Hellenic Diabetological Chronicles 32, 3: 150-155, 2019

New insights in NAFLD and diabetic nephropathy in patients with diabetes mellitus type 2

Grigorios G. Dimas

Senior Lecturer in Nephrology, Director of Outpatient Clinic in Nephrology & Hypertension, Responsible of Renal Research Laboratory of the Department & Chief Physician in Clinical Nephrology of 1st Propaedeutic Medical Department of Internal Medicine AHEPA University Hospital, Aristotle University of Thessaloniki, Secretary of Hellenic College of Nephrology and Hypertension (EKONY), Chairman of Scientific committee of International Cardiothorasic-Renal Academy, ICRA 2014-2020, Greece

Non-alcoholic fatty liver disease (NAFLD) is characterized by the accumulation of fat in the liver of people who take minimal or no alcohol. It incorporates a spectrum of conditions ranging from simple steatosis to steatohepatitis, advanced fibrosis and cirrhosis[1].

NAFLD is emerging as the most common cause of chronic liver disease worldwide. The global prevalence of NAFLD is believed to be as high as 25%[1]. In Europe, the prevalence in the general population has been shown to be between 2% and 44%[1,2]. The prevalence of NAFLD is observed to be much higher (24%-69.5%) in patients with diabetes mellitus[3-5]. The variation in prevalence estimates relates to the methods used in the diagnosis of NAFLD. Chronic Kidney Disease (CKD) is a global public health problem, affecting >25% of individuals above the age of 65 years in Western adult populations[6,7].

The US Renal Data System reports that over 670.000 people in the USA received some form of renal replacement therapy (RRT) at the end of 2014, and this number is predicted to reach 2.2 million by 2030[7]. The association between NAFLD, CKD and cardiovascular disease (CVD) has been of increasing interest in recent years. Despite being regarded as the hepatic component of the metabolic syndrome, which includes diabetes, hypertension and obesity, NAFLD has been shown to be an independent risk factor associated with CVD[8-10]. In patients with NAFLD, a high incidence and prevalence of CKD have been observed and a strong association between the two conditions has been reported[11-15]. CKD in itself is an independent risk factor for CVDs, and the majority of patients do not reach end-stage renal disease (ESRD) due to the high risk of mortality associated with cardiovascular events[16-18]. The presence of NAFLD in advanced CKD patients is likely to compound their cardiovascular risk.

All recent studies were not conducted to gain insight into the prevalence of NAFLD in advanced CKD and to investigate whether NAFLD had any influence on three primary outcomes:

i) all-cause mortality

ii) non-fatal cardiovascular events (NFCVEs) and

iii) rate of progression of CKD in a large cohort of non-dialysis CKD patients.

The most recent observational study has given further insights into the association of NAFLD with CVD, CKD progression and mortality in patients with CKD. The prevalence of NAFLD was 17.9% in their secondary care CKD cohort.

Prevalence was much higher (30.7%) in diabetics[19]. These data are similar to the reported prevalence of NAFLD in other international populations[2,20,21]. The prevalence was almost the same as that reported in a large US general population survey (19%) that used ultrasound in the diagnosis of NAFLD[22]. Although a very high prevalence (85.5%) of NAFLD as determined by fibroscan has been reported in a CKD cohort, this was a small study, involving only 62 patients[23]. The wide variation in prevalence estimates depicts the methods used in the diagnosis of NAFLD.

In overall CKD populations, patients with NAFLD were more likely to have components of the metabolic syndrome including hypertension, diabetes, hyperlipidaemia and high body mass index, lending support for the association of NAFLD with the metabolic syndrome[24-26]. The total cholesterol HDL ratio was significantly greater in the NAFLD group, which also reinforces the link to the metabolic syndrome[27]. The United States National Health and Nutrition Examination Survey (NHANES-III) study also showed similar all-cause mortality of all age groups in participants with and without NAFLD[28,29].

Recent research has shown that liver fat related to hypovitaminosis D may increase the risk of hypertension, vascular disease, diabetes mellitus, obesity and Metabolic Syndrome[30]. Several pro-inflammatory and oxidative stress mechanisms have been postulated to explain the relationship between these two conditions [fig. 1].

This association of NAFLD with CVD has been consistently shown in meta-analyses and systematic reviews of the general population[31,32]. NAFLD is closely linked to obesity[33,34]. Several potential pathophysiological mechanisms, including the role of pro-oxidant, proinflammatory and procoagulant mediators, have been postulated to be responsible for the increased CVD risk in NAFLD patients[35-38].

We have previously studied how fast and easily mobilisable is hepatic fat with proper diet and organized lifestyle intervention within 4-8 weeks. In 62 out of 100 diabetics with marked hepatic fat, 20 minutes walking a day and Mediterranean diet (fish, vegetables, raw olive oil...) was reduced to elimination the hepatic fat within 30-60 days[39-43]. Irisin, a hormone very recently discovered at Harvard Medical School, produced at mouse and human muscles may form the bases for new treatments against obesity and diabetes[44,45].

Recently it has been shown an association of visceral obesity and liver fat[46]. The metabolic active products of adipose tissue concern lipokines (TNF-

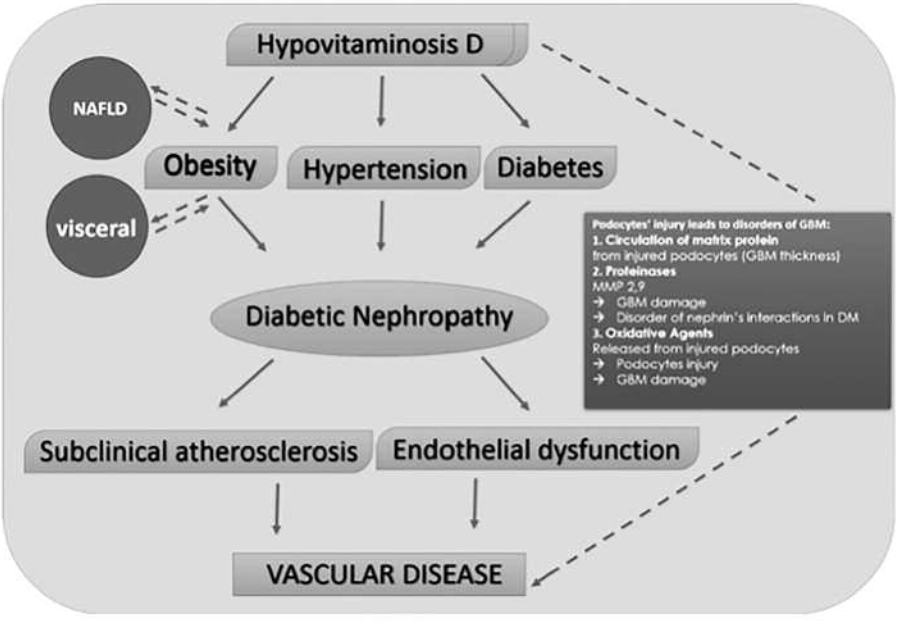

Figure 1. *Association of obesity, hypertension, diabetic nephropathy and vascular disease with hypovitaminosis D.*

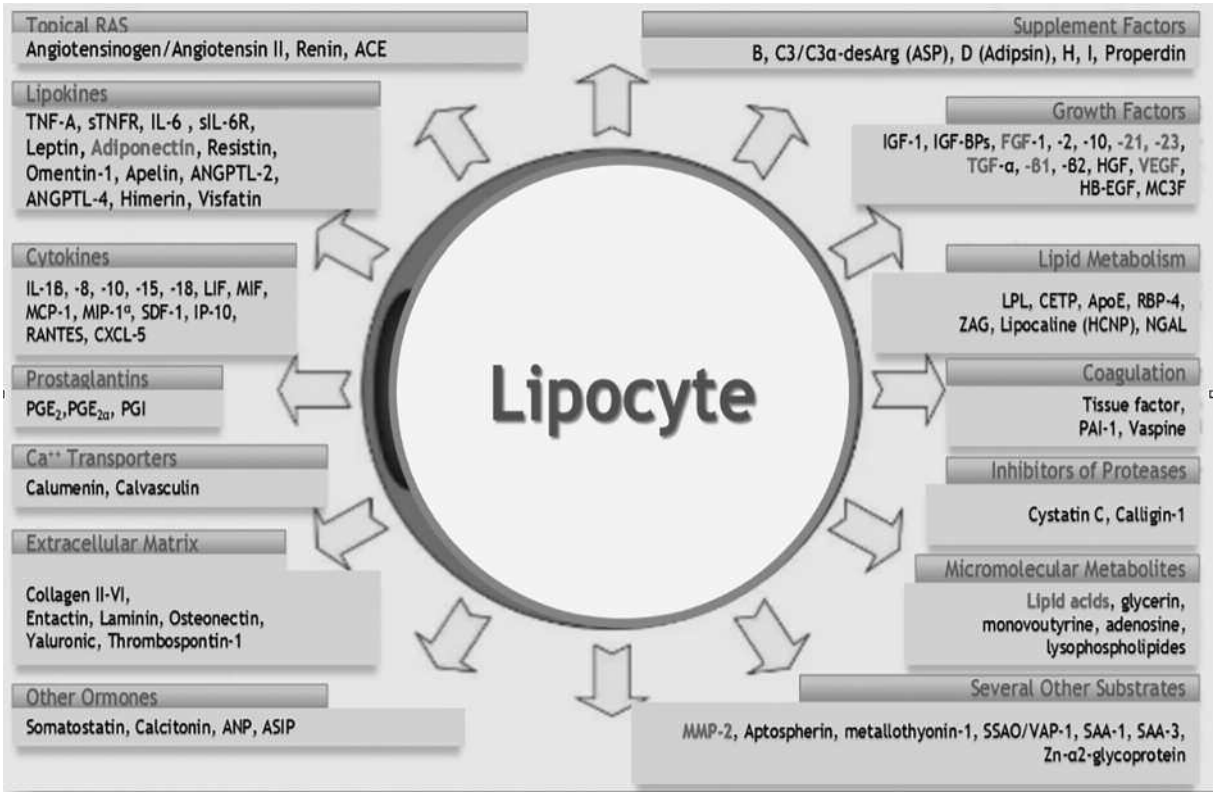

Figure 2. *Metabolic active products of adipose tissue.*

a, leptin, adiponectin), cytokines (MMP-2, IL-1β, IL-6), prostaglantins, extracellular matrix molecules (Col II-VI, laminin, yaluronic, thrombospontin), growth factors (IGF-1, FGF-1-2-10-21-23, TGF-a, VEGF), molecules of lipid metabolism (apo-E, NGAL), inhibitors of proteases (Cystatin C) and other substrates [fig. 2].

Fetuin A is a hepatokine that represents a key player in obesity, liver fat, diabetes, nephropathy and CVD. Fetuin A induces cytokine expression and suppresses adiponectin production[47]. It has been shown the association of fetuin A with insulin resistance and fat accumulation in the liver of humans[48]. Fetuin A is associated with diabetes type-2 and CVD[49,50].

Increased ECM production in fibrosis is due to overproduction of its physiological components, such as fibronectin, laminin, proteoglycans and type IV collagen, as well as the accumulation of proteins that do not normally occur in ECM, such as type I and III collagen in its mesangium glomerulus.

VEGF plays a major role to those interactions [fig. 3, 4].

Thus, the proposed human model includes diabetics with increased levels and vessels' expression of VEGF-A, FGF-23, fetuin-A, decreased levels of adiponectin and irisin, increased levels of IL-6 are associated in patients who will develop albuminuria and hypertension: from 4 to 10 fold higher.

VEGF-A g FGF-23 g Fetuin-Ag / Adiponecting / Irising IL-6

The disorders of filtration barrier in proteinuric disease include fusion of podocytes foot processes, detachment of podocytes loss in urine, focal and segmental stripping of GBM sections, focal adhesions of GBM with epithelial wall of Bowman's capsule leading to segmental glomerulosclerosis and loss of podocytes' number and finally proteinuria[51,52].

The causes of previous disorders concern detachment or apoptosis, absence of proliferation, DNA damage and hypertrophy[53].

Intact Podocytes are found in urine of glomerular disease, diabetic or not. More sensitive marker of renal damage than proteinuria is related to the intensity of proteinuria and the extend of glomerulosclerosis (detected when the number of podocytes is

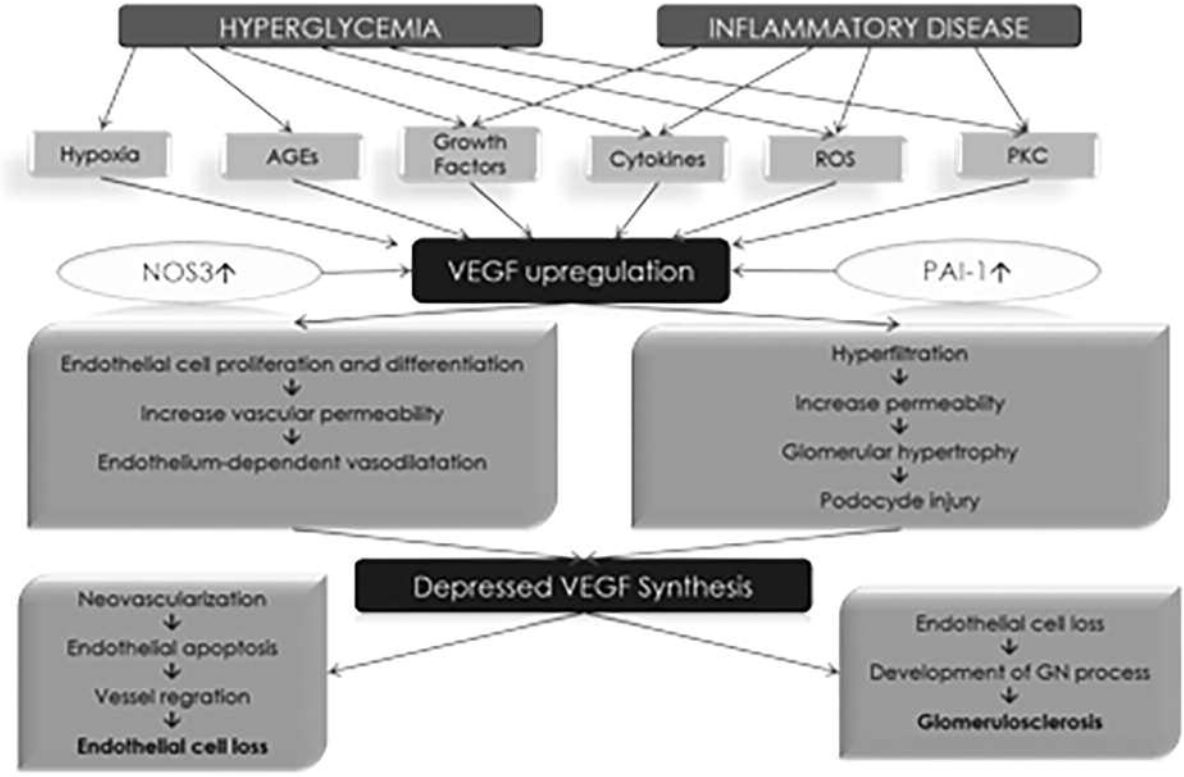

Figure 3. *Schematic overview of the role of VEGF in vessels and kidney alterations of Diabetic Nephropathy and Primary Chronic Glomerulonephritis.*

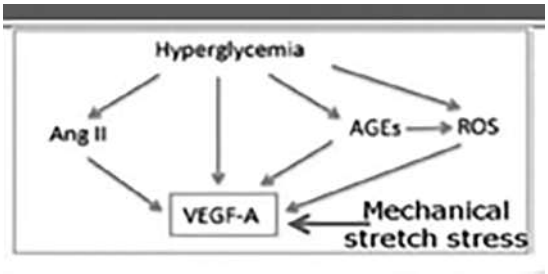

Figure 4. *Interactions of VEGF in Diabetes.*

reduced by 20%)[51-53]. Diabetic glomerular disease depends on podocyte number and this decrease seems more pronounced on the presence of NAFLD.

Disruption to any part of the filtration barrier may lead to proteinuria with or without fusion of podocyte foodpads. All three sections of the filtration barrier are in constant communication (molecular and biochemical) by interaction of extracellular matrix cells, growth factors (VEGF, TGF-β) and interaction of receptors – connectors[51-53].

Serra et al. studied the architecture of renal biopsies in 95 patients undergoing surgical treatment for severe obesity and had normal renal function. FSGS (Focal Segmental Glomerulosclerosis) was found in only 5/95 patients and not at all in the controls[54]. Increased mesangial hyperplasia, podocyte hypertrophy and generally glomerulomegaly were found more often in obese patients than in controls. This study showed that obesity increases the risk for both renal disease and chronic renal failure. Performing renal biopsy in relation with the study of renal function in patients with severe obesity without yet having impaired renal dysfunction (e.g. proteinuria) has helped enough the Nephrologists to investigate the pathophysiology of the kidneys and the pathogenesis of their histological damage[54].

In another recent study of Chen et al. concerning the investigation of obesity-related glomerulonephritis (ORG) of 90 patients it was found that most patients with ORG had normal renal function and FSGS[55].

However, a few studies have found NAFLD a risk factor associated with all-cause mortality, but these have been population-based studies with no mention of renal stages.

Although liver biopsy is the gold standard for the diagnosis of fatty liver disease, its invasive na-

ture clearly precludes its use in routine screening[56]. Fibroscan and magnetic resonance spectroscopy are more accurate techniques, but their use in the clinical setting is limited by their costs and availability[57]. Although ultrasound lacks sensitivity for the diagnosis of early steatosis in advanced CKD patients, due to increased renal cortical echogenicity in CKD, overall, because of its low cost, safety and accessibility, ultrasound is the recommended imaging technique for screening for fatty liver in the clinical and general population settings[56,57].

CKD patients are likely to be receiving RAS blockers, statins and some diabetics, metformin, which are all treatments used in management in NAFLD in the general population. Several scoring systems have been developed to help in early diagnosis, and utilization of other biomarkers may have a role in the future[56,57]. Further evaluation of the importance of NAFLD in the outcome of patients with advanced CKD should include consideration of concomitant treatments that might confound the results of studies.

ln conclusion, it is obvious that NAFLD is a strong and independent risk factor for cardiovascular events in patients with advanced CKD, a group already at high cardiovascular risk. The presence of NAFLD did not have an impact either on all-cause mortality or CKD progression. However, prospective studies with diagnostic techniques better suited to advanced CKD are needed to further evaluate the replicability of the findings described. We recommend the use of routine ultrasound screening for all higher risk CKD patients for early identification of this hidden risk factor so that targeted interventions can be planned to prevent future cardiovascular events.

References

1. *Younossi ZM, Koenig AB, Abdelatif D, et al*. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016; 64: 73-84.
2. *Blachier M, Leleu H, Peck-Radosavljevic M, et al*. The burden of liver disease in Europe: a review of available epidemiological data. J Hepatol 2013; 58: 593-608.
3. *Williamson RM, Price JF, Glancy S, et al*. Prevalence of and risk factors for hepatic steatosis and nonalcoholic fatty liver disease in people with type 2 diabetes: the Edinburgh type 2 diabetes study. Diabetes Care 2011; 34: 1139-1144.
4. *Targher G, Bertolini L, Padovani R, et al*. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diabetes Care 2007; 30: 1212-1218.
5. *Gaiani S, Avogaro A, Bombonato GC, et al*. Nonalcoholic fatty liver disease (NAFLD) in nonobese patients with diabetes: prevalence and relationships with hemodynamic alterations detected with Doppler sonography. J Ultrasound 2009; 12:1-5.
6. *McCullough K, Sharma P, Ali T, et al*. Measuring the population burden of chronic kidney disease: a systematic literature review of the estimated prevalence of impaired kidney function. Nephrol Dial Transplant 2012; 27: 1812-1821.
7. *Stevens PE, Levin A*. Guideline evaluation and management of chronic kidney disease: synopsis of the Kidney Disease: Improving Global Outcomes. 2012 Clinical. Ann Intern Med 2014; 158: 825-831.
8. *Liu FI, Lu H-Y*. Nonalcoholic fatty liver disease and cardiovascular disease. World J Gastroenterol 2014; 20: 8407-8415.
9. *Ahmed MH, Barakat S, Almobarak AO*. Non-alcoholic fatty liver disease and cardiovascular disease: has the time come for cardiologists to be hepatologists. J Obes 2012; 2012: 483135.
10. *Mellinger JL, Pencina KM, Massaro JM, et al*. Hepatic steatosis and cardiovascular disease outcomes: an analysis of the Framingham Heart Study. J Hepatol 2015; 63: 470-476.
11. *Targher G, Bertolini L, Rodella S, et al*. 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 2008; 51: 444-450.
12. *Targher G, Mantovani A, Pichiri I, et al*. Nonalcoholic fatty liver disease is independently associated with an increased incidence of chronic kidney disease in patients with type 1 diabetes. Diabetes Care 2014; 37: 1729-1736.
13. *Marcuccilli M, Chonchol M*. NAFLD and chronic kidney disease. Int J Mol Sci 2016; 17: 1-15.
14. *Targher G, Chonchol M, Zoppini G, et al*. Risk of chronic kidney disease in patients with non-alcoholic fatty liver disease: is there a link? J Hepatol 2011; 54: 1020-1029.
15. *Musso G, Gambino R, Tabibian JH, et al*. Association of non-alcoholic liver disease with chronic kidney disease: a systematic review and meta-analysis. PLoS Med 2014; 11: e1001680.
16. *Samak MJ, Levey AS, Schoohverth AC, et al*. Kidney disease as a risk factor development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, Blood Pressure Research, Clinical Cardiology, and Epidemiology a Prevention. Circulation 2003; 108: 2154-2169.
17. *Rahman M, Xie D, Feldman H, et al*. Association between chronic kidney disease progression and cardiovascular disease: Results from the CP study. Am J Nephrol 2014; 40: 399-407.
18. *Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, et al*. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet 2013; 382: 339-352.
19. *Chinnadurai R, Ritchie J, Green D and Kalra PA*. Non-alcoholic fatty liver disease and clinical outcomes in chronic kidney disease. Nephrol Dial Transplant 2019; 34: 449-457.
20. *Loomba R, Sanyal AJ*. The global NAFLD epidemic. Nat Rev Gastroenterol Hepatol 2013; 10: 686-690.
21. *Armstrong MJ, Houlihan DD, Bentham L, et al*. Presence and several non-alcoholic fatty liver disease in a large prospective primary care cohort. J Hepatol 2012; 56: 234-240.

22. *Lazo M, Hemaez R, Eberhardt MS, et al*. Prevalence of nonalcoholic liver disease in the United States: the Third National Health and Nutrition Examination Survey, 1988-1994. Am J Epidemiol 2013; 178: 38-45.
23. *Mikolasevic I, Racki S, Bubic I, et al*. Chronic kidney disease and nonalcoholic fatty liver disease proven by transient elastography. Kidney Blood Res 2013; 37: 305-310.
24. *Hamaguchi M, Kojima T, Takeda N, et al*. Nonalcoholic fatty liver disease a novel predictor of cardiovascular disease. World J Gastroenterol 2007; 13: 1579-1584.
25. *Azzam H, Malnick S*. Non-alcoholic fatty liver disease - the heart of the matter. World J Hepatol 2015; 7: 1369-1376.
26. *Wójcik-Cichy K, Koślińska-Berkan E and Piekarska A*. The influence of NAFLD on the risk of atherosclerosis and cardiovascular diseases. Clin Exp Hepatol. 2018; 4: 1-6.
27. *Ahn A-L, Choi J-K, Kira M-N, et al*. Non-alcoholic fatty liver disease and chronic kidney disease in Koreans aged 50 years or older. Korean J Fam Med 2013; 34: 199-205.
28. *Kim D, Kim WR, Kim HJ, et al*. Association between noninvasive fibrosis markers and mortality among adults with nonalcoholic fatty liver disease in the United States. Hepatology 2013; 57: 1357-1365.
29. *Musso G, Gambino R, Cassader M, et al*. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Ann Med 2011; 43: 617-649.
30. *Oruc CU, Akpinar YE, Amikishiyev S, et al*. Hypovitaminosis D is Associated with Endothelial Dysfunction in Patients with Metabolic Syndrome. Curr Vasc Pharmacol. 2017; 15: 152-157.
31. *Wu S, Wu F, Ding Y, et al*. Association of non-alcoholic fatty liver disease with major adverse cardiovascular events: a systematic review and meta-analysis. Sci Rep 2016; 6: 33386.
32. *Lu H, Liu H, Hu F, et al*. Independent association between nonalcoholic fatty liver disease and cardiovascular disease: a systematic review and meta-analysis. Int J Endocrinol 2013; 2013: 1.
33. *Fabbrini E, Sullivan S and Klein S*. Obesity and Nonalcoholic Fatty Liver Disease: Biochemical, Metabolic and Clinical Implication. Hepatology 2010; 51: 679-689.
34. *Nimptsch K, Konigorski S, Pischon T*. Diagnosis of obesity and use of obesity biomarkers in science and clinical medicine. Metabolism 2019; 92: 61-70.
35. *Bonora E, Targher G*. Increased risk of cardiovascular disease and chronic kidney disease in NAFLD. Nat Rev Gastroenterol Hepatol 2012; 9: 372-381.
36. *Francque SM, van der Graaff D, Kwanten WJ*. Non-alcoholic fatty liver disease and cardiovascular risk: Pathophysiological mechanisms and implications. J Hepatol 2016; 65: 425-443.
37. *He L, Deng L, Zhang Q, et al*. Diagnostic value of CK-18, FGF-21, and related biomarker panel in nonalcoholic fatty liver disease: a systematic review and meta-analysis. BioMed Research International 2017; 2017: 9729107.
38. *Dimas GG, Iliadis FS, Tegos TJ, et al*. Circulating FGF-23 as an independent correlate of hypertension and atherosclerosis in early stages of CKD. J Hypertens 2015; 33 Suppl 1: e50.
39. *Dimas GG, Iliadis FS, Tegos TJ, et al*. Increased circulating levels of VEGF-A as an independent correlate of proteinuria in early stages of chronic kidney disease. BANTAO Journal 2011; 9: 2 (Suppl.1).
40. *Dimas GG, Iliadis FS, Grekas DM*. Matrix metalloproteinases, atherosclerosis, proteinuria and kidney disease: Linkage-based approaches. Hippokratia 2013; 17: 292-7.
41. *Dimas GG, Iliadis FS, Tegos TJ, et al*. Serum levels of TIMP-1 and IL-6 are associated with hypertension and atherosclerosis in patients with early stages of chronic kidney disease and type 2 diabetic nephropathy. J Hypertens 2015; 33 Suppl 1: e55.
42. *Dimas GG, Balanikas G, Iliadis FS, et al*. Effect of anti-VEGF agents for diabetic retinopathy and sub-clinical atherosclerosis in hypertensive patients with diabetic nephropathy in early stages. Joint Meeting of International and European Societies of Hypertension, Athens, June 13-16, 2014 (oral session 7A: "Therapeutic Aspects"). J Hypertens 2014; Vol 32: e92 (e-Supplement 1).
43. *Dimas GG, Didangelos TP, Grekas DM*. Matrix Gelatinases in Atherosclerosis and Diabetic Nephropathy: Progress and Challenges. Curr Vasc Pharmacol 2017; 15(6): 557-565.
44. *Kabak B, Belviranli M, Okudan N*. Irisin and myostatin responses to acute high-intensity interval exercise in humans. Horm Mol Biol Clin Investig 2018; doi: 10.1515/hmbci-2018-0008.
45. *Reza MM, Subramaniyam N, Sim CM, et al*. Irisin is a pro-myogenic factor that induces skeletal muscle hypertrophy and rescues denervation-induced atrophy. Nature Communications 2017; 8: doi:10.1038/s41467-017-01131-0.
46. *Ha Y, Seo N, Shim JH, et al*. Intimate association of visceral obesity with non-alcoholic fatty liver disease in healthy Asians: a case control study. J Gastroenterol Hepatol 2015; 30: 1666-1672.
47. *Hennige AM, Staiger H, Wicke C, et al*. Fetuin-A Induces Cytokine Expression and Suppresses Adiponectin Production. PLoS One. 2008; 3:e1765. doi: 10.1371/journal.pone.0001765.
48. *Stefan N, Hennige AM, Staiger H, et al*. Fetuin A is associated with insulin resistance and fat accumulation in the liver in humans. Diabetes Care 2006; 29: 853-857.
49. *Stefan N, Fritsche A, Weikert C, et al*. Plasma fetuin-A levels and the risk of type 2 diabetes. Diabetes 2008; 57: 2762-7.
50. *Weikert C, Stefan N, Schulze MB, et al.* Plasma fetuin-a levels and the risk of myocardial infarction and ischemic stroke. Circulation 2008; 118: 2555-62.
51. *Zhang A, Huang S*. Progress in Pathogenesis of Proteinuria. Int J Nephrol 2012: 314251.
52. *D'Amico G and Bazzi C*. Pathophysiology of proteinuria. Kidney Int 2003; 63: 809-825.
53. *Jarad G and Miner JH*. Update on the glomerular filtration barrier. Curr Opin Nephrol Hypertens 2009; 18: 226-232.
54. *Serra A, Romero R, Lopez D, et al*. Renal injury in the extremely obese patients with normal renal function. Kidney Int 2008; 73: 947-755.
55. *Chen HM, Li Sj, Chen HP, et al*. Obesity-Related Glomerulopathy in China: A case series of 90 Patients. Am J Kidney Dis 2008; 52: 58-65.
56. *Musso G, Cassader M, Cohney S, et al*. Emerging liver-kidney interact in nonalcoholic fatty liver disease. Trends Mol Med 2015; 21: 645-662.
57. *Hemaez R, Lazo M, Bonekamp S, et al.* Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. Hepatology 2011; 54: 1082-1090.