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REVIEW

# Non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease: An open question

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**KEYWORDS**
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**Abstract** *Aims:* To review available data concerning the basic science and epidemiological-clinical evidence for an association of NAFLD and cardiovascular disease.
*Data synthesis:* Non-alcoholic fatty liver disease (NAFLD) defines alcohol-like hepatic histological lesions seen in the non-alcoholic, insulin resistant patient representing the hepatic counterpart of the metabolic syndrome. Along with insulin resistance, additional genetic, endocrine and vascular changes together with environmental stimuli—which are also involved in the pathogenesis of atherosclerosis—play a prominent role in the development and progression of NAFLD. Clinical and epidemiological studies seem to indicate that NAFLD is associated with an increased risk for cardiovascular disease but further studies are needed to confirm the available data. The mainstay of NAFLD treatment is based on the correction of the same metabolic changes that predispose to atherosclerosis.
*Conclusions:* Non-invasive evaluation of risk for cardiovascular events is recommended in all individuals presenting with NAFLD and conversely, the presence

*Abbreviations:* MS, metabolic syndrome; T2DM, type 2 diabetes mellitus; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; IR, insulin resistance; GH, growth hormone; CRP, C-reactive protein; PPAR-gamma, peroxisome proliferator-activated receptor gamma; UCP-2, uncoupling protein-2.

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of NAFLD should always be looked for in subjects with features belonging to the metabolic syndrome. Further studies are needed on the mechanisms linking fatty liver and vascular diseases.


## Introduction

Non-alcoholic steatohepatitis (NASH) is the critical link in the chain of metabolic fatty liver disorders (non-alcoholic fatty liver disease or NAFLD) that span steatosis to cryptogenic cirrhosis [1]. What is now defined as NAFLD has been variously named in the past: *diabetic hepatitis; non-alcoholic steatonecrosis; alcohol-like liver disease in the non-alcoholic; non-alcoholic fatty liver hepatitis; bright liver syndrome; and non-alcoholic steatosis syndromes* [2]. Evidence that insulin resistance (IR) has a key role in NAFLD's development and progression has been reviewed elsewhere, leading to the proposal to replace the terms NAFLD and NASH with IR-related (or metabolic syndrome-related) liver disease [2].

The aims of the present review are to understand whether and why NAFLD is associated with cardiovascular risk.

## Pathogenesis of NAFLD

The pathogenesis of NAFLD will be detailed schematically into separate sections including the endocrine derangements, vascular alterations and subcellular and molecular mechanisms (Fig. 1). IR is deemed to put together different steps/hits/levels providing a unitary explanation for most of the features observed in NAFLD [3].

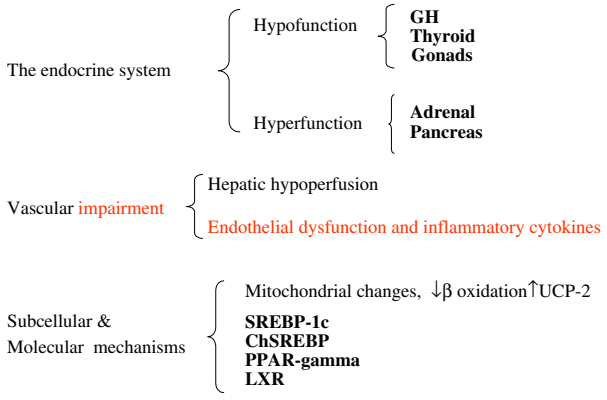


**Figure 1** Principal steps involved in the pathogenesis of NAFLD.

## Endocrine derangements in NAFLD

The endocrine system—via endocrine and paracrine hormones—controls both metabolism and inflammation, which are the two independent determinants of NAFLD [4].

### Endocrine hormones

NAFLD, like obesity, displays a hormonological profile including hyperinsulinaemia/insulin resistance, activated hypothalamic-pituitary-adrenal axis and absolute/relative deficiency in growth hormone (GH) and thyroid hormones [4]. MS and IR, which are recognised in most series of NAFLD [5] represent the major factor linking NAFLD and increased cardiovascular risk [6]. However, it is unclear whether IR is the primary mechanism in NAFLD or if it represents, in turn, the final phenomenon of other hormonal/adipokine derangements. For instance, GH deficiency might well account for the development of progressive NAFLD which has been observed following surgery for hypothalamic-hypophyseal disease [7]. Furthermore, hypothyroidism is twice as common in NAFLD than in controls [8]. In addition, a subtle hypothalamic-pituitary-adrenal disturbance manifested by increased urinary cortisol excretion and reduced cortisol suppression by dexamethasone has been reported in NAFLD [9,132]. This may be due to increased amounts of visceral adipose tissue which, compared with subcutaneous fat, has higher activity of 11beta-hydroxysteroid dehydrogenase and thus leads to increased conversion of inactive cortisone to active cortisol [10]. Finally, some types of physiological (i.e. ageing in men) [11] and pathological hypogonadism (e.g. Turner's syndrome and ovariectomy) may mimic the IR syndrome [4], including the development of NAFLD in either gender.

### Adipokines

Some adipokines such as TNF-alpha have been extensively evaluated in animal models of NAFLD [12]. Studies in humans, however, have found no statistically significant difference in serum TNF-alpha levels of subjects with NAFLD vs. controls [13,14]. In contrast, serum adiponectin concentrations are decreased in NAFLD [15,16] and predict the severity of liver fibrosis [9,15]. Adiponectin