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Nonalcoholic Fatty Liver Disease – An Update on Biomarkers and Disease Severity

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Abstract

Nonalcoholic fatty liver disease is a chronic liver disease with prevalence 9-40 percent in different areas of the world. It is estimated that it will become the most common cause for liver transplantation in the coming years. The major causes implicated for fatty liver who consume no or minimal alcohol are toxins environmental like carbon tetrachloride, ethionine, hepatitis B and C, chemicals like insecticides, pesticides, excess fat diet or defective nutrition like protein deficiency, essential nutrient deficiency like vitamin B 12, choline, methionine. In this research biochemical parameters like fasting glucose, insulin, Kidney function tests, liver function tests, lipid profile, serum electrolytes, total proteins and albumin, LDH and others were measured. Two novel biomarkers Adiponectin and Leptin were also measured with Enzyme linked immunosorbent assay. The extent and severity of these biochemical markers were statistically correlated with fibroscan, an established imaging study of liver which quantifies the extent of fatty infiltration called steatosis expressed in kilopascals and controlled attenuated parameters CAP expressed in decibels per meter. The study showed that there may be a correlation of these parameters with disease severity especially of Adiponectin. It may also be used as a therapeutic target in NAFLD.

Keywords: Nafld; Nutrition; Biomarkers; Severity

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Background

Nonalcoholic fatty liver disease is the presence of liver disease in the absence of significant alcohol intake [1]. Nonalcoholic fatty liver disease is the most common chronic liver disease worldwide [2]. It is estimated that in the coming years this is going to be the most common cause of liver transplantation [3]. It is considered the hepatic component of metabolic syndrome. Metabolic Syndrome is characterized by hypertriglyceridemia, hyperlipidemia, hypertension, abdominal obesity, visceral fat deposition, insulin resistance, presence or absence of diabetes mellitus and or cardiovascular diseases [4]. Spectrum of disease includes mild with no clinical findings to severe fat deposition, inflammation and fibrosis progressing to irreversible stages like cirrhosis, end stage liver disease and hepatocellular carcinoma [5]. The disease has been renamed as Metabolic associated fatty liver disease or MAFLD in recent times [6]. Liver is the major organ of our body at the crossroads of all metabolic pathways [7]. Liver dysfunction causes disruption of the normal metabolic pathways and predominance of alternative pathways for metabolism of carbohydrates, fats and proteins that ultimately lead to ageing of liver cells and organ dysfunction [8]. Liver has a capacity of regeneration but in advanced long standing malnourished diseased states this capacity is lost [9].

The prevalence of NAFLD is 9-40 percent depending of geographical location, food habits, lifestyle, and genetic predisposition. There is a variant called lean NAFLD where patients are not obese but metabolically deranged [10]. The most common cause of death in NAFLD is due to cardiovascular disease [11].

This research studies the biomarkers that regulate the metabolic and hormonal pathways in liver leading to cell signaling, cell growth and proliferation, protein modification, protein translocation, transporter channels, enzyme activity, gene transcription [12].

The aim and objective

This study was to find if there exists any correlation between the levels of biomarkers and disease severity in NAFLD.31-40

Lacunae in Knowledge

Liver biopsy is the only way to conclusively prove disease progression and extent of damage in NAFLD. There is an urgent need for noninvasive biomarkers that will exemplify the disease diagnosis in early stages so that progression may be halted [13]. Imaging based latest technologies like Magnetic resonance elastography MRE and Fibroscan have recently been of comparative value as liver biopsy [14].

Materials and Method

Research was conducted in a tertiary care center in departments of gastroenterology and biochemistry [15]. Known cases of NAFLD, adult males and females, aged 18 years and above were included in the study. Sample size calculated was 75 NAFLD cases. Exclusion criteria were cirrhosis, hepatic carcinoma, Wilson's disease, Hepatitis, HIV, autoimmune hepatitis. Subjects of NAFLD confirmed by ultrasound and fibroscan imaging studies were analyzed for serum biomarkers. Biomarker panels were analyzed. The diagnostic gold standard was the fibroscan report that gives the fibrosis values in liver in kilopascal kPa, range 0-75, as a measure of elasticity of liver, majority of the values lie between 4-15 and steatosis or fat content of liver given by controlled attenuated parameter expressed in dB/m or decibels per meter. Anthropometry, height, weight, body mass index, MI, waist circumference was measured. Serum fasting blood sugar levels, Kidney function tests, creatinine, urea, uric acid, liver function tests, total, direct, indirect bilirubin, Aspartate amino transferase, AST, alanine amino transferase, ALT, alkaline phosphatase, gamma glutamhyl transpeptidase, c reactive protein, total protein, albumin, globuliln, lipid profile, total cholesterol, triglycerides, low density cholesterol, very low density cholesterol, high density cholesterol, serum electrolytes, sodium, potassium, calcium, magnesium, chloride, phosphate, lactate dehydrogenase, serum iron, total iron binding capacity (TIBC), percent saturation and unbound iron binding capacity were done in vitrous 5600 autoanalyzer. Serum fasting Insulin, vitamin D, thyroid profile, Free T3, freeT4, thyroid stimulating hormone, measurements were done on electrochemiluminescence ECIQ autoanalyzer in batch. Serum samples collected in serum separator vacutainer tubes were centrifuged for 15 minutes at 4000 rotation per minute and supernatant serum samples were aliquot and stored at -80 degrees Celsius prior to assay. Novel biomarker Adiponectin and Insulin like growth factor-1, IGF-1, assessment were done by Enzyme linked immunosorbent assay ELISA by Biorad washer and automated analyzer. History, anthropometry, serum biochemistry, Elisa records were stored in excel file and analyzed by spss version 28 software.

Results and Analysis

Demographics

Total NAFLD subjects were 75. Out of 75 subjects, 42 were male and 33 were female. Age and sex distribution were normally distributed.

Anthropometry

Body mass index were on the higher side for both male and female, majority were overweight and obese in this study. Waist circumference is a sensitive indicator of abdominal obesity and visceral fat deposits. Waist circumference in the study of both male and female were high.

Biomarker Panels

Fib 4 index were high, 3.14 in the study. So was APRI, BAAT index.

Routine biochemistry

Kidney function tests, liver function tests, total proteins, serum albumin, AG ratio, lipid profile, serum electrolytes, lactate dehydrogenase, iron profile, were done. Significant results are being elaborated. Patients weighted towards higher fasting blood glucose levels. Blood glucose estimation was done by glucose oxidase peroxidase method in dry chemistry Vitros 5600 autoanalyzer. Serum fasting insulin was measured in Electrochemiluminescence autoanalyzer machine and then Homeostatic model of Assessment for insulin resistance, HOMA-IR was calculated. This research showed HOMA IR> 2.5. The normal reference range for HOMA IR is 0.4-1.4. This proves presence of significant insulin resistance among NAFLD patients. Among the liver function tests, AST: ALT ratio was higher, 1.8, than normal, 0.8, in the study. An AST: ALT ratio greater than 2 is suggestive of progression of NAFLD to Nonalcoholic steatohepatitis NASH, hepatitis Cirrhosis, and hepatocellular carcinoma.

Immunoassay

Adiponectin immunoassay is a sandwich ELISA where the standard curve comes out to be a straight line. The reference interval for Adiponectin is 0.4 -19.4 depending on the age, BMI of patient. Adiponectin measures are useful parameters to assess risk for diabetes mellitus, cardiovascular diseases, and visceral obesity. IGF-1 immunoassay is a competitive ELISA where the graph is a hyperbola. The reference range varies according to age normal range being 90-300 IU/ml IGF-1 varies with growth and development, ageing, carbohydrate, fat and protein metabolism. These results were correlated with fibroscan results the LSM values and the CAP scores.

Discussion

Adiponectin is an adipocytokine secreted from adipose tissue. It increases insulin sensitivity and regulates glucose utilization and promotes fatty acid oxidation in liver and muscles. Adiponectin is a 30 kDa protein of 244 amino acids. Its sequence resembles collagen type 7 and complement C1q. It causes vasodilation by enhancing nitric oxide production in endothelial cells. It inhibits cell adhesion to endothelial surface by decreasing expression of surface adhesion molecules. It inhibits expression of SRB1 receptors which are responsible for cholesterol influx into macrophages through an unregulated pathway causing macrophage transformation to foam cells. It has antidiabetic, anti-inflammatory and antiatherogenic functions. SIGNAL TRANSDUCTION CASCADE OF ADIPONECTIN Adiponectin acts through AdipoR1 and AdipoR2 receptors. Adiponectin activates

PPAR α in muscles which activates Acetyl Co A oxidase (ACO) and uncoupler protein 1 (UCP1), which increases fatty acid oxidation and decreases steatosis. PPAR α also Adiponectin stimulates the Liver kinase B 1, LKB1, adenosine monophosphate kinase AMPK pathway. AMPK pathway is the central regulator of metabolism. AMP and ADP rise inside cell in response to physiological stress and activate a host of metabolic reactions inside cells. It decreases steatosis inside liver cells by decreasing steroid response element binding protein (SREBP). It decreases gluconeogenesis and fasting glucose by decreasing phosphoenolpyruvate carboxykinase, PEPCK, and glucose 6 phosphatase, G6Pase. It decreases inflammation by decreasing Tumor necrosis factor alpha TNFα and Monocyte chemoattractant protein 1, MCP1 either by adipoR 2 receptor activation directly or through PPAR α activation. IGF-1 is a small molecule of 7 kDa and 70 amino acids. It is also called somatomedin and effects cellular growth and proliferation. IGF is transported through plasma transport proteins. IGF1 receptor is similar to insulin receptor and is a heterodimer alpha 2 beta2 with a tyrosine kinase activity. Their signal transduction cascade is similar to insulin. IGF1 have a role in skeleton growth including cartilage

SIGNAL TRANSDUCTION PATHWAY FOR IGF-1

IGF-1 is a Insulin-like growth factors (IGFs) bind specifically to the IGF1 receptor on the cell surface of targeted tissues. Ligand binding to α subunit of the receptor leads to a conformational change in the β subunit, resulting in the activation of receptor tyrosine kinase activity. Activated receptor phosphorylates several substrates, including insulin receptor substrates (IRSs) and Src homology collagen (SHC). Phosphotyrosine residues in these substrates are recognized by certain Src homology 2 (SH2) domain-containing signaling molecules. These include, for example, an 85 kDa regulatory subunit (p85) of phosphatidylinositol 3-kinase (PI 3-kinase), growth factor receptor-bound 2 (GRB2) and SH2-containing protein tyrosine phosphatase 2 (SHP2/Syp). These bindings lead to the activation of downstream signaling pathways, PI 3-kinase pathway and Ras-mitogen-activated protein kinase (MAP kinase) pathway. Activation of these signaling pathways is known to be required for the induction of various bioactivities of IGFs, including cell proliferation, cell differentiation and cell survival.

Summary and Conclusion

Adiponectin is a potential marker for diagnosis, follow up and treatment of patients of NAFLD. It acts by increasing insulin sensitivity, improves fat metabolism and pathways, increases glycolysis, glycogenesis, decreases gluconeogenesis and resets body back to normalcy. IGF-1 is also a potential marker with actions on the fat and carbohydrate metabolism, growth, and aging. De Ritz ratio or AST/ALT ratio was 1.8 in the study which is higher than the normal ratio for healthy liver of 0.8 HOMA IR in the study was 2.5 which showed significant insulin resistance. Estimated average glucose is the conversion of HbA1c value to average blood glucose levels. Formula for estimated average glucose is 28.7xA1c -46.7 there is a need for novel noninvasive marker for disease characterization in NAFLD and these two markers may be useful.

Acknowledgement

None

Conflict of Interest

None

References

1 Berardo C, Di Pasqua LG, Cagna M, Richelmi P, Vairetti M, et al. (2020) Nonalcoholic Fatty Liver Disease and Non-Alcoholic Steatohepatitis: Current Issues and Future Perspectives in Preclinical and Clinical Research. Int J Mol Sci 21: E9646.

2 Marques V, Afonso MB, Bierig N, Duarte Ramos F, Santos Laso Á, et al. (2021) Adiponectin, Leptin, and IGF-1 Are Useful Diagnostic and Stratification Biomarkers of NAFLD. Front Med 8: 683250.

3 Younossi Z (2019) Non-alcoholic fatty liver disease – A global public health perspective. J Hepatol 70: 531-544.

4 Giraudi PJ, Stephenson AM, Tiribelli C, Rosso N (2021) Novel high-throughput applications for NAFLD diagnostics and biomarker discovery. Hepatoma Res 7: 2.

5 Younossi Z, Guyatt G, Kiwi M, Boparai N, King D, et al. (1999) Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. Gut 45: 295-300.

6 Ajmera V, Perito E, Bass N, Terrault N, Yates K, et al. (2016) Novel plasma biomarkers associated with liver disease severity in adults with nonalcoholic fatty liver disease. Hepatology. 65: 65-77.

7 Fan J, Kim S, Wong V (2017) new trends on obesity and NAFLD in Asia. J Hepatol 67: 862-873.

8 Gad H (2018) Study of Plasma Adiponectin and Insulin Resistance in Subjects with Non-Alcoholic Fatty Liver Disease. Arch Intern Med 02: 23-26.

9 Finelli C (2013) what is the role of adiponectin in obesity related non-alcoholic fatty liver disease. World J Gastroenterol 19: 802.

10 Utzschneider K, Kahn S (2006) the Role of Insulin Resistance in Nonalcoholic Fatty Liver Disease. The J J Clin Endocrinol 91: 4753-4761.

11 Hui J, Hodge A, Farrell G, Kench J, Kriketos A, et al. (2004) Beyond insulin resistance in NASH: TNF-? Or adiponectin?. Hepatology 40: 46-54.

12 Xue Y, Changming K, Hanhua L, Chunhua Q (2018) Serum cystatin C and cystatin C/albumin ratio for the evaluation of liver function in patients with cirrhosis. Biomed Res 29: 1254-1258.

13 Donahue R, Stranges S, Rejman K, Rafalson L, Dmochowski J, et al. (2007) Elevated Cystatin C Concentration and Progression to Pre-Diabetes: The Western New York Study. Diabetes Care 30: 1724-1729.

14 Sim E, Lee H, Choi H, Jeong D, Son S, et al. (2016) The Association of Serum Cystatin C with Glycosylated Hemoglobin in Korean Adults. Diabetes Metab J 40: 62.

15 Liu X, Liu Y, Chen F (2016) Soluble fibrinogen like protein 2 (sFGL2), the novel effector molecule for immunoregulation. Oncotarget 8: 3711-3723.