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Ital J Gender-Specific Med 2019; 5(3): 131-135

Non-alcoholic fatty liver disease and cardiovascular risk: gender differences

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Summary. Non-alcoholic fatty liver disease is characterized by fat accumulation in the liver in people who do not drink alcohol. Non-alcoholic fatty liver disease prevalence is constantly increasing. Prevalence is greater in males than in premenopausal females. It is associated with various cardiovascular risk factors and metabolic syndrome and this review aims to shed light on the association between sex and risk of cardiovascular diseases.

Key words. Non-alcoholic fatty liver disease, cardiovascular risk, gender differences.

Steatosi epatica non alcolica e rischio cardiovascolare: differenze di genere

Riassunto. La steatosi epatica non alcolica è caratterizzata da accumulo di grasso nel fegato in persone che non bevono alcolici. La prevalenza della steatosi epatica non alcol correlata è in costante aumento. La prevalenza è maggiore negli uomini rispetto alle donne in premenopausa. Essa è associata a vari fattori di rischio cardiovascolare e alla sindrome metabolica e questa revisione della letteratura scientifica vuole far luce sull'associazione tra sesso e rischio di malattie cardiovascolari in pazienti con diagnosi di NAFLD.

Parole chiave. Steatosi epatica non alcol correlata, rischio cardiovascolare, differenze di genere.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by fat accumulation in the liver above 5-10% by weight, or a percentage of hepatocytes that contain lipid droplets greater than 5%, when analyzed with an optical microscope[1]. It develops in people who are not heavy drinkers and in the absence of other known liver pathologies. The pathobiology of NAFLD is complex and multi-phasic and includes dysfunctional adipose tissue, systemic inflammation, insulin resistance (IR), hepatic lipid accumulation and intestinal dysbiosis[2]. NAFLD includes a spectrum of hepatic pathologies that ranges from simple steatosis (namely non-alcoholic fatty liver or NAFL) and non-alcoholic steatohepatitis (NASH), the intermediate form of liver damage, to the most advanced stages of liver disease, namely cirrhosis and hepatocellular carcinoma (HCC)[3,4]. The identification of individuals who have NASH with fibrosis has significant prognostic implications. Follow-up studies of patients with NASH and fibrosis demonstrates that almost 30% of these individuals become cirrhotic within 5-10 years. In contrast, only about 3% of individuals with milder forms of NAFLD develop cirrhosis after more than a decade of follow-up. Therefore, NASH with fibrosis progresses to cirrhosis both more consistently and more rapidly than simple NAFL[5]. The prevalence of NAFLD in adults and children in the general population is not certain and is difficult to assess accurately because there is a lack of simple, non-invasive diagnostic tests. The 'gold standard' for diagnosing NAFLD and its severity is represented by liver biopsy, but this invasive technique is neither feasible nor ethical to use in healthy populations. Even in clinical practice, liver biopsies are used to clarify the diagnosis in chronic hepatitis (for example, in patients with indeterminate or discordant results unable to exclude advanced fibrosis)[6,7]. Consequently, its prevalence is usually estimated by serum biomarkers of NAFLD and/or evidence of fatty liver on ultrasonography (US) or magnetic resonance imaging (MRI). Nevertheless, NAFLD is considered the most common chronic liver disease worldwide and its prevalence has been estimated to be approximately around 20-30% in the general population (NAFLD 16-24%, NASH 2.1-6.3%), to be higher in obese people (mean prevalence 34.2%)[8,9], and to range from 29.6% to 87.1% in type 2 diabetes mellitus (T2DM) subjects[10]. Fatty liver can be present since childhood, with an estimated prevalence of about 7-10%, which reaches 34.2% in obese children[11]. NAFLD has been widely associated with the cardio-metabolic syndrome and its components: hepatic and systemic insulin resistance (IR), dyslipidemia, visceral obesity, hypertension, impaired fasting glucose and increased stroke risk[12-14]. The Dionysos nutrition and liver study reported the risk factors for NAFLD in a representative sample of the general population. They were: body mass index ≥30, glucose >110, insulin, HOMA and HDL-cholesterol alteration, triglycerides >150, blood pressure >130/80[15]. Interestingly, these are the same risk factors that are associated with cardiovascular diseases (CVD)[16]. Moreover, in NAFLD patients, liver enzymes have been demonstrated to predict the incidence of

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CVDs, independently of the traditional risk factors, including C-reactive protein and metabolic syndrome (MS). As a matter of fact, the extent of liver damage has been correlated with early carotid atherosclerosis, suggesting that the injury to both vessels and liver share similar inflammatory mediators[16]. For these reasons, NAFLD has been recently proposed as an early marker of atherosclerosis and endothelial dysfunction and, consequently, as an independent cardiovascular risk factor[17]. Musso et al. in 2008 reported that the causes of death in patients with NAFLD are represented by ischemic heart diseases in 25% of cases, thus demonstrating that CVDs have an important weight in NAFLD[17].

There are many differences based on sex in NAFLD[18]. The study of sex differences is a rapidly growing area of medicine and there is an increase in the number of publications on this specific topic. With the aim of better clarifying the sex differences in NAFLD, we carried out a review of the literature highlighting the gender specific findings published in the literature. The biological sex differences in normal physiology and diseases originate mainly from sex chromosomes and sex hormones[11,19].

Prevalence of NAFLD and gender differences

A meta-analysis of 74 studies demonstrated that NAFLD prevalence in children/adolescents was higher on average in males than females, both in the general population and in clinical studies[11]. However, when stratified by diagnostic method and gender, in general population studies NAFLD prevalence estimates were similar in males and females using USS as the diagnostic method, whereas they were higher in males in those studies that used alanine aminotransferase (ALT) to assess NAFLD[11]. On the contrary, in clinical studies, pooled estimates were consistently higher in males, regardless of the diagnostic method used[11]. When considering only obese children/adolescents, both in the general population and clinical studies, the prevalence was consistently higher in males than in females, with the exception of general population studies using USS, in which prevalence estimates were similar in both sexes[11]. Menopause or age-specific sex difference was infrequently considered in published studies, but when examined, NAFLD prevalence and incidence were higher in men than in premenopausal women (or aged ≤ 50-60 years) while they tended to become more common in women after menopause (or aged ≥ 50-60 years)[20]. However, after menopause, NAFLD occurs at a higher rate in women, suggesting a protective effect of estrogen[2]. In fact, postmenopausal women on hormone replacement therapy (HRT) had a lower prevalence of NAFLD compared to postmenopausal women not on HRT[2,20].

Cardiovascular risk and NAFLD

NAFLD can be considered as a hepatic manifestation of the metabolic syndrome. A significant number of patients with either clinical or histological diagnosis of NAFLD develop metabolic problems[21]. NAFLD appears to be a feature of the metabolic syndrome, and its detection on abdominal ultrasound should alert to the existence of an increased cardiovascular risk[21]. Indeed, it has been widely associated with cardio-metabolic syndrome and its components: hepatic and systemic insulin resistance (IR), dyslipidemia, visceral obesity, hypertension, impaired fasting glucose and increased stroke risk[22,23]. These conditions are well-known cardiovascular risk factors, and patients affected by this syndrome have an elevated probability of developing a cardiovascular pathology that, in turn, represents one of the main causes of death in this population[24]. In recent years, the role of NAFLD in inducing CVDs has been highlighted to the point that it has been considered as an independent risk factor for cardiovascular pathologies[25,26]. Among the several processes involved in the mechanism linking NAFLD and CVDs, oxidative stress and endothelial dysfunction (in turn, strongly inter-correlated) appear to play an important pathogenic role[27]. Recent studies have shown that NAFLD is associated to endothelial dysfunction, which is characterized by oxidative stress accumulation and considered as a surrogate marker of CVD[28]. Even though a large number of insights on the link between IR and liver damage are not known yet, what we do know is that IR is responsible for endothelial dysfunction, for example via the imbalance of the enzymatic system of nitric oxide (NO) production[29]. Insulin, in fact, induces endothelial Nitric Oxide Synthase (eNOS) activation, resulting in vasodilation and vascular protection[30]. When IR appears, it can also lead to endothelial dysfunction, through the impairment of NO production and the inhibition of insulin-induced vasorelaxation[31], and eNOS function impairment has been widely associated with it[32]. IR, widely demonstrated in NAFLD, might be the main trigger of eNOS dysfunction, which, therefore, might play a crucial role in the onset of NAFLD[33,34]. Moreover, endothelial dysfunction with impaired NO production is involved in the progression of advanced liver diseases[33,34] and is associated with increased vascular resistance (resulting in portal hypertension) and hepatic stellate cell activation in the liver and collagen deposition in the space of Disse (resulting in fibrosis)[35]. IR-associated eNOS dysfunction may represent a peculiar and essential mechanism of liver damage in NAFLD, which might also represent a pathological link between NAFLD and CVDs[14,35]. In insulin-resistant subjects, the presence of fatty liver has been correlated with an impairment of the systemic oxidant/antioxidant balance

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(indicated as oxidative stress) and endothelial dysfunction, independently of the presence of MS, adiposity and high levels of adipokines[35,36]. It is well known that oxidative stress is associated with endothelial dysfunction and CVDs[37,38] and, in NAFLD patients, it triggers an inflammatory cascade and extracellular matrix deposition in the liver, promoting the development of non-alcoholic steatohepatitis (NASH). Even though the mechanisms linking NALFD to increased oxidative stress and endothelial dysfunction have not yet been fully clarified, impaired mitochondrial β-oxidation, high levels of oxidized low-density lipoprotein (LDL), dietary saturated fat and reduced antioxidant intake have been proposed as potential pathogenetic factors[39-42].

Gender difference and CVDs in NAFLD

In the general population, the male sex has a greater risk of developing CVDs under the age of 50 years compared to women but, after menopause, the incidence in women drastically increases until it reaches that of males[43,44]. Sex modulates the association of NAFLD with incident CVDs/mortality in studies in which the diagnosis of NAFLD was based on surrogate indices, such as raised liver enzymes. Most of the population-based cohort studies and meta-analyses reported an independent association between raised gamma-glutamyl-transpeptidase (GGT) and incident CVDs in both sexes[44,45]. Conversely, a German population-based cohort study found that increased GGT was associated with higher risk of CVDs only in men but not in women, and this association was stronger in men who had a diagnosis of steatosis by USS[46]. Increased ALT has been variably associated with incident CVDs either in both sexes[44,47,48] or in men only[49]. In 2016, a South Korean study, in which the diagnosis of NAFLD was based on USS, reported that men had a higher prevalence of NAFLD and carotid plaques, and higher values of carotid intima-media thickness (IMT) than women, but NAFLD independently predicted subclinical carotid atherosclerosis (IMT and plaques) only in women[50]. No gender differences were reported regarding the association between NAFLD assessed with USS and incident CVDs[51]. Another study, based on a Danish registry, showed that patients with a hospital discharge diagnosis of NAFLD had CVDs similar between two sexes[44,51]. A Japanese study, conducted on apparently healthy subjects, found that the USS diagnosis of NAFLD was a predictor of CVDs in both sexes equally[52]. A significant correlation between NAFLD (based on CT scanning findings) and prevalence of coronary artery calcification (CAC) was found in the only study carried out in postmenopausal women. However, NAFLD was not independently associated with CAC[53].

Key messages

- NAFLD is a constantly increasing disease in the population.
- There is a higher prevalence of NAFLD in males compared to pre-menopausal females.
- In postmenopausal age, the prevalence of NAFLD is very similar between male and female sex.
- NAFLD seems to be associated with CVD independently of metabolic factors in both sexes.

Conclusions

NAFLD is a disease that is constantly increasing its prevalence among the global population. The data currently available in the literature shows a higher prevalence in men than in pre-menopausal women. In post-menopausal age, its prevalence seems to equalize between male and female sex[2,11,20]. Male patients carry an increased risk of CVDs. However, NAFLD seems to be associated with CVDs independently of metabolic factors in both sexes[42]. Few data are available in postmenopausal women and studies should specifically be conducted to ascertain whether NAFLD is a specific/independent cardiovascular risk factor in this population of patients[43].

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Acknowledgments
Research activity of Antonietta Gerarda Gravina was supported by the Valere Program.

Conflict of interest statement: the Authors declare no conflicts of interest.

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