Cardiovascular risk in NAFLD: Management of the metabolic syndrome

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Key messages:

1. Non-alcoholic fatty liver disease (NAFLD) is more prevalent among obese subjects and also in patients with type 2 diabetes independently of degree of obesity.
2. Hepatic overproduction of glucose, very low-density lipoproteins (VLDLs), C-reactive protein (CRP) and coagulation factors increase the risk of type 2 diabetes and cardiovascular disease

Learning objectives:

1. Insulin resistance and metabolic syndrome in subjects with NAFLD
2. Mechanisms linking NAFLD to increased cardiometabolic risk

Abstract:

Non-alcoholic fatty liver disease (NAFLD) is a chronic condition, ranging from benign steatosis, i.e. hepatic triglyceride accumulation >5.5% [1], to more significant liver injury including lobular inflammation, hepatocyte ballooning, fibrosis and cirrhosis, i.e. non-alcoholic steato-hepatitis (NASH).

NAFLD is often associated with central obesity and insulin resistance and in general with factors of the metabolic syndrome (figure 1). Excess liver fat is extremely common and prevalence of NAFLD has been increasing mainly because of the increased prevalence of obesity. It has been estimated that as many as 30% of adults in USA and other Western countries have NAFLD [2], while NASH may be present in up to 3% of the general population and in up to two thirds of individuals with morbid obesity or type 2 diabetes [2, 3]. The prevalence increases to 57% in obese subjects, 70% in diabetic subjects and 90% in morbidly obese people. NAFLD is more prevalent among obese subjects and also in patients with type 2 diabetes independently of degree of obesity [4]. In addition to hepatic complications, patients with NAFLD are at increased risk for cardio-metabolic complications such as type 2 diabetes (T2DM) and cardiovascular disease (CVD) [2, 5].

NAFLD and metabolic syndrome. There is no consensus for the diagnosis of metabolic syndrome (Table 1), but despite different limits, all criteria include similar factors, i.e., increased waist circumference as a marker of increased visceral fat, increased triglyceride and glucose concentrations, decreased HDL concentration, increased blood pressure and in two criteria (WHO and EGIR) presence of insulin resistance or glucose intolerance [6-8]. All these factors are associated with increased cardio-metabolic risk.

Several studies have highlighted that fatty liver disease (FLD) is associated with factors of metabolic syndrome [9-11]. In NAFLD prevalence of the MS varies from 18% in normal-weight to 67% in obese subjects [12-14]. In a large group of South Korean subjects, Sun et al. found that having fatty liver increases the risk of having coronary calcification and to develop type 2 diabetes [15] and in a Japanese cohort age, obesity (body mass index (BMI) ≥25 kg•m-2), hypertriglyceridemia and, to a lesser extent, hypertension were among the variables that predicted development of fatty liver [16]. Previously it has been shown that hypertriglyceridemia is present in up to 64% [11] and indeed triglyceride and gamma glutamyl transferase concentration, waist circumference and BMI are among the best predictors of fatty liver disease and related co-morbidities [9, 17].

Insulin resistance is a major characteristic of subject with metabolic syndrome but only the WHO and EGIR criteria for metabolic syndrome include insulin resistance or glucose intolerance status as one of the factors of metabolic syndrome (Table 1). Insulin resistance is often present in subjects with NAFLD not only at the level of the muscle but also at the level of the liver and adipose tissue [4, 18]. As a consequence, subjects with NAFLD, despite high circulating insulin levels, have increased fasting endogenous glucose production, diminished postprandial glucose clearance and increased free fatty acid and triglyceride concentrations [4, 9, 18]. In particular increased adipose tissue insulin resistance index, which reflects the inability of insulin to suppress peripheral lipolysis, has been recently shown as a marker of hepatic liver injury in a larger group of subjects with NAFLD [18]. However, NAFLD cannot be considered a cause for insulin resistance but rather a consequence. Studies in subjects with genetic predisposition to NAFLD, i.e. with either mutation for PNPLA3 gene [19] or familial apolipoprotinemia [20, 21], have highlighted that despite increased fat accumulation, peripheral and hepatic insulin resistance are comparable to normal subjects. On the other hand, insulin resistant subjects, especially those with type 2 diabetes (T2DM), tends to accumulate both hepatic and visceral fat [4]. Hepatic and visceral fat are related to each other [4] but independently predict the presence of metabolic syndrome [22].

NAFLD and cardiovascular disease. It is not surprising that patients with NAFLD have an increased risk for CVD events as it has been highlighted by several epidemiological reports [5, 23]. However, the real prevalence of CVD events in patients with NAFLD is still not known and probably underestimated. NAFLD is often not diagnosed since in the great majority of NAFLD subjects hepatic enzymes are within normal ranges and ultrasound technique is unable to detect NAFLD when fat infiltration is below 30% or [24, 25]. In general the cardio-metabolic risk is increased in subjects with NAFLD, even if they do not have the metabolic syndrome and they are at low risk for CVD [9].

NAFLD is associated with increased intima media thickness, endothelial and cardiac dysfunction [9, 23, 26-28]. Moreover, several studies have highlighted the association between FLD, increased coronary atherosclerosis, and in general with coronary artery disease (CAD) [5]. It is plausible that the increased CVD risk is related to the fact that subjects with NAFLD

have increased lipolysis and VLDL secretion [29, 30], hepatic overproduction of glucose, fibrinogen and CRP [4, 30, 31]. Hyperglycemia induces a series of alterations, including endothelial dysfunction, cellular proliferation, changes in extracellular matrix conformation and impairment of LDL receptor-mediated uptake, decreasing the in vivo clearance of LDL. Small dense LDLs associated with high circulating VLDLs have a higher affinity for intimal proteoglycans, leading to the penetration of more LDL particles into the arterial wall [32]. CRP can also accelerate atherosclerosis by increasing the expression of plasminogen activator inhibitor-1 and adhesion molecules in endothelial cells, inhibiting nitric oxide formation and increasing LDL uptake into macrophages [32]. All these metabolic abnormalities have been shown to directly or indirectly promote atherosclerosis as confirmed by studies that showed increased IMT and coronary atherosclerosis in subjects with FLD [5, 9, 15, 23, 31]. Lifestyle interventions, i.e. diet and exercise, have been shown to be successful in decreasing cardiometabolic risk, preventing metabolic syndrome and type 2 diabetes and decreasing liver fat.

In summary, NAFLD is associated with features of metabolic syndrome and is more prevalent among obese subjects and also in patients with type 2 diabetes independently of degree of obesity. The increased risk for cardiometabolic diseases in NAFLD is caused by the hepatic overproduction of glucose, very low-density lipoproteins (VLDLs), C-reactive protein (CRP), coagulation factors and in general by the increased insulin resistance. Lifestyle intervention is suggested to decrease liver fat and cardiometabolic risk.

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Disclosure of conflicting interests:
None declared

Figure1:

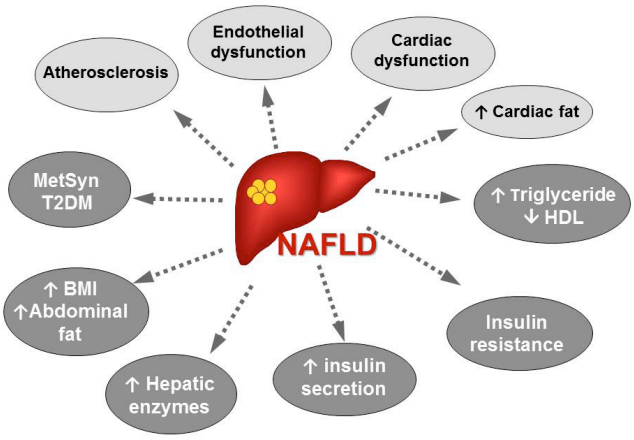

Table 1:

Table 1. Definition and criteria of Metabolic syndrome

Clinical Measure	WHO (1998)	EGIR (1999)	NHLBI/AHA (2005)	IDF (2009)
Waist (cm) or Waist/Hip	M: W/H>0.9 F: W/H>0.85	M: W>94 cm F: W>80 cm	M: W>102 cm F: W>88 cm	**Europe** M: W>94 cm F: W>80 cm **USA** M: W>102 cm F: W>88 cm
HDL (mg/dl)	M<35, F<39	HDL<39mg/dl	M<40, F<50 or Rx for HDL	M<40, F<50 or Rx for HDL
Triglyceride (mg/dl)	≥150 mg/dl	≥150 mg/dl	≥150 mg/dl or Rx for TG	≥150 mg/dl or Rx for TG
Blood pressure mmHg	≥140/≥90	≥140/≥90 or Rx for HTN	≥130/≥85 or Rx for HTN	≥130/≥85 or Rx for HTN
Fasting glucose (mg/dl)	≥100 mg/dl or IGT/T2D	≥100 mg/dl or IGT (no T2D)	≥110 mg/dl orRx for T2D	≥100 mg/dl or T2D
Presence of MS if	**IGT/IFG/T2D + 2 of the above**	**Insulin>75th + 2 of the above**	**3 or more of the above**	**IFG or T2D+ 2 of the above**