proper management strategies need to develop with newly develop identification with productive aspects of new biomarkers are quite helpful for early management of T2DM and NAFLD with the related cardiovascular diseases (CAD/CVD/CABG). Although, for this several progressions had been attempted. Still we need to develop proper R&D. New biomarkers those are quite helpful. Developed biomarkers very useful for the management of these diseases and their prevention. We have developed as new biomarkers and obtained from liver in our novel research innovation.

Limitations:

Further more research is needed to confirm the efficacy and optimal dosing strategies of GSH interventions in diverse populations for NAFLD, NASH, T2DM and CVDs.

CONCLUSION:

NAFLD poses a significant challenge to patients, healthcare providers, and public health. Healthcare providers must discuss the impact of sustainable lifestyle modification strategies for preventing NAFLD progression and complications were addressing NAFLD requires deliberate actions at the individual, provider, community, and policy levels. We reported that new biomarkers Galectin 3, Withdrawal of Cardioprotective beta-blockers, BNP and pro-peptide N-terminal pro-peptide BNP (NT-proBNP), Cardiac troponin (T and I), Galectin-3 inhibitors, Mineralocorticoid antagonists, Beta-adrenoreceptor down-regulation are very good biomarkers for NAFLD, NASH, T2DM and CVDs is to embrace a healthier lifestyle increase the physical activity, result in weight loss and decreased insulin resistance. The potential to improve insulin sensitivity and protect the liver from damages. So, many complexities and numerous contributing factors including with combination of medications and multifaceted treatment involving lifestyle adjustments and medication therapy is quite important. We encourage the young talents in higher institutions and research scientist are most well come for collaboration with us proper management in the near future for our nation and the world wide is very much essential for common public.

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