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Association of Non -Alcoholic Fatty Liver Disease in Diabetes Mellitus-Chronic Kidney Disease Patients

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Abstract **Original Research Article**

Introduction: Non-Alcoholic Fatty Liver Disease (NAFLD) is now the most common chronic liver condition in the world, affecting up to 9% of people in the developing and up to 30% in the developed world. The aim of the study was to find out the association of Non-Alcoholic Fatty Liver Disease with Diabetes Mellitus-chronic kidney disease (DM-CKD). The aim of the study was to find out the association of Non-Alcoholic Fatty Liver Disease with Diabetes Mellitus-chronic kidney disease (DM-CKD). ***Methods:*** This cross-sectional observational study was carried out at the Nephrology department of Chittagong Medical College Hospital, Chittagong for 6 months, where 50 patients of DM-CKD were enrolled. Data was collected by pretested questionnaire through face-to-face interview from those patients who gave consent and fulfilled inclusion criteria. ***Result:*** Most of the respondents were male 64% and from upper middle class 48%. Among the respondents 34% had non-alcoholic fatty liver disease. Triglyceride level in presence of NAFLD was more (NAFLD pr.=335.12, SD=158.98) vs NAFLD absent (NAFLD ab.=169.64, SD=35.84) and mean LDL level of the patients without NAFLD was more (NAFLD ab.= 124.76 SD=39.24) vs with NAFLD (NAFLD pr.=71.82, SD= 37.16). Mean LDL level of the patients in absence of NAFLD is more (NAFLD ab.= 124.76, SD=39.24) than those NAFLD present (NAFLD pr.=71.82, SD= 37.16). In this study we found a significant relation between Serum Cretinine level and NAFLD (p=0.022). We also found a higher RBS level in patients with NAFLD t (50) =3.699, p= 0.001. ***Conclusion:*** The study found that among DM-CKD patients with NAFLD male from upper middle socio-economic class are more likely to develop the disease. That indicates poor renal function and progression to end stage renal disease is more likely in those patients. Early treatment and strict control of risk factors as well as special attention may halt disease progression in these patients.

Keywords: Diabetes, Cardiac Kidney Diseases, Fatty-Liver Disease, NAFLD.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) in its whole spectrum of disease ranging from simple steatosis to steatohepatitis and cirrhosis due to accumulation of hepatic fat in the absence of alcohol ingestion is one of the most common causes of chronic liver disease [1-3]. Prevalence of NAFLD has been estimated to be in the 15 to 30% range in the general population in various countries [4, 5] which is almost certainly increasing. Epidemiological studies clearly show a very high prevalence of NAFLD in conditions associated with insulin resistance, such as obesity, Type 2 Diabetes Mellitus (T2DM) and metabolic syndrome

[6-13]. The prevalence of NAFLD is 75% and 90% in obese [7, 12, 13] and morbidly obese patients [9, 10] respectively and present in a high proportion (ranging 50%–75%) of patients affected by Type 2 Diabetes Mellitus [6, 11]. So strongly associated with metabolic syndrome [6, 11] that it is often considered the hepatic component of metabolic syndrome [14]. The liver plays a key role in regulating both glucose and lipid metabolism. Derangements in these metabolic pathways are typical features of both NAFLD and T2DM [15]. Fatty liver is not only a target of cytokines like acyl-CoA, ceramide, acyl-carnitines, activate several kinases, including protein kinase C (PKC), mTOR and S6K (which suppress IRS-1 tyrosine phosphorylation and downstream signaling) [16-19] but also the source of several proinflammatory, proatherogenic and nephrotoxic factors that may play a role in the development and progression of both cardiovascular disease (CVD) and chronic kidney disease (CKD) [17-20]. Moreover, NAFLD enhances cardiovascular risk through the contribution to hepatic/systemic insulin resistance and atherogenic dyslipidemia. Additionally, NAFLD may contribute to the pathogenesis of T2DM through the release of some liver-secreted proteins with diabetogenic properties, such as fetuin-A, fibroblast growth factor-21, and retinol binding protein-4 [20]. In T2DM, fasting hyperglycemia results from unopposed endogenous hepatic glucose production, insulin resistance, and postprandial hyperglycemia caused by reduced glucose uptake in skeletal muscle and adipocyte inflammation. Both fasting and postprandial hyperglycemia are, at least in part, linked to the amount of hepatic steatosis [15, 21-23]. Presence of NAFLD raises a suspicion of metabolic syndrome which in turn in DM and CKD patient may cause cerebro-vascular diseases and other vascular complication [24, 25]. NAFLD appears to be associated also with increased prevalence and incidence of CKD among patients with T2DM [20]. Data from the Valpolicella Heart Diabetes Study [26] showed an almost double prevalence of CKD among T2DM patient with ultrasound-diagnosed NAFLD in comparison to those without it. Importantly, the same group reported that NAFLD was associated with an increased risk of incidence of CKD at follow-up in a cohort of 1800 diabetic patients, independently of other renal risk factors [24, 26, 27]. So NAFLD in CKD patient not only increases risk of developing T2DM and CKD, but also worsens glycemic control and contributes to the pathogenesis of major chronic complications of diabetes, such as CVD [28-31]. So if we diagnose NAFLD in DM-CKD patient early, we can at least take measure to pause the progression of NAFLD, hence progression of CKD [29-31]. Compared with individuals without diabetes, patients with T2DM seem to be at increased risk for developing NAFLD and certainly have a higher risk for developing fibrosis and cirrhosis [32-35]. For these reasons, we want to find proportion of NAFLD in DM-CKD under controlling the effects of confounding factors, including age, gender, lifestyle factors, blood glucose, blood lipids, and serum alanine aminotransferase (ALT). NAFLD may be diagnosed by ultra-sonogram of liver [26], which is a noninvasive, cheap, available even in the remotest area of Bangladesh and technical advancement in radiology have led to identification of liver echo-texture more easily. The General objective is to find out the association of NAFLD with DM-CKD. Specific objectives are to find out the proportion of NAFLD in DM-CKD patients, to describe the socio-demographic picture of hospitalized patients with NAFLD and CKD, the difference of biochemical parameter between DM-CKD patients stratified by presence of NAFLD and to find out relation between NAFLD and staging of CKD. There are several studies regarding association of NAFLD in DM-CKD patients in western world, but Study in Bangladesh is limited. So, if we can give a snap shot of NAFLD in DM- CKD, it will help in further large-scale study. Aim of the present study was to find out the association of NAFLD with diabetic CKD patients admitted in CMCH which covers around 15 districts of Bangladesh.

OBJECTIVE

General Objective

- To find out the association of Non-Alcoholic Fatty Liver Disease with Diabetes Mellitus-chronic kidney disease (DM-CKD)

METHODS

This cross-sectional observational study was carried out at the Nephrology department of Chittagong Medical College Hospital, Chittagong. The study duration was 6 months, from July 2017 to December 2017. The study was conducted with a total of 50 patients of DM-CKD from all CKD patients attending the Nephrology department in the study hospital. Diagnosed cases of diabetic CKD patients were thoroughly informed about the aims, objectives and detail procedure of the study before examination. Informed written consent was obtained from all 50 patients participating in the study, and participants were allowed freedom to withdraw from the study whenever they liked, even after participation. Ethical approval was also obtained from the ethical review committee of the study hospital. From the 50 eligible participants, clinical history was taken, and clinical examination was done to elicit findings related to NAFLD and its complication in nonalcoholic Diabetic patients. BP was assessed in triplicate with a standard mercury manometer. Information on daily alcohol consumption, smoking status, and use of medications was obtained from all participants by questionnaire. Hepatic ultrasonography scanning was performed on all participants by experienced radiologist, who was blinded to participants' details. Diagnosis of hepatic steatosis was made on the basis of characteristic sonographic features: evidence of diffuse hyper echogenicity of liver relative to kidneys, ultrasound beam attenuation, and poor visualization of intrahepatic

structures. Other related investigations were done. All relevant data were noted in the pre-tested data sheet. All data were checked and rechecked to avoid error. Data were processed and analyzed using computer software SPSS (Statistical Package for Social Sciences), version 20. Student's t-Test was done at p-value < 0.05 were considered significant.

RESULTS

The table 1 showed that among the respondents most of them were male 32 (64%) and others were female18 (36%). Of them, 18 (36%) respondents were housewives, followed by businessman 17 (34%), service holder 10 (20%), farmer (3). Socio-economic status showed, most are from upper middle class 24 (48%), followed by lower middle, upper class 12 (24%) each and lower class 2 (4%). Table also shows that the mean age of respondents was 56.50 years, SD 9.45, lowest age 32 years and highest age 75 years. The table 1 showed that among the respondents 17 (34%) had non-alcoholic fatty liver disease and rest of the respondents 33 (66%) had not. The table 2 showed that among the respondents the mean cholesterol level of the patients in absence of NAFLD was more (NAFLD ab.= 205.70, SD=38.56) than those NAFLD present (NAFLD pr.=178.53, SD= 44.83) on the other hand mean triglyceride level in presence of NAFLD was more (NAFLD pr.= 335.12, SD=158.98) than those NAFLD absent (NAFLD ab.=169.64, SD= 35.84). Again, mean Low Density Lipoprotein (LDL) level of the patients in absence of NAFLD was more (NAFLD ab.= 124.76, SD=39.24) than those NAFLD present (NAFLD pr.=71.82, SD= 37.16) and mean High Density Lipoprotein (HDL) level of the patients in absence of NAFLD was more (NAFLD ab.= 42.24, SD=5.09) than those NAFLD present (NAFLD pr.=39.76, SD= 7.82). To find out the statistical significance of these differences an independent sample t-test was done, after observing normality of the distribution of the data. The result showed that these differences were highly statistically significant in serum cholesterol [t (50)=2.223, p=0.03], triglyceride [t(50)=5.754, p=0.003] and LDL level [t(50)=5.754, p=0.003], two tailed (assuming equal variances). The table 3 showed that among the respondents regarding biochemical markers the mean ALT level of the patients in presence of NAFLD was more (NAFLD pr.=26.59, SD=5.14) than those NAFLD absent (NAFLD ab.=26.36, SD= 5.12). Mean RBS level of the patients in presence of NAFLD was more (NAFLD pr.=13.62, SD=2.86) than those NAFLD absent (NAFLD ab.=10.83, SD=2.35). Mean prothrombin time of the patients in absence of NAFLD was more (NAFLD ab.= 12.70, SD=0.81) than those NAFLD present (NAFLD pr.=12.65, SD=0.81) and mean Serum Creatinine level of the patients in presence of NAFLD was more (NAFLD pr.=8.58, SD=3.82) than those NAFLD absent (NAFLD ab.=6.04, SD=3.45). To find out the statistical significance of these differences, independent sample t-tests were done after observing normality of the distribution of the data. The result shows that this difference was not significant statistically in case of ALT level [t (50) =0.147, p=0.884] and prothrombin time [t (50) = 0.186, p=0.853] but the result was found significant for RBS level [t (50) =3.699, p=0.001] and Serum Creatinine [t (50) =2.373, p=0.022] two tailed (assuming equal variances). The table 4 showed that among the respondents the mean GFR of the patients in absence of NAFLD was more (NAFLD ab.=16.45, SD=12.72) than those NAFLD present (NAFLD pr.=8.74, SD= 4.95). To find out the statistical significance of this difference an independent sample t-test was done after observing normality of the distribution of the data. The result shows that this difference was significant statistically t(50)=2.395, p=0.021 two tailed (assuming equal variances).

Table-1: Socio-demographic characteristics of respondents (n=50).

Characteristics		Number (%)
Sex	Male	32(64)
	Female	18(36)
Occupation	House Wife	18(66)
	Businessman	17(34)
	Service Holder	10(20)
	Farmer	3(6)
	Others	2(4)
Socio-economic Status	Lower Class	2(4)
	Lower Middle Class	12(24)
	Upper Middle Class	24(48)
	Upper Class	12(24)
Age(years)	Mean ± SD	56.50 ± 9.45
	Age Range	32-75
Non- alcoholic fatty liver disease	Present	17(34)
	Absent	33(66)

Table-2: Difference in Lipid profile between NAFLD present and absent respondents (n=50).

Lipid profile	Category according to presence or absence of NAFLD	n	MEAN	± SD	t test p value
Serum cholesterol	NAFLD Present	17	178.53	44.83	**t** = 2.233
	NAFLD Absent	33	205.70	38.56	p = 0.030
Triglyceride level	NAFLD Present	17	335.12	158.98	**t** = 5.754
	NAFLD Absent	33	169.64	35.84	p = 0.003
Low Density Lipoprotein (LDL) level	NAFLD Present	17	71.82	37.16	**t** = 4.681
	NAFLD Absent	33	124.76	39.24	p = 0.0004
Serum High Density Lipoprotein (HDL) level	NAFLD Present	17	39.76	7.82	**t** = 1.353
	NAFLD Absent	33	42.24	5.09	p = 0.183

Table-3: Difference in Biochemical markers between NAFLD present and absent respondents (n=50).

Biochemical markers	Category according to presence or absence of NAFLD	n	MEAN	± SD	t test value P value
Alanine Transaminase (ALT) level	NAFLD Present	17	26.59	5.14	**t** = 0.147
	NAFLD Absent	33	26.36	5.12	P = 0.884
RBS level	NAFLD Present	17	13.62	2.86	**t** = 3.699
	NAFLD Absent	33	10.83	2.35	P = 0.001
Prothrombin time	NAFLD Present	17	12.65	1.06	**t** = 0.186
	NAFLD Absent	33	12.70	0.81	P = 0.853
Serum Creatinine	NAFLD Present	17	8.58	3.82	**t** = 2.373
	NAFLD Absent	33	6.04	3.45	P = 0.022

Table-4: Difference in Estimated Glomerular Filtration rate (eGFR) between NAFLD present and absent respondents (n=50).

NAFLD Status	n	MEAN	± SD	t test value p value
NAFLD Present	17	8.74	4.95	**t** = 2.395
NAFLD Absent	33	16.45	12.72	p= 0.021

DISCUSSION

This observational study was conducted with a view to determine the association between NAFLD with DM-CKD. All patients of diabetic CKD who were admitted in the CMCH during the study period were selected as cases. There are several studies regarding association of NAFLD in DM-CKD patients in the western world, but Study in Bangladesh is limited. To fill up this data gap, initiative was taken to conduct this observational study. In our study we found that among the respondents (N= 50), 34% (17) had non-alcoholic fatty liver disease and rest of the respondents (33) had no NFALD. 64% of respondents were male and 36% were female, the mean age was 56.5 years with SD ± 9.45 and 48% were from upper middle class. In a previous study, mean age of CKD was 49.5 years [28] and the prevalence of NAFLD increased with increasing age [28, 36]. This may be due early treatment seeking behavior of their population. In our study, serum triglyceride level was significantly higher in patients with NAFLD (p= 0.003) and LDL and Serum cholesterol were significantly more in patients without NAFLD. In previous studies, they also found relationship between NALFD and Serum triglyceride [37]. In our study we also found a significantly raised RBS level in NAFLD patients (p= 0.001) which corresponded with previous study (OR 2.8, 95% CI 1.5–5.20) [38]. In this study, there was no significant difference of serum HDL, serum ALT and prothrombin time between two groups were not significantly different; these correspond to other studies [39, 40] The serum creatinine level in NAFLD patients was significantly higher. We had calculated e-GFR of the patients and found that it was also statistically significantly different in two groups (p=0.02). Some of the earlier studies found no significant relation between serum Creatinine level and NAFLD [25, 40, 41]. But in one study, NAFLD patients had higher (p<0.001) age- and sex-adjusted prevalence rates of CKD (15 vs 9%) than counterparts without NAFLD [26]. In this study logistic regression analysis showed NAFLD was associated with increased rates of CKD (odds ratio 1.87; 95% CI 1.3–4.1, p=0.020) independently of age, sex, BMI, waist circumference, hypertension, diabetes duration, HbA1c, lipids, smoking status and medications use, and they also have proliferative/laser-treated retinopathy (odds ratio 1.75; 1.1–3.7, p=0.031). Nonalcoholic fatty liver disease, diagnosed by liver ultrasound and exclusion of other common causes of chronic liver disease, was associated with a moderately

increased risk for CKD (hazard ratio 1.69; 95% confidence interval 1.3 to 2.6; *P* = 0.001) [42]. Adjustments for gender, age, body mass index, waist circumference, BP, smoking, diabetes duration, glycosylated hemoglobin, lipids, baseline estimated GFR, microalbuminuria and medications (hypoglycemic, lipid-lowering, antihypertensive, or antiplatelet drugs) did not appreciably attenuate this association (hazard ratio 1.49; 95% confidence interval 1.1 to 2.2; *P* = 0.01) [21]. All these findings correspond with the fact that NAFLD exacerbates hepatic insulin resistance. Growing evidence also indicates that NAFLD may worsen glycemic control in people with type 2 Diabetes Mellitus and may contribute to the development and progression of the most important chronic complications of diabetes, such as cardiovascular disease and chronic kidney disease.

Limitations of the Study

The study was conducted in a single hospital with small sample size. So, the results may not represent the whole community. There was no long term follow-up of the patients

CONCLUSION

In contrast with previous studies, our study found that among DM CKD patients NAFLD was more common in male of upper middle socioeconomic class. Serum triglyceride and creatinine level were higher in patients with NAFLD and e-GFR was lower. That indicates poor renal function and progression to end stage renal disease is more likely in DM-CKD patients with NAFLD.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

RECOMMENDATION

Early treatment of NAFLD and strict control of risk factors as well as special attention in this special group of patients with diabetic-chronic kidney disease may halt disease progression.

REFERENCES

1. Athyros, V. G., Tziomalos, K., Gossios, T. D., Griva, T., Anagnostis, P., Kargiotis, K., & GREACE Study Collaborative Group. (2010). Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. *The Lancet*, *376*(9756), 1916-1922.
2. Younossi, Z. M., Stepanova, M., Afendy, M., Fang, Y., Younossi, Y., Mir, H., & Srishord, M. (2011). Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. *Clinical gastroenterology and hepatology*, *9*(6), 524-530.
3. Ratziu, V., Bellentani, S., Cortez-Pinto, H., Day, C., & Marchesini, G. (2010). A position statement on NAFLD/NASH based on the EASL 2009 special conference. *Journal of hepatology*, *53*(2), 372-384.
4. Clark, J. M., Brancati, F. L., & Diehl, A. M. (2003). The prevalence and etiology of elevated aminotransferase levels in the United States. *The American journal of gastroenterology*, *98*(5), 960-967.
5. Bedogni, G., Miglioli, L., Masutti, F., Tiribelli, C., Marchesini, G., & Bellentani, S. (2005). Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. *Hepatology*, *42*(1), 44-52.
6. Akbar, D. H., & Kawther, A. H. (2003). Nonalcoholic fatty liver disease in Saudi type 2 diabetic subjects attending a medical outpatient clinic: prevalence and general characteristics. *Diabetes care*, *26*(12), 3351-3352.
7. Bellentani, S., Saccoccio, G., Masutti, F., Crocè, L. S., Brandi, G., Sasso, F., ... & Tiribelli, C. (2000). Prevalence of and risk factors for hepatic steatosis in Northern Italy. *Annals of internal medicine*, *132*(2), 112-117.
8. de Alwis, N. M. W., & Day, C. P. (2008). Non-alcoholic fatty liver disease: the mist gradually clears. *Journal of hepatology*, *48*, S104-S112.
9. Dixon, J. B., Bhathal, P. S., & O'brien, P. E. (2001). Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. *Gastroenterology*, *121*(1), 91-100.
10. Garcia-Monzón, C., Martín-Pérez, E., Iacono, O. L., Fernández-Bermejo, M., Majano, P. L., Apolinario, A., & Moreno-Otero, R. (2000). Characterization of pathogenic and prognostic factors of nonalcoholic steatohepatitis associated with obesity. *Journal of hepatology*, *33*(5), 716-724.
11. Gupte, P., Amarapurkar, D., Agal, S., Baijal, R., Kulshrestha, P., Pramanik, S., ... & Amarapurkar, A. (2004). Non-alcoholic steatohepatitis in type 2 diabetes mellitus. *Journal of gastroenterology and hepatology*, *19*(8), 854-858.
12. Luyckx, F. H., Desaive, C., Thiry, A., Dewe, W., Scheen, A. J., Gielen, J. E., & Lefebvre, P. J. (1998). Liver abnormalities in severely obese subjects: effect of drastic weight loss after gastroplasty. *International journal of obesity*, *22*(3), 222-226.
13. Nomura, H., Kashiwagi, S., Hayashi, J., Kajiyama, W., Tani, S., & Goto, M. (1988). Prevalence of fatty liver in a general population of Okinawa,

Japan. *Japanese journal of medicine*, *27*(2), 142-149.
14. Wang, Y., Li, Y. Y., Nie, Y. Q., Zhou, Y. J., Cao, C. Y., & Xu, L. (2013). Association between metabolic syndrome and the development of non-alcoholic fatty liver disease. *Experimental and therapeutic medicine*, *6*(1), 77-84.
15. Tiikkainen, M., Bergholm, R., Vehkavaara, S., Rissanen, A., Häkkinen, A. M., Tamminen, M., ... & Yki-Järvinen, H. (2003). Effects of identical weight loss on body composition and features of insulin resistance in obese women with high and low liver fat content. *Diabetes*, *52*(3), 701-707.
16. Nagle, C. A., Klett, E. L., & Coleman, R. A. (2009). Hepatic triacylglycerol accumulation and insulin resistance. *Journal of lipid research*, *50*, S74-S79.
17. Samuel, V. T., Liu, Z. X., Qu, X., Elder, B. D., Bilz, S., Befroy, D., ... & Shulman, G. I. (2004). Mechanism of hepatic insulin resistance in non-alcoholic fatty liver disease. *Journal of Biological Chemistry*, *279*(31), 32345-32353.
18. Chen, M. T., Kaufman, L. N., Spennetta, T., & Shrago, E. (1992). Effects of high fat-feeding to rats on the interrelationship of body weight, plasma insulin, and fatty acyl-coenzyme A esters in liver and skeletal muscle. *Metabolism*, *41*(5), 564-569.
19. Holland, W. L., Brozinick, J. T., Wang, L. P., Hawkins, E. D., Sargent, K. M., Liu, Y., ... & Summers, S. A. (2007). Inhibition of ceramide synthesis ameliorates glucocorticoid-, saturated-fat-, and obesity-induced insulin resistance. *Cell metabolism*, *5*(3), 167-179.
20. Targher, G., & Byrne, C. D. (2013). Nonalcoholic fatty liver disease: a novel cardiometabolic risk factor for type 2 diabetes and its complications. *The Journal of Clinical Endocrinology & Metabolism*, *98*(2), 483-495.
21. Bedogni, G., Miglioli, L., Masutti, F., Tiribelli, C., Marchesini, G., & Bellentani, S. (2005). Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. *Hepatology*, *42*(1), 44-52.
22. Browning, J. D., Szczepaniak, L. S., Dobbins, R., Nuremberg, P., Horton, J. D., Cohen, J. C., ... & Hobbs, H. H. (2004). Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology*, *40*(6), 1387-1395.
23. Abenavoli, L., & Beaugrand, M. (2012). Transient elastography in non-alcoholic fatty liver disease. *Annals of hepatology*, *11*(2), 172-178.
24. Targher, G., Chonchol, M., Bertolini, L., Rodella, S., Zenari, L., Lippi, G., ... & Muggeo, M. (2008). Increased risk of CKD among type 2 diabetics with nonalcoholic fatty liver disease. *Journal of the American Society of Nephrology*, *19*(8), 1564-1570.
25. Wong, V. W. S., Vergniol, J., Wong, G. L. H., Foucher, J., Chan, H. L. Y., Le Bail, B., ... & de Lédinghen, V. (2010). Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. *Hepatology*, *51*(2), 454-462.
26. Targher, G., Bertolini, L., Rodella, S., Zoppini, G., Lippi, G., Day, C., & Muggeo, M. (2008). Non-alcoholic fatty liver disease is independently associated with an increased prevalence of chronic kidney disease and proliferative/laser-treated retinopathy in type 2 diabetic patients. *Diabetologia*, *51*(3), 444-450.
27. Hwang, S. T., Cho, Y. K., Yun, J. W., Park, J. H., Kim, H. J., Park, D. I., ... & Jin, W. (2010). Impact of non-alcoholic fatty liver disease on microalbuminuria in patients with prediabetes and diabetes. *Internal medicine journal*, *40*(6), 437-442.
28. Smith, B. W., & Adams, L. A. (2011). Nonalcoholic fatty liver disease and diabetes mellitus: pathogenesis and treatment. *Nature Reviews Endocrinology*, *7*(8), 456-465.
29. Zoppini, G., Targher, G., Trombetta, M., Lippi, G., & Muggeo, M. (2009). Relationship of Serum γ-Glutamyltransferase to Atherogenic Dyslipidemia and Glycemic Control in Type 2 Diabetes. *Obesity*, *17*(2), 370-374.
30. Ryysy, L., Häkkinen, A. M., Goto, T., Vehkavaara, S., Westerbacka, J., Halavaara, J., & Yki-Järvinen, H. (2000). Hepatic fat content and insulin action on free fatty acids and glucose metabolism rather than insulin absorption are associated with insulin requirements during insulin therapy in type 2 diabetic patients. *Diabetes*, *49*(5), 749-758.
31. Seppälä-Lindroos, A., Vehkavaara, S., Häkkinen, A. M., Goto, T., Westerbacka, J., Sovijärvi, A., ... & Yki-Järvinen, H. (2002). Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. *The Journal of Clinical Endocrinology & Metabolism*, *87*(7), 3023-3028.
32. Adams, L.A., Angulo, P., Lindor, K.D. (2005). Nonalcoholic fatty liver disease. CMAJ 172:899–905
33. Day, C.P. (2006). Nonalcoholic fatty liver disease: current concepts and management strategies. Clin Med 6:19–25
34. McCullough AJ (2006) Pathophysiology of non-alcoholic steato hepatitis. J Clin Gastroenterol 40 (Suppl 1):S17–S29
35. Marchesini, G., Marzocchi, R., Agostini, F., Bugianesi, E. (2005). Nonalcoholic fatty liver disease and the metabolic syndrome. Curr Opin Lipidol 16:421–427
36. US Renal Data System: USRDS. (2003). Annual Data Report: Atlas of End-Stage Renal Disease in the United States, Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2003.

37. de Vinuesa, S. G., Ortega, M., Martinez, P., Goicoechea, M., Campdera, F. G., & Luño, J. (2005). Subclinical peripheral arterial disease in patients with chronic kidney disease: prevalence and related risk factors. *Kidney International*, *67*, S44-S47.
38. O'Hare, A.M. (2005). Management of peripheral arterial disease in chronic kidney disease.Cardiology clinics, *23*(3); 225-36.
39. Dhaliwal, G., & Mukherjee, D. (2007). Peripheral arterial disease: epidemiology, natural history, diagnosis and treatment. *International Journal of Angiology*, *16*(02), 36-36.
40. Selvin, E., & Erlinger, T. P. (2004). Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999–2000. *Circulation*, *110*(6), 738-743.
41. McDermott, M. M., Mehta, S., & Greenland, P. (1999). Exertional leg symptoms other than intermittent claudication are common in peripheral arterial disease. *Archives of Internal Medicine*, *159*(4), 387-392.
42. Jimba, S., Nakagami, T., Takahashi, M., Wakamatsu, T., Hirota, Y., Iwamoto, Y., & Wasada, T. J. D. M. (2005). Prevalence of non-alcoholic fatty liver disease and its association with impaired glucose metabolism in Japanese adults. *Diabetic medicine*, *22*(9), 1141-1145.