We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

Open access books available
International authors and editors
Downloads

Countries delivered to
TOP 1%
Contributors from top 500 universities

Our authors are among the
most cited scientists

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
Association Between Fatty Liver and Cardiovascular Disease: Mechanism and Clinical Implications

Nseir W.1,3 and Assy N.2,3

1Departments of Internal Medicine, Holy Family Hospital, Nazareth,
2Liver Unit, Ziv Medical Center, Safed
3Faculty of Medicine, Technion, Haifa, Israel

1. Introduction

NAFLD is associated with major cardiovascular risk factors including type 2 diabetes mellitus (T2DM), obesity, dyslipidemia, hypertension and insulin resistance and constitutes a new component of the metabolic syndrome (MetS) [1-2]. The association of MetS and NAFLD is so strong that NAFLD is considered as the hepatic manifestation of MetS [3]. The clinical implication of NAFLD and nonalcoholic steatohepatitis (NASH) are mainly derived from their common occurrence in the general population (15%-30%) and their potential to contribute to CAD, extra hepatic cancer, diabetes, and progression to fibrosis (30%-40%), cirrhosis (20%-30%) and hepatocellular carcinoma [4-5]. Although the mechanisms underlying liver disease progression remain unclear, insulin resistance and obesity-related inflammation, obesity related ectopic fat and lipotoxicity play a key role, along with possible genetic, dietary and lifestyle factors [6].

Most studies show that MetS is associated with a two-fold increase in CAD risk and a 5-fold increased risk for incidences of T2DM [7-12]. The importance of NAFLD component within the MetS is now increasingly recognized, and this has stimulated an interest in the possible relationship between NAFLD and cardiovascular disease (CVD). This review focuses on the relationship between NAFLD and CAD, the biological mechanisms linking NAFLD and CAD and a proposed new treatment approach for patients with NAFLD.

2. The relationship between NAFLD and CAD

Prevalence: NAFLD affects 15-30% of the general population [13]. The prevalence is also high in overweight and obese children [14]. Factors contributing to NAFLD include sedentary life style, and increased consumption of foods with high fat and high fructose corn syrup content (soft drinks). Steatosis is associated with an increased prevalence and incidence of CAD and cardiovascular mortality. [15, 16].

Clinical studies: Targher et al showed a significant increase of carotid intima-media thickness (IMT) in the presence of NAFLD [17]. Brea et al showed that patients with NAFLD had increased intima-media thickness (IMT), independently by the MetS [18]. Lin et al
showed that patients with NAFLD were more likely to have CAD compared to patients without NAFLD, independent of obesity and other risk factors [19]. Villanova et al showed that NAFLD patients have a significant decrease in brachial artery flow-mediated vasodilatation, which correlates with the extent of liver disease. Furthermore, the 10-year probability of coronary heart disease (as calculated according to the Framingham risk score) was moderately increased in NAFLD patients, and particularly in patients with NASH [20]. This study and others provide evidence of severe endothelial dysfunction and increased risk of cardiovascular events in NAFLD [21]. Targher et al showed an increased prevalence of CAD in patients with T2DM and NAFLD as compared with diabetic patients without NAFLD [22] and that the severity of liver histology among NAFLD patients is strongly associated with early carotid atherosclerosis, independent of classical risk factors, insulin resistance, and the presence of MetS [23]. Akabame et al showed that NAFLD is a novel risk factor for vulnerable plaques, using a multislice computed tomography (MSCT) [24]. Recently, we showed that patients with NAFLD, even without MetS, have more vulnerable coronary soft plaques than healthy controls. [25] (Figure 1). Pacifico et al demonstrated that obese children with NAFLD have a marked increase in carotid IMT in comparison with control healthy children, and that the carotid IMT was higher for obese children with NAFLD than obese children without liver involvement but with similar body mass index (BMI) [26].

**Graph of coronary plaque in patients with or without metabolic syndrome (MS) and in controls *P<0.07; fatty liver without metabolic syndrome versus fatty liver with metabolic syndrome **P<0.001 ;all fatty liver versus controls.(reference 25)**

**Fig. 1. Presence of coronary plaque in patients with Non Alcoholic Fatty Liver Disease**

3. **Cause of death in patients with NAFLD**

The mortality rate among patients with NAFLD followed for 8 years was higher than in the general population, [27]. In another study consisting of biopsy-proven, NAFLD patients
who were followed for 18 years, CVD was among the common causes of death after all of the cancers combined [28]. In the Valpolicella Heart Diabetes Study, Targher et al showed that NAFLD patients have been associated with an increased incidence of major CVD events after excluding classical risk factors, diabetes duration, glycemic control, medication use, and components of the metabolic syndrome [29-30]. Dunn et al showed that NAFLD patients had significantly increased all-cause mortality and cardiovascular mortality, especially in the 45-54 years age group [31]. A strong association between mildly elevated serum liver enzymes as a surrogate marker of NAFLD and increased risk for CVD mortality and morbidity was reported in several population-based cohort studies [21, 32, 33]. Dunn et al showed that NAFLD patients had significantly increased all-cause mortality and cardiovascular mortality, especially in the 45-54 years age group [31]. A strong association between mildly elevated serum liver enzymes as a surrogate marker of NAFLD and increased risk for CVD mortality and morbidity was reported in several population-based cohort studies [21, 32, 33].

A Swedish study consisting of 129 patients with NAFLD showed that patients with NASH had higher incidences of cardiovascular mortality compared to the reference population [34]. Recently, other studies with 28 years follow up showed that CAD was the leading cause of death in patients with NAFLD, followed by hepatic and extra hepatic malignancy and finally by cirrhosis and its complications [35, 36, Table 1].

Table 1. Causes of Death in 143 patients with NAFLD (death= 43)

| Cause of death               | Number of patients | %   |
|------------------------------|--------------------|-----|
| CAD                          | 15                 | 35.0|
| Extra hepatic cancer         | 12                 | 28.0|
| Liver cancer, cirrhosis      | 8                  | 18.6|
| Diabetes mellitus            | 3                  | 7.0 |
| Poisoning                    | 3                  | 6.8 |
| Intestinal Perforation       | 1                  | 2.3 |
| Alcohol abuse                | 1                  | 2.3 |

4. Classical and emerging risk factors for atherosclerosis

The new risk factors for CAD include markers for inflammation (e.g. CRP, lipoprotein A), homocystine, markers of fibrinolytic and homeostatic function (e.g. fibrinogen, tissue plasminogen activator, and plasminogen activator inhibitor-1). These markers are also associated with NAFLD [37-41]. The classic common risk factors for NAFLD and CAD are age and gender [42, 43], physical inactivity [44-47], T2 DM [48-52], hyperlipidemia [53-56], obesity [57-63], and hypertension [64-66]. These risk factors are well known and beyond the scope of this review.

5. Mechanisms linking NAFLD and CAD

The biological mechanisms potentially responsible for accelerated atherogenesis in NAFLD patients may either have origin in the liver or have the liver as the target of systemic abnormalities. Here we will discuss the biological mechanisms linking NAFLD and CAD, the novel risk factors for CAD, and the common pathways of both diseases (Figure 2)

A) Oxidative stress

Oxidative stress plays an important role in the progression from simple steatosis to steatohepatitis [67]. The role of oxidative stress is supported by different animal models of
Fig. 2. Biological mechanism of accelerated atherosclerosis in patients with NAFLD. Fat accumulation in the liver induces hyperglycemia, subclinical inflammation, atherogenic dyslipidemia, lipotoxicity, and the secretion of cytokines. Thus, inducing insulin resistance, atherosclerosis, and diabetes mellitus. All contribute to coronary artery diseases.

NASH which show either increased reactive oxygen species (ROS) formation or evidence of extensive lipid peroxidation [68,69]. The association between oxidative stress and NAFLD in humans is supported by the immunohistochemical detection of lipid peroxidation products and 8-hydroxy-deoxyguanosine in the plasma and liver biopsies from patients with NAFLD [70, 71]. The earliest events in the pathogenesis of atherosclerosis are thought to be changes in endothelial functions, in turn triggered by oxidative modification of low-density lipoproteins (LDL), leading to the formation of oxidized LDL in the subintimal space [72]. The expression of chemotactic factors such as monocyte chemotactic protein-1 (MCP-1) is enhanced by oxidative stress and oxidized LDL. Endothelial expression of vascular cell adhesion molecule-1 (VCAM-1), which is regulated through a redox-sensitive mechanism, promotes the adhesion of monocytes to the endothelium. The release of macrophage colony-stimulating factor (M-CSF) is also stimulated by modified LDL. Expression of these factors results in the attraction and adhesion of monocytes to the arterial wall and the promotion of their differentiation into tissue macrophages. Exposure to the superoxide ion, a ROS, activates the nuclear factor kappa-B (NF-kappa B) regulatory complex and triggers the transcription of several atherosclerosis-related genes (VCAM-1, MCP-1, tumor necrosis factor (TNF), matrix metalloproteinase (MMP)-9, and procoagulant
tissue factor). This series of events leads to the accumulation of macrophages in the arterial wall, which then avidly incorporate oxidized LDL to form foam cells. Oxidized LDL, in turn, stimulates the release of interleukin-1 from macrophages. The activity of MMPs is also regulated by oxidative stress and appears to be closely linked to smooth muscle cell activation and migration. MMPs have also been implicated in the physiopathology of plaque rupture. Furthermore, ROS can lead to platelet activation and thrombus formation. Therefore, oxidative stress appears to be important in both the early and later stages of the atherosclerotic process [73, 74].

B) Insulin resistance
NAFLD is strongly associated with hepatic and adipose tissue insulin resistance (IR), as well as reduced whole-body insulin sensitivity [75]. Previous studies have documented a reduction of 45-50% in glucose disposal, and an impaired ability of insulin to suppress endogenous glucose production (hepatic IR) in subjects with NAFLD [76]. The spectrum of metabolic disturbances associated with IR extends beyond hyperglycemia and includes dyslipidemia, obesity, hypercoagulability, and inflammation. In long-term follow-up of patients with T2DM, IR was independently predictive of CAD, with a 1-unit increase in IR assessed by the homeostasis model assessment (HOMA) associated with a 5.4% increased risk for CAD [77]. Increased levels of fatty acids, (NEFA), lipotoxicity and disturbances in adipokine secretion, are believed to be related to insulin resistance. Increased levels of NEFA might affect the endothelial nitric oxide production, thereby impairing endothelium-dependent vasodilation. They may increase myocardial oxygen requirements and, therefore, ischemia. Recent evidence in older men with CAD has shown that NEFAs are independently associated with cardiovascular mortality [78]. The Insulin Resistance and Atherosclerosis Study (IRAS) also confirmed the relation between IR and atherosclerosis in the carotid artery [79]. Overall, growing evidence suggests that hepatic insulin resistance is sufficient to induce several components of the metabolic syndrome and promote progression to cardiovascular disease

C) Sub clinical inflammation
Targher et al showed that in healthy non-smoking volunteers, plasma CRP, fibrinogen, von Willebrand factor (v-WF) and plasminogen activator inhibitor-1 (PAI-1) activity levels were markedly higher in subjects with hepatic steatosis than in those without, even after controlling for other confounders such as age, BMI, blood pressure, insulin resistance and triglyceride levels [80]. Recently, IL-6 and CRP have been shown to correlate with higher degrees of fibrosis and inflammation (i.e. NASH) in patients with NAFLD [81]. Thus, NAFLD/NASH should be considered a chronic inflammatory condition. Recent advances in basic science have established a fundamental role for inflammation in mediating all stages of atherosclerosis from initiation through progression and, ultimately, the thrombotic complications of atherosclerosis. Prospective epidemiological studies have found increased vascular risk in association with increased inflammatory markers such as, IL-6, TNF-α, CRP and fibrinogen [82-85]. Elevated values of circulating inflammatory markers commonly accompany acute coronary syndrome (ACS). Such elevations correlate with in-hospital and short-term prognosis [85, 86]. Chronic subclinical inflammation is a common finding in NAFLD and in atherosclerosis. Moreover, chronic sub clinical inflammation is strongly involved in IR and MetS, as mainly demonstrated by mechanistic studies in animal models [87]. Ectopic fat deposition in visceral adipose depots, heart and other depots increases the expression of visceral
proinflammatory mediators such as monocyte chemotactic protein-1 and IL-6, leading to local macrophage infiltration and associated systemic chronic inflammation [88]. Hepatic steatosis is associated with increased production of pro-inflammatory cytokines by hepatocytes and non-parenchymal cells, including Kupffer cells and hepatic stellate cells. Increased intra-hepatic cytokine expression results from local NF-kB activation, mediated by hepatocellular damage and fat-derived factors, and is likely to play a major role in NAFLD progression and CVD pathogenesis [81, 88-90].

An atherogenic role of liver inflammation is supported by the observation that CAD risk is greater in NASH than in simple hepatic steatosis [27, 28].

D) Adiponectin
Liver fat accumulation, NEFAs, adiponectin, low-grade inflammation in the context of insulin resistance patient with fatty liver, might explain the development of endothelial dysfunction and early cardiovascular disease. Mature adipocytes act as an active endocrine and paracrine organ, secreting an increasing number of growth factors that participate in diverse metabolic processes, particularly IR. Patients with NAFLD exhibit reduced levels of adiponectin, which are inversely correlated with the severity of NAFLD histology [91-93]. The reduced production of adiponectin associated with obesity may contribute to the progression of NAFLD [89]. Adiponectin increases the expression of messenger RNA and protein production of tissue inhibitor of metalloproteinase in macrophages through the induction of IL-10 synthesis and selectively suppresses endothelial cell apoptosis [94, 95]. This suggests that adiponectin protects plaque rupture by the inhibition of matrix metalloproteinase function. Endothelium-dependent vasoreactivity is impaired in people with hypoadiponectinemia, which might be at least one cause of hypertension in visceral obesity [96]. The protein inhibits the expression of adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), ICAM-1 and E-selectin, through the inhibition of NF-κB activation; it also suppresses foam-cell formation. From this, it is clear that adipokines are capable of contributing to remodeling of the myocardial extracellular matrix [96].

E) Myocardial Lipotoxicity
Increasing plasma free fatty acids for few hours causes endothelial dysfunction and induces the production of systemic inflammation, and pro coagulants in vitro, in animal models and in humans. Of interest, free fatty acid impairs nitric oxide production by endothelial cells through the activation of an IKKb-mediated response. For instance, subjects with either glucose intolerance or T2DM have a significant increase in myocardial triglyceride content. There is a significant correlation between the development of fatty liver and abnormalities in left ventricular energy metabolism. [97]. In Diabetic patients with NAFLD, fatty liver and elevated aminotransferases coexist with myocardial insulin resistance and coronary dysfunction [97].

F) Atherogenic dyslipidemia
Liver fat accumulation originate from peripheral fats stored in adipose tissue that flow to the liver via the plasma nonesterified fatty acid (NEFA, 60%) pool, fatty acids newly made within the liver through de novo lipogenesis (DNL, 30%), and from dietary fatty acid uptake (10%). The fat of lipids entering the liver may be secreted as very low-density lipoprotein (VLDL) triglycerides, oxidized or stored. The major component of dyslipidemia in NAFLD patients is an elevation of serum triglycerides (TG) which comes mainly from increased concentration of VLDL. In addition to increased synthesis of VLDL, there is also decreased clearance of triacylglycerol-rich lipoprotein (TRLs) induced by a decrease in lipoprotein lipase activity [98]. Other components of dyslipidemia, such as formation of small dens low-density lipoprotein (LDL), are closely associated with IR and hypertriglyceridemia [99].
VLDL1 triglyceride is a major predictor of LDL size. It seems that stimulated hepatic lipase activity favors the formation of small dense LDL particles. The increased activity of hepatic lipase in IR conditions such as in NAFLD and obesity produces smaller HDL particles, leading to increased HDL elimination [100]. In addition, increased levels of VLDL1 alter the composition of HDL, leading finally to an increased catabolism of these particles, which explains the inverse correlation of HDL and liver fat [101]. In summary, patients with NAFLD have increased levels of VLDL, TG, and small dense LDL particles and decreased levels of HDL. The presence of small dense LDL particles is associated with increased CVD risk [102]. Small dense LDL particles can move through endothelial fenestrations, entering the subendothelial space where inflammation and transformation into plaque can occur, and leading finally to coronary artery diseases [103]. Further, alterations in smooth muscle ion channels, Ca$^{2+}$ handling, and cell signaling may be important mechanisms leading to coronary micro vascular dysfunction [103].

G) Postprandial lipemia
Exaggerated postprandial lipemia is an established CVD risk in T2DM [104]. Studies comparing the postprandial response of TG and FFA to a fat rich meal in nondiabetic subjects with biopsy proven NASH to control subjects showed that patients with NASH had significantly higher postprandial TG levels than healthy control subjects [105]. Other studies support a close relationship between dietary habits, postprandial lipemia and CAD [106]. The atherosclerotic risk of postprandial hyperlipidemia is derived from an increase of remnant lipoproteins (RLPs) [107]. In patients with IR, an increase of postprandial RLP values usually occurs and becomes a coronary risk factor. The RLP is easily taken into the macrophage in the arterial wall via the apolipoprotein B48 receptor, promoting foam cell formation of macrophages and performing the atherosclerotic lesion as is oxidized LDL [108]. Stanhope et al showed that consumption of fructose-sweetened but not glucose-sweetened beverages for 10 weeks increases de novo lipid synthesis and the 24-hour postprandial TG including increased levels of apoB, LDL, oxidized LDL, RLP triglyceride, and the apoB / apoA1 ratio (all biomarkers of increased for CAD) [109]. Dietary habits and genetic determinants, including microsomal transfer protein (MTP) polymorphisms, may promote NASH and atherogenesis via hypo adiponectinaemia [110,111]. Recently, Musso et al reported that the risk of adiponectin single-nucleotide polymorphisms (SNPs) 45TT and 276 GT are significantly more prevalent in NAFLD than in the general population and are associated with the severity of liver disease. In addition, an association with an atherogenic postprandial lipoprotein profile in NASH was detected independently of fasting adipokine and lipid levels [112].

H) Pro-coagulation and hypofibrinolysis
The prothrombotic state in the atherosclerosis process encompasses platelets hyperaggregability, hypercoagulability and hyperfibrinolysis. Markers of fibrinolytic and hemostatic function (e.g. fibrinogen, tissue plasminogen activator, and plasminogen activator inhibitor 1-antigens), are strongly associated with NAFLD. Plasminogen activator inhibitor-1(PAI-1) is expressed in visceral adipose tissue. It is mainly expressed in stromal cells including monocytes, smooth muscle cells and pre-adipocytes [113]. Plasma PAI-1 levels are more closely related to fat accumulation and PAI-1 expression in the liver than in adipose tissue, suggesting that, among insulin-resistant individuals, the fatty liver is an important site of PAI-1 production [114]. We showed also that there is an association between the thrombotic risk factors and the extent of fibrosis in patients with NAFLD [40]. This confirms the central role of the liver in these processes. Fibrinogen, von
Willebrand factor (vWF) and PAI-1 are also considered markers of the acute-phase reaction of inflammation and thrombosis, and has been closely linked to CAD and diabetes mellitus [115]. CRP increases PAI-1 expression and activity in human aortic endothelial cells [116].

6. Clinical implications

It is evident that patients with NASH are more prone to develop CAD (increased mortality by 86%) than patients with simple steatosis (increased mortality by 55%, 117); however, it has not been clear until now whether the treatment of NAFLD patients will prevent CAD development. We suggest adding a new modality of approaching patients with NAFLD. Once the diagnosis of NAFLD was made, the first step will be a lifestyle intervention using a combination of diet, active walking, and behavior modification [118], with a goal of >10% weight reduction [119]. Mediterranean diet derived mainly from olive oil (rich in omega-9) is recommended [120,121]. We advise to reduce or discontinue the consumption of fast foods and regular soft drinks, which contain fructose [122]. Recently Dunn et al showed that modest wine drinking (20-30 gram/daily) offers protection against suspected NAFLD [123].

The second step is to assess the risk of hepatic fibrosis: There are two modalities of assessment of fibrosis in NAFLD: The noninvasive methods of fibrosis include BARD score or Angulo score [124,125]. The invasive methods (liver biopsy) remains the only reliable means to determine prognosis based on the severity of fibrosis. The third step will include the assessment of cardiovascular risk stratification: We suggest the use of the Framingham score with effort test and/or measurements of the carotids arteries (IMT) as well as biomarkers of inflammation (CRP, fibrinogen), oxidative stress, (MDA, Paraoxonase), Insulin Resistance, (HOMA), lipotoxicity (TG, HDL, LDL, TC), OGTT, and microalbumin/creatinin ratio [126].

The fourth step includes the assessment of malignancy: For patients older than > 45. Colonoscopy, mammography, chest X-ray, gynecology consultation, and tumor markers (CEA, AFP, PSA, and CA19-9, and CA125, stool blood) are recommended since malignancy is the second most common cause of death in patients with NAFLD [127]. The final step is to initiate an appropriate therapy according to the comorbidities, and the clinical status of each patient. A combination therapy is favored.

A) Patients with metabolic syndrome

The most effective antidiabetic agent is metformin especially in obese T2DM or pioglitazone in non-obese patients [128,129]. We advice to delay early insulin therapy because it may increase fibrosis and weight [130]. Whether insulin increases the risk of HCC or not is still under debate. Exenatide induces significant weight loss, which may lead to an insulin-sensitizing effect [131]. Glitpinds are a group of drugs, which increase incretin levels by inhibiting the enzyme DPP-4. These agents are relatively new and, as for the GLP-1 analogues, improve insulin resistance in prediabetic individuals and patients with T2DM after weight loss [132]. Lipid-lower agents are mandatory treatment in diabetic patients with NAFLD, statins and fibrates for dyslipidemic and diabetic patients [133-135] are recommended. Renin-angiotensin system (RAS) inhibitors or alpha-blockers for hypertensive patients [136,137]. However, these types of medicines are not approved solely for fatty liver. Low dose aspirin is reasonable for patients with 10 years cardiovascular disease risk >10% and no risk factors for bleeding.
B) Patients without metabolic syndrome

Best evidence for metformin or pioglitazone for 1-2 year in treating NAFLD patients without MetS. However, routine prescription of this drug (pioglitazone) needs further clarification. Vitamin E (400 IU/day) and omega-3 may be recommended [138,139]. However, vitamin E is not approved yet and high dosage may increase all cause mortality (140). Ursodeoxycholic acid has no benefit for NASH patients as compared to placebo (141). Statins for dyslipidemic patients. Aspirin to prevent CAD according to Framingham score (142). Diagnosis of NAFLD may be a clear indication for diabetes screening, and cardiovascular risk screening and should be performed with the use of existing risk calculators and should be guided by established cardiovascular risk factors.

a. For patients with metabolic syndrome: tailored therapy
   - Metformin/ Pioglitazon/Insulin for T2DM.
   - However, routine prescription needs further clarification
   - Statins /Fibrates for atherogenic dyslipidemia
   - Renin angiotensin system inhibitors/ α- blockers for hypertension

b. For patients without metabolic syndrome:
   - Best evidence for metformin/ pioglitazone or vitamin E.
   - However, high dose vitamin E (>400 IU/day) may increase mortality
   - Currently, high dose ursodeoxycholic acid has no benefit for NASH patients
   - Omega-3 and vitamin D (2000 IU/day) may be beneficial.

c. For the future:
   - Promising agents awaiting randomized controlled trials (Fatostatin, Aramchol, DPP-4 inhibitors, GLP-1 agonists and combination therapy)

Table 2. Pharmacologic treatment of patients with NAFLD

7. Conclusion

NAFLD is a growing public health problem worldwide. The clinical impact of NAFLD on CAD risk deserves particular attention in view of the implications for screening and surveillance strategies in the growing number of NAFLD patients. NAFLD is associated with increased biomarkers level of chronic inflammation and atherosclerosis. Pharmacotherapy should be given for patients at high risk for complications (NASH, T2DM, obesity, atherogenic dyslipidemia). However, it is not currently known whether improving NAFLD will prevent the development and progression of CAD. Moreover, the prognostic value of NAFLD in CAD risk stratification has yet to be determined. NAFLD patients should be candidate not only for aggressive treatment of their liver disease, but also for aggressive treatment of underlying CAD risk factors, because many patients with NAFLD will have major CAD events and die prior to the development of advanced liver disease.

8. References

[1] Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 2002; 346: 1221-1231.
[2] Targher G, Arcaro G. Non-alcoholic fatty liver disease and increased risk of cardiovascular disease. Atherosclerosis 2007; 191:2:235-240.
[3] Marchesini G, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology 2003;4: 917-923.

[4] Younossi Z, Diehl AM, Ong JP. Nonalcoholic fatty liver disease: an agenda for clinical research. Hepatology 2002; 35:746-52.

[5] Bruke A, Lucey MR. Non-alcoholic fatty liver disease, non-alcoholic steatohepatitis and orthotopic liver transplantation. Am J Transplant 2004;5: 686-693.

[6] Petersen KF, Dufour S, Hariri A, Nelson-Williams C, Foo JN, Zhang XM, et al. Apolipoprotein C3 gene variants in nonalcoholic fatty liver disease. N Engl J Med 2010; 362:1082-1089.

[7] Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systemic review and meta-analysis of longitudinal studies. J Am Coll Cardiol 2007; 30:4:403-414.

[8] Ford ES, Schulze MB, Pischon T, Bergmann MM, Joost HG, Boeing H. Metabolic syndrome and risk of incident diabetes: findings from the European Prospective Investigation into Cancer and Nutrition-Potsdam Study. Cardiovasc Diabetol 2008; 7:35.

[9] Ford ES, Li C, Sattar N. Metabolic syndrome and incident diabetes: current state of the evidence. Diabetes Care 2008;9:1898-904.

[10] Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002;21:2709-2716.

[11] Isomaa B, Almgren P, Tuomi T, Forsén B, Lahti K, Nissén M, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001; 24:683-689.

[12] Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. Circulation 2004;10:1245-1250.

[13] Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al. Prevalence of hepatic steatosis in an urban population in the United States: importance of ethnicity. Hepatology 2004; 40:1387-1395.

[14] Sagi R, Reif S, Neuman G, Webb M, Phillip M, Shalitin S. Nonalcoholic fatty liver disease in overweight children and adolescents. Acta Paediatr 2007; 96:1209-1213.

[15] Hamaguchi M, Kojima T, Takeda N, Nagata C, Takeda J, Sarui H, et al. Nonalcoholic fatty liver disease is a novel predictor of cardiovascular disease. World J Gastroenterol 2007;13:1579-1584.

[16] Abid A, Taha O, Nseir W, Farah R, Grosovski M, Assy N. Soft drink consumption is associated with fatty liver disease independent of metabolic syndrome. J Hepatol 2009; 51:918-924.

[17] Targher G, Bertolini L, Padovani R, Zenari L, Zoppini G, Falezza G. Relation of nonalcoholic hepatic steatosis to early carotid atherosclerosis in healthy men: role of visceral fat accumulation. Diabetes Care 2004;10:2498-2500.

[18] Brea A, Mosquera D, Martin E, Arizti A, Cordero JL, Ros E. Nonalcoholic fatty liver disease is associated with carotid atherosclerosis: a case-control study. Arterioscler Thromb Vasc Biol 2005; 5:1040-1050.
[19] Lin YC, Lo HM, Chen JD. Sonographic fatty liver, overweight and ischemic heart disease. World J Gastroenterol 2005;11:4838-4842.
[20] Villanova N, Moscatiello S, Ramilli S, Bugianesi E, Magalotti D, Vanni E, et al. Endothelial dysfunction and cardiovascular risk profile in nonalcoholic fatty liver disease. Hepatology 2005; 2:473-480.
[21] Schindhelm RK, Diamant M, Bakker SJ, van Dijk RA, Scheffer PG, Teerink T, et al. Liver alanine aminotransferase, insulin resistance and endothelial dysfunction in normotriglyceridaemic subjects with type 2 diabetes mellitus. Eur J Clin Invest 2005;6:369-374.
[22] Targher G, Bertolini L, Padovani R, Poli F, Scala L, Tessari R, et al. Increased prevalence of cardiovascular disease in Type 2 diabetic patients with non-alcoholic fatty liver disease. Diabet Med 2006; 23:403-409.
[23] Targher G, Bertolini L, Padovani R, Rodella S, Zoppini G, Zenari L, et al. Relation between carotid artery wall thickness and liver histology in subjects with nonalcoholic fatty liver disease. Diabetes Care 2006; 29:1325-1330.
[24] Akabame S, Hamaguchi M, Tomiyasu K, Tanaka M, Kobayashi- Takenaka Y, Nakano K, et al. Evaluation of vulnerable coronary plaques and non-alcoholic fatty liver disease (NAFLD) by 64-detector multislice computed tomography (MSCT). Circ J 2008;72:618-625.
[25] Assy N, Djibre A, Farah R, Grosovski M, Marmor A. Presence of coronary plaques in patients with nonalcoholic fatty liver disease. Radiology 2010; 254:393-400.
[26] Pacifico L, Cantisani V, Ricci P, Osborn JF, Schiavo E, Ferrara E, et al. Nonalcoholic fatty liver disease and carotid atherosclerosis in children. Paediatr Res 2008; 63:423-427.
[27] Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology 2005;1:113-121.
[28] Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology 1999; 6:1413-1419.
[29] Targher G, Bertolini L, Poli F, Rodella S, Scala L, Tessari R, et al. Nonalcoholic fatty liver disease and risk of future cardiovascular events among type 2 diabetic patients. Diabetes 2005; 54:3541-3546.
[30] Targher G, Bertolini L, Rodella S, Tessari R, Zenari L, Lippi G, et al. Nonalcoholic fatty liver disease is independently associated with an increased incidence of cardiovascular events in type 2 diabetic patients. Diabetes Care 2007; 8:2119-2121.
[31] Dunn W, Xu R, Wingard DL, Rogers C, Angulo P, Younossi ZM, et al. Suspected nonalcoholic fatty liver disease and mortality risk in a population-based cohort study. Am J Gastroenterol 2008;9:2263-2271.
[32] Ruttmann E, Brant LJ, Concini H, Diem G, Rapp K, Ulmer H. Gamma-glutamyltransferase as a risk factor for cardiovascular disease mortality: an epidemiological investigation in a cohort of 163,944 Austrian adults. Circulation 2005;14:2130-2137.
[33] Lee DS, Evans JC, Robins SJ, Wilson PW, Albano I, Fox CS, et al. Gamma glutamyl transferase and metabolic syndrome, cardiovascular disease, and mortality risk: the Framingham Heart Study. Arterioscler Thromb Vasc Biol 2007;1:127-133.
[34] Ekstedt M, Franzen LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology 2006; 40: 865-873.

[35] Ong JP, Pitts A, Younossi ZM. Increased overall mortality and liver-related mortality in non-alcoholic fatty liver disease. J Hepatol 2008; 49:608-612.

[36] Soderberg C, Stal P, Askling J, Glaumann H, Lindberg G, Marmur J, et al. Decreased survival of subjects with elevated liver function tests during a 28-year follow-up. Hepatology 2010;2:595-602.

[37] Park SH, Kim BI, Yun JW, Kim JW, Park DI, Cho YK, et al. Insulin resistance and C-reactive protein as independent risk factors for non-alcoholic fatty liver disease in non-obese Asian men. J Gastroenterol Hepatol 2004; 6:694-698.

[38] Lee S, Jin Kim Y, Yong Jeon T, Hoi Kim H, Woo OH S, Park Y, et al. Obesity is the only independent factor associated with ultrasound-diagnosed non-alcoholic fatty disease: a cross-sectional case-control study. Scand J Gastroenterol 2006; 51:566-572.

[39] Hirsch S, Poniachick J, Avendano M, Cséndes A, Burdiles P, Smok G, et al. Serum folate and homocysteine levels in obese females with non-alcoholic fatty liver. Nutrition 2005; 2: 137-141.

[40] Assy N, Bekirov I, Mejritsky Y, Solomon L, Szvalb S, Hussein O. Association between thrombosis risk factors and extent of fibrosis in patients with non-alcoholic fatty liver diseases. World J Gastroenterol 2005;37:5834-5839.

[41] Sookoian S, Castano GO, Burgueno AL, Rosselli MS, Gianotti TF, Mallardi P, et al. Circulating levels and hepatic expression of molecular mediators of atherosclerosis in nonalcoholic fatty liver disease. Atherosclerosis 2010; 2:585-591.

[42] Ruhl CE, Everhart JE. Epidemiology of nonalcoholic fatty liver. Clin Liver Dis 2004;3:501-519.

[43] Carulli L, Lonardo A, Lombardini S, Marchesini G, Loria P. Gender, fatty liver and GGT. Hepatology 2006; 44:278-279.

[44] Powell KE, Thompson PD, Caspersen CJ, Kendrick JS. Physical activity and the incidence of coronary heart disease. Annu Rev Public Health 1987; 8:253-287.

[45] Hsieh SD, Yoshinaga H, Muto T, Sakurai Y. Regular physical activity and coronary risk factors in Japanese men. Circulation 1998; 97: 661-665.

[46] Church TS, Kuk JL, Ross R, Priest EL, Biltoft E, Blair SN. Association of cardiorespiratory fitness, body mass index, and waist circumference to nonalcoholic fatty liver disease. Gastroenterology 2006;7:2023-2030.

[47] Zelber-Sagi S, Nitzan- Kaliski D, Goldsmith R, Webb M, Zvieli B, Goldiner I, et al. Role of leisure-time physical activity in alcoholic fatty liver disease: a population-based study. Hepatology 2007;48:1791-1798.

[48] Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993; 16:434-444.

[49] Adlerberth AM, Rosengren A, Wilhelmsen L. Diabetes and long-term risk of mortality from coronary and other causes in middle-aged Swedish men. A general population study. Diabetes Care 1998; 21:539-545.

[50] De Marco R, Locatelli F, Zoppini G, Verlato G, Bonora E, Muggeo M. Cause-specific mortality in type 2 diabetes. The Verona Diabetes Study. Diabetes Care 1999; 22:756-761.
[51] Marchesini G, Marzocchi R, Agostini F, Bugianesi E: Nonalcoholic fatty liver disease and metabolic syndrome. Curr Opin Lipidol 2005;16:421-427.
[52] Hanley AJ, Williams K, Festa A, Wagenknecht LE, D’Agostino RB Jr, Kempf J, et al. Insulin resistance atherosclerosis study. Diabetes 2004; 53:2623-2632.
[53] Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart continues and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). JAMA 1986; 256:2823-2828.
[54] Assy N, Kaita K, Mymin D, Levy C, Rosser B, Minuk G. Fatty infiltration of liver in hyperlipidemic patients. Dig Dis Sci 2000; 45:1929-1934.
[55] Clark JM, Diehl AM. Nonalcoholic fatty liver disease: an underrecognized cause of cryptogenic cirrhosis. JAMA 2003; 289:3000-3004.
[56] Radu C, Grigoriscu M, Crisan D, Lupsor M, Constantin D, Dina L. Prevalence and associated risk factors of non-alcoholic fatty liver disease in hospitalized patients. J Gastrointestin Liver Dis 2008; 17:255-260.
[57] Rabkin SW, Mathewson FA, Hsu PH. Relation of body weight to development of ischemic heart disease in a cohort of young North American men after a 26 year of observation period: the Manitoba study. Am J Cardiol 1977;39:452-458.
[58] Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation 1983; 67:968-977.
[59] Ruhl CE, Everhart JE. Determination of the association of overweight with elevated serum alanine aminotransferase activity in the United States. Gastroenterology 2003; 124:71-79.
[60] Marcos A, Fisher RA, Ham JM, Olzinski AT, Shiffman ML, Sanyal AJ, Luketic VA, et al. Selection and outcome of living donors for adult-to-adult right lobe transplantation. Transplantation 2000; 69:2410-2415.
[61] Hilden M, Christoffersen P, Juhl E, Dalgaard JB. Liver histology in a 'normal' population- examination of 503 consecutive fatal traffic casualties. Scand J Gastroenterol 1977; 12:593-597.
[62] Lee RG. Nonalcoholic steatohepatitis a study of 49 patients. Hum Pathol 1989; 20: 594-598.
[63] Gholam PM, Kotler DP, Flanchaum LJ. Liver pathology in morbidity obese patients undergoing Roux-en-Y gastric bypass surgery. Obes Surg 2000; 12:49-51.
[64] Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood pressure-lowering drugs. Lancet 2000; 356:1955-1964.
[65] Donati G, Stagni B, Piscaglia F, Venturoli N, Morselli-Labate AM, Rasciti L, et al. Increased prevalence of fatty liver in arterial hypertensive patients with normal liver enzymes: role of insulin resistance. Gut 2004; 53:1020-1023.
[66] Yokohama S, Yoneda M, Haneda M, Okamoto S, Okada M, Aso K, et al. Therapeutic efficacy of an angiotensin II receptor antagonist in patients with nonalcoholic steatohepatitis. Hepatology 2004; 40:1222-1225.
[67] Day CP. Non-alcoholic steatohepatitis (NASH): where are we now and where are we going? Gut 2002;50:585-588.
[68] Yang S, Zhu H, Gabrielson K, Trush MA, Diehl AM. Mitochondrial adaptation to obesity-related oxidant stress. Arch Biochem Biophys 2000; 378:259-268.
[69] Leclercq IA, Farrel GC, Field J, Bell DR, Gonzalez FJ, Robertson GR. CYP2E1 and CYP4A as microsomal catalysts of lipid peroxides in murine nonalcoholic steatohepatitis. J Clin Invest 2000;105:1067-1075.

[70] Seki S, Kitada T, Yamada T, Sakaguchi H, Nakatani K, Wakasa K. In situ detection of lipid peroxidation and oxidative DNA damage in non-alcoholic fatty liver disease. J Hepatol 2002; 37:56-62.

[71] Chalasani N, Deeg MA, Crabb DW. Systemic levels of lipid peroxidation and its metabolic and dietary correlates in patients with nonalcoholic steatohepatitis. Am J Gastroenterol 2004; 99:1497-1502.

[72] Berliner JA, Navab M, Fogelman AM, Frank J, Demer LL, Edwards PA, et al. Atherosclerosis: basic mechanisms. Oxidation, inflammation, and genetics. Circulation 1995;91:2488-2496.

[73] Nishio E, Watanabe Y. The involvement of reactive oxygen species and arachidonic acid in alpha 1-adrenoceptor induced smooth muscle cell proliferation and migration. Br J Pharmacol 1997;121:665-70.

[74] Schulz E, Anter E, Keaney JF. Oxidative stress, antioxidants, and endothelial function. Curr Med Chem 2004; 11:1093-1104.

[75] Bugianesi E, McCullough AJ, Marchesini G. Insulin resistance: a metabolic pathway to chronic liver disease. Hepatology 2005; 42:987-1000.

[76] Seppala-Lindroos A, Vehkavaara S, Hakkinen AM, Goto T, Westerbacka J, Sovijarvi A, et al. 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. J Clin Endocrinol Metab 2002; 87:3023-3028.

[77] Bonora E, Formentini G, Calcatera F, Lombardi S, Marini F, Zenari L, et al. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. Diabetes Care 2002; 25:1135-1141.

[78] Pilz S, Scharmagl H, Tiran B, Seelhorst U, Wellnitz B, Boehm BO, et al. Free fatty acids are independently associated with all-cause and cardiovascular mortality in subjects with coronary artery disease. J Clin Endocrinol Metab 2006;91:2542-2547.

[79] Howard G, O’Leary DH, Zaccaro D, Haffner S, Hamman R, et al. Insulin sensitivity and atherosclerosis: the Insulin Resistance Atherosclerosis Study (IRAS) Investigators. Circulation 1996; 93:1809-1817.

[80] Targher G, Bertolini L, Scala L, Zoppini G, Zenari L, Faleza G. Non-alcoholic hepatic steatosis and its relation to increased plasma biomarkers of inflammation and endothelial dysfunction in non-diabetic men. Role of visceral adipose tissue. Diabet Med 2005; 22:1354-1358.

[81] Wieckowska A, Papouchado BG, Li Z, Lopez R, Zein NN, Feldstein AE. Increased hepatic and circulating interleukin-6 levels in human nonalcoholic steatohepatitis. Am J Gastroenterol 2008;103:1372-1379.

[82] Ridker PM, Rifai N, Pfeffer M, Sacks F, Lepage S, Braunwald E. Elevation of tumor necrosis factor-alpha and increased risk of recurrent coronary events after myocardial infarction. Circulation 2000; 101:2149-2153.

[83] Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation 2000; 101:1767-1772.
[84] Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000; 342:836-843.

[85] Toss H, Lindahl B, Siegbahn A, Wallentin L. Prognostic influence of increased fibrinogen and C-reactive protein levels in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. Circulation 1997; 96:4204-4210.

[86] Rebuzzi AG, Quaranta G, Liuzzo G, Caligiuri G, Lanza GA, Gallimore JR, et al. Incremental prognosis value of serum levels of troponin T and C-reactive protein on admission in patients with unstable angina pectoris. Am J Cardiol 1998; 82:715-719.

[87] Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest 2006; 116:1793-1801.

[88] Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. Nature 2006; 444:875-880.

[89] Day CP. From fat to inflammation. Gastroenterology 2006; 130: 207-210.

[90] Marra F, Gastaldelli A, Svegliati Baroni G, Tell C, Tiribelli C. Molecular basis and mechanisms of progression of non-alcoholic steatohepatitis. Trends Mol Med 2008; 14:72-81.

[91] Libby P. Inflammation in atherosclerosis. Nature 2002; 420:868-874.

[92] Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008; 359:2195-2207.

[93] Hui JM, Hodge A, Farrell GC, Kench JG, Kriketos A, George J. Beyond insulin resistance in NASH: TNF-alpha or adiponectin? Hepatology 2004; 40:46-54.

[94] Kumada M, Kihara S, Ouchi N, Kobayashi H, Okamoto Y, Ohashi K, et al. Adiponectin specifically increased tissue inhibitor of metalloproteinase-1 through interleukin-10 expression in human macrophages. Circulation 2004; 109:2046-2049.

[95] Kobayashi H, Ouchi N, Kihara S, Walsh K, Kumada M, Abe Y, et al. Selective suppression of endothelial cell apoptosis by the high molecular weight form of adiponectin. Circ Res 2004; 94:e27-31.

[96] Schram K, Sweeney G. Implications of myocardial matrix remodeling by adipokines in obesity-related heart failure. Trends Cardiovasc Med. 2008; 18:199-205.

[97] Lautamäki R, Borra R, Iozzo P, Komu M, Lehtimäki T, Salmi M, Jalkanen S, Airaksinen KE, Knuuti J, Parkkola R, Nuutila P. Liver steatosis coexists with myocardial insulin resistance and coronary dysfunction in patients with type 2 diabetes. Am J Physiol Endocrinol Metab. 2006; 291:E282-90.

[98] Taskinen MR. Lipoprotein lipase in diabetes. Diabetes Metab Rev 1987; 3:551-570.

[99] Verges B. New insight into the pathophysiology of lipid abnormalities in type 2 diabetes. Diabetes Metab 2005; 31:429-439.

[100] Frenais R, Nazih H, Ouguerram K, Maugeais C, Zair Y, Bard JM, et al. In vivo evidence for the role of lipoprotein lipase activity in the regulation of Apolipoprotein AI metabolism: a kinetic study in control subjects and patients with type II diabetes mellitus. J Clin Endocrinol Metab 2001; 86:1962-1967.

www.intechopen.com
[101] Adiels M, Taskinen MR, Packard C, Caslake MJ, Soro-Paavonen A, Westerbacka J, et al. Overproduction of large VLDL particles is driven by increased liver fat content in man. Diabetologia 2006;49:755-765.

[102] Gardner CD, Fortmann SP, Krauss RM. Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women. J Am Med Assoc 1996;276:875-881.

[103] Kwiterovich PO. Clinical relevance of the biochemical, metabolic, and genetic factors that influence low-density lipoprotein heterogeneity. Am J Cardiol 2002;90:30i-47i.

[104] Adiels M, Olofsson SO, Taskinen MR, Boren J. Diabetic dyslipidemia. Curr Opin Lipidol 2006;17:238-246.

[105] Cassader M, Gambino R, Muss G, Depetris N, Mecca F, Cavallo-Perin P, et al. Postprandial triglyceride-rich lipoprotein metabolism and insulin sensitivity in nonalcoholic steatohepatitis patients. Lipids 2001;36:1117-1124.

[106] Roche HM, Gibney MJ. The impact of postprandial lipemia in accelerating atherothrombosis. J Cardiovasc Risk 2000;7:317-324.

[107] Tanaka A. Postprandial hyperlipidemia and atherosclerosis. J Atheroscler Thromb 2004;11:322-329.

[108] Brown ML, Ramprasad MP, Umeda PK, Tanaka A, Kobayashi Y, Watanabe T, et al. A macrophage receptor for apolipoprotein B48: cloning, expression, and atherosclerosis. Proc Natl Acad Sci USA 2000;97:7488-7493.

[109] Stanhope KL, Schwarz JM, Keim NL, Griffen SC, Bremer AA, Graham JL, et al. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. J Clin Invest 2009;119:1322-1334.

[110] Musso G, Gambino R, Durazzo M, Biroli G, Carello M, Faga E, et al. Adipokines in NASH: postprandial lipid metabolism as a link between adiponectin and liver disease. Hepatology 2005;42:1175-1183.

[111] Musso G, Gambino R, De Michieli F, Cassader M, Rizzetto M, Durazzo M, et al. Dietary habits and their relations to insulin resistance and postprandial lipemia in nonalcoholic steatohepatitis. Hepatology 2003;37:909-916.

[112] Musso G, Gambino R, De Michieli F, Durazzo M, Pagano G, Cassader M. Adiponectin gene polymorphisms modulate acute adiponectin responses to dietary fat: Possible pathogenetic role in NASH. Hepatology 2008;47:1167-1177.

[113] Bastelica D, Morange P, Berthet B, Borghi H, Lacroix O, Grino M, et al. Stromal cells are the main plasminogen activator inhibitor-1-producing cells in human fat: evidence of differences between visceral and subcutaneous deposits. Arterioscler Thromb Vasc Biol 2002;22:173-178.

[114] Alessi MC, Bastelica D, Mavri A, Morange P, Berthet B, Grino M, et al. Plasma PAI-1 levels are more strongly related to liver steatosis than to adipose tissue accumulation. Arterioscler Thromb Vasc Biol 2003;23:1262-1268.

[115] Esmon CT. The interactions between inflammation and coagulation. Br J Haematol 2005;131:417-430.

[116] Devaraj S, Xu DY, Jialal I. C-reactive protein increases plasminogen activator inhibitor-1 expression and activity in human aortic endothelial cells: implication for the metabolic syndrome and atherothrombosis. Circulation 2003;107:398-404.
[117] Targher G. Non-alcoholic Fatty Liver Disease and Cardiovascular Disease. Curr Cardiovasc Risk Rep 2010;4:32-39.

[118] Kantartzis K, Thamer C, Peter A, Machann J, Schick F, Schramm C, et al. High cardiorespiratory fitness is an independent predictor of the reduction in liver fat during a lifestyle intervention in non-alcoholic fatty liver disease. Gut 2009; 58:1281-1288.

[119] Promrat K, Kleiner DE, Niemeier HM, Jackvony E, Kearns M, Wands JR, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology 2010; 51:121-129.

[120] Assy N, Nassar F, Nasser G, Grosovski M. Olive oil consumption and non-alcoholic fatty liver disease. World J Gastroenterol 2009;15:1809-1815.

[121] Estruch R, Martinez-Gonzalez MA, Corella D, Salas-Salvado J, Ruiz-Gutierrez V, Covas MI, et al; PREDIMED study Investigators. Effect of a Mediterranean diet supplemented with nuts on metabolic syndrome status: one-year results of the PREDIMED randomized trial. Arch Intern Med 2008;22:2449-2458.

[122] Nseir W, Nassar F, Assy N. Soft drinks consumption and nonalcoholic fatty liver disease. World J Gastroenterol 2010;16: 2579-2588.

[123] Dunn W, Xu R, Schwimmer JB. Modest wine drinking and decreased prevalence of suspected nonalcoholic fatty liver disease. Hepatology 2008; 47:1947-1954.

[124] Harrison SA, Oliver D, Arnold HL, Gogia S, Neuschwander-Terani BA. Development and validation of a simple NAFLD clinical scoring system for identifying patients without advanced disease. Gut 2008; 57:1441-1447.

[125] Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. Hepatology 2007; 45:846-854.

[126] Hwang ST, Cho YK, Yun JW, Park JH, Kim HJ, Park DJ, et al. Impact of NAFLD on microalbuminurin in patients with prediabetes and diabetes. Intern Med J 2009; May 8. [Epub ahead of print]

[127] Smith RA, Cokkinides V, Brooks D, Saslow D, Brawley OW. Cancer screening in the United States, 2010: a review of current American Cancer Society guidelines and issues in cancer screening. CA Cancer J Clin 2010; 60:99-119.

[128] Marchesini G, Brizi M, Bianchi G, Tomassetti S, Zoli M, Melchiora N. Metformin in non-alcoholic steatohepatitis. Lancet 2001; 9285:893-894.

[129] Promrat K, Lutchman G, Uwailo GI, Freedman RJ, Soza A, Heller T, et al. A pilot study of pioglitazone treatment for nonalcoholic steatohepatitis. Hepatology 2004; 1:188-196.

[130] Paradis V, Perlemuter G, Bonvoust F, Dargere D, Parfait B, Vidaud M, et al. High glucose and hyperinsulinemia stimulate connective tissue growth factor expression: a potential mechanism involved in progression to fibrosis in nonalcoholic steatohepatitis. Hepatology 2001; 34:73-84.

[131] Klonoff DC, Buse JB, Nielsen LL, Guan X, Bowlus CL, Holcombe JH, et al. Exenatide effects on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated for at least 3 years. Curr Med Res Opin 2008;1:275-286.

[132] Balaban YH, Korkusuz P, Simsek H, Gokcan H, Gedikoglu G, Pinar A, et al. Dipeptidyl peptidase IV (DDP IV) in NASH patients. Ann Hepatol 2007; 4:242-250.
Antonopoulos S, Mikros S, Mylonopoulou M, Kokkoris S, Giannoulis G. Rosuvastatin as a novel treatment of non-alcoholic fatty liver disease in hyperlipidemic patients. Atherosclerosis 2006;1:233-234.

Gomez-Dominguez E, Gisbert JP, Moreno-Montereguido JA, García-Buey L, Moreno-Otero R. A pilot study of atorvastatin treatment in dyslipidemid, non-alcoholic fatty liver patients. Aliment Pharmacol Ther 2006;11:1643-1647.

Browning JD. Stains and hepatic steatosis: perspectives from the Dallas Heart Study. Hepatology 2006; 44:466-471.

Yoshiji H, Kuriyama S, Yoshii J, Ikenaka Y, Nakatani T, Tsujinoue H, et al. Angiotensin-II type 1 receptor interaction is a major regulator for liver fibrosis development in rats. Hepatology 2001; 34:745-750.

Georgescu EF, Ionescu R, Niculescu M, Mogoanta L, Vancica L. Angiotensin-receptor blockers as therapy for mild-to-moderate hypertension-associated non-alcoholic steatohepatitis. World J Gastroenterol 2009;8:942-954.

Sanyal AJ, Mofrad PS, Contos MJ, Sargeant C, Luketic VA, Sterling RK, et al. A pilot study of vitamin E versus vitamin E and pioglitazone for the treatment of nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol 2004;12:1107-1115.

Masterton GS, Plevris JN, Hayes PC. Review article: omega-3 fatty acids- a promising novel therapy for non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2010;7:679-692.

Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med. 2005 ;142:37-46.

Leuschner UF, Lindenthal B, Herrmann G, Arnold JC, Rössle M, Cordes HJ, Zeuzem S, Hein J, Berg T; NASH Study Group. High-dose ursodeoxycholic acid therapy for nonalcoholic steatohepatitis: a double-blind, randomized, placebo-controlled trial. Hepatology. 2010;52:472-9.

Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. N Engl J Med. 2010 30;363:1341-50.
In this book we examined a periprocedural complication of coronary angiography, and coronary intervention. That includes related to cardiac catheterization and diagnostic coronary angiography, and those that occur as a consequence of the specific equipment. However, improvements in devices, the use of stents, and aggressive antiplatelet therapy have significantly reduced the incident of major periprocedural complications. This book giving knowledge and experiences many of interventional cardiologists from all over the world, and provide possibility to recognize new approach in this domain. Book gives lecture on how we image and how we decide on what to treat, how to treat it, and then results of that treatment. They offer many answers to what we have today and what we will have tomorrow.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Nseir W. and Assy N. (2011). Association Between Fatty Liver and Cardiovascular Disease: Mechanism and Clinical Implications, Coronary Angiography - The Need for Improvement in Medical and Interventional Therapy, Prof. Baskot Branislav (Ed.), ISBN: 978-953-307-641-6, InTech, Available from: http://www.intechopen.com/books/coronary-angiography-the-need-for-improvement-in-medical-and-interventional-therapy/association-between-fatty-liver-and-cardiovascular-disease-mechanism-and-clinical-implications
© 2011 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike-3.0 License, which permits use, distribution and reproduction for non-commercial purposes, provided the original is properly cited and derivative works building on this content are distributed under the same license.