Review paper

Atopic dermatitis and non-alcoholic fatty liver disease: current state of evidence and possible pathogenetic correlations

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Abstract

Relationships between inflammatory diseases and metabolic abnormalities are recently raising much scientific interest. Convincing evidence on the association between atopic dermatitis (AD) and constituents of metabolic syndrome (MS) has already been established. In this article we aim to summarize current data on the link between AD and non-alcoholic fatty liver disease (NAFLD), which is considered a hepatic manifestation of MS. By reviewing animal models, human studies and possible pathogenetic points of contiguity we want to present the current state of knowledge and goals for further investigations. To our best knowledge, this is the first review of this topic so far.

Key words: atopic dermatitis, non-alcoholic fatty liver disease, liver steatosis, gut-skin axis.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory disease, presenting with dermatologic symptoms such as erythema, papulations, pruritus and excoriation. This common entity is most prevalent in paediatric population as symptoms tend to decrease or disappear with age, however in some patients AD persists until adulthood [1]. Pathogenesis of AD is considered multifactorial and is probably a combination of different abnormalities including skin barrier disfunction, immune system dysregulation, genetic and environmental factors [2]. Pathogenic models of the disease are still under investigation.

Recent scientific research suggests an association between AD and constituents of metabolic syndrome (MS) [3], such as obesity and dyslipidaemia, which pose a major challenge for contemporary healthcare systems due to their high prevalence, chronic course and long-term complications. Non-alcoholic fatty liver disease (NAFLD), which is considered a hepatic manifestation of MS, seems to be the least investigated entity in terms of possible metabolic AD comorbidities.

NAFLD is a condition characterized by accumulation of excess lipid molecules in hepatocytes, which cannot be justified by secondary factors, such as increased alcohol or medication intake. Up to 30% of NAFLD cases coexist with a chronic inflammatory process in the liver parenchyma, called non-alcoholic steatohepatitis (NASH) which may progress to fibrotic change and cirrhosis [4].

The relation between AD and NAFLD has not been well documented so far. In this article we aim to summarize existing scientific findings and hypotheses regarding their potential link.

Animal models

Hypothetical mechanisms linking AD symptoms and liver lipid metabolism alterations remain unclear. Two animal models, one described by Jong *et al.* in 1998 [5] and another by Seino *et al.* in 2011 [6] proved the association between genetic variants in mice and coexistence of dermatitis and lipid metabolism abnormalities.

Jong *et al.* investigated apolipoprotein C1 (APOC1) in transgenic mice for dermatitis and hyperlipidaemia [5]. APOC1 is an apolipoprotein with strong expression in liver and skin cells, in particular macrophages and keratinocytes. APOC1 is known to maintain high homology in mice and humans. APOC1 influences lipid homeostasis, which is essential in preserving skin barrier integrity. Jong *et al*. performed molecular mRNA measurements and serum lipid analysis which showed overexpression of APOC1 in the liver and skin to be associated with signifi-

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cantly elevated total serum cholesterol (TC) and triglycerides (TG) levels. Furthermore, APOC1 overexpressing mice developed dry skin, epidermal scaling, hair loss and pruritus, whereas the histological examination revealed sebaceous gland atrophy, epidermal thickening and lack of subcutaneous adipose tissue in comparison to wild-type mice. Although this study did not include histological or biochemical liver lipid content analysis, other report confirms the correlation of APOC1 overexpression and liver steatosis in mice [7].

Similar results were achieved by Nagelkerken *et al*. [8] who also described symptoms of AD in APOC1 transgenic mice. Authors evaluated skin sections for presence of a different type of inflammatory cells, as well as serum for IgE levels. Results showed elevated numbers of eosinophils, macrophages, CD4+ T-cells and mast cells, as well as an increased level of serum IgE correlating with a number of IgE+ mast cells in the skin and disease progression. In this study mice showed a positive response to corticosteroid treatment.

Seino *et al*. [6] used other genetic strain of mice called NC/Nga, which also expresses several features characteristic for AD. When bred in conventional circumstances or after sensitization with specific antigens these mice develop skin lesions clinically and histologically resembling human AD. They also present elevated serum IgE levels. Authors performed biochemical analysis of serum and liver lipid levels in NC/Nga mice previously sensitized with picryl chloride (PiCl) to induce allergy. These mice demonstrated a significantly higher concentration of TG, TC and phospholipids in the liver compared to the control group. There were no significant differences in serum lipid levels.

Human AD and NALFD

As of today, a few clinical studies investigating coexistence of AD and liver steatosis in humans have been published.

H. Kimata is the author of three articles regarding prevalence of NAFLD and dyslipidaemia in Japanese paediatric population. All three studies were prospective, used ultrasound to detect and grade liver steatosis and excluded obese subjects. The first study [9] compared children suffering from AD to age-matched non-atopic controls as well as patients with bronchial asthma and allergic rhinitis. The results showed liver steatosis to be significantly more prevalent in the AD group (17.6%) compared to the control group (17.6% vs. 3.2%; $p < 0.05$). Both mild and moderate fatty liver rates, as well as serum lipid levels were higher in the AD group. The youngest child with AD and liver steatosis was 6 months old, whereas all control group children with fatty liver were older than 2 years. Another study [10] also revealed increased occurrence of liver steatosis (both mild and moderate) in the AD group (18.5–33.9% vs. 5.4–12.5%; $p < 0.05$), but serum lipid levels did not exhibit significant differences between groups. The last study [11] concentrated on infants under 1 year of age and confirmed higher rates of liver steatosis among children with AD (3.7–9.8% vs. 2.4–5.0%; p – not given by the author). Moderate steatosis was discovered in several cases among the AD group, whereas it was absent in the control group. It is worth mentioning that all subjects included in this trial were breastfed and weaned similarly.

A smaller paediatric population from northern India was analysed by Reddy *et al.* [12] to compare the prevalence of MS and liver steatosis among AD children to sex- and age-matched healthy controls. Results showed MS to be significantly more common in the AD group. NAFLD occurred exclusively in children with moderate or severe AD (6% vs. 0%, $p = 0.242$).

Manuscripts concerning adult populations are even fewer and do not support the hypothesis of AD and NAFLD coincidence so far. The articles we refer to are both retrospective studies.

Maurelli *et al.* compared liver steatosis rates between patients with a history of malignant melanoma (MM), who were considered healthy controls, and patients suffering from inflammatory skin diseases, precisely AD and psoriasis (PsO) [13]. The prevalence of NAFLD diagnosed with ultrasound in MM and AD groups was almost identical (23.2% and 24.1%; p – non significant), whereas it was significantly higher in the PsO group (49.8%, $p < 0.01$). It should be mentioned that patients with PsO also had significantly elevated BMI, serum GGT and triglyceride levels compared to both AD and MM groups. The PsO group was also considerably bigger ($n = 466$) than AD ($n = 144$) and MM ($n = 99$) groups.

Gau *et al.* used data from the National Health Insurance Research Database (NHIRD) in Taiwan to assess incidence of new onset AD in a cohort of patients previously diagnosed with NAFLD [14]. In this study, the risk of developing AD was lower in the NAFLD group than in healthy controls (0.37/1000 person-years vs. 0.39/1000 person-years; HR = 0.94).

Gut-skin axis

A hypothesis called the "gut-skin axis", which refers to interplay between the digestive system and skin health has recently aroused much interest. A substantial part of the gut-skin axis research focuses on gut microbiome homeostasis, which seems to be a significant factor influencing or even inducing various chronic diseases. Lately it has been taken into consideration in both AD and NAFLD pathogenesis. Several studies found that patients with AD demonstrate decreased microbial diversity, decreased levels of *Bifidobacterium* and *Bacteroides* and an increased amount of *Enterobacteriaceae* [15–17]. Main abnormalities that have been observed in patients with NAFLD also include increased *Enterobacteriaceae* as well as *Proteobacteria* abundance [18–20].

Another gut-related factor reported in both conditions is elevated intestinal permeability. Impairment of the intestinal mucosal barrier, leading to abnormal response to food allergens, is involved in AD pathogenesis in at least some phenotypes of the disease [21, 22]. There is growing evidence that it may also be an important cause of a chronic low-grade inflammatory state and fat infiltration of the liver and other organs [23, 24]. Recent studies prove increased gut permeability in NAFLD patients in comparison with healthy controls [25, 26]. It is suspected that small amounts of bacterial components and metabolites translocated through damaged intestinal barrier and transported by portal circulation into the liver induce inflammation. Lipopolysaccharide (LPS), which is the main component of Gram-negative bacteria outer membrane, has been widely investigated and proven to be elevated in serum of NAFLD patients by up to 40% in comparison to healthy controls [27]. Simultaneously increased fatty acid absorption may lead to accumulation of fat in hepatocytes. Moreover, intestinal barrier disfunction is probably positively correlated to disease severity and progression in NAFLD [25, 26, 28].

Although there is no direct evidence so far, certain microbiome alterations combined with increased gut permeability could possibly induce fatty liver in patients with AD.

Cytokines

Another factor presumably contributing to both conditions is the expression of cytokines, which play a role in modulating inflammatory response. Particular attention should be paid to adiponectin, which is produced mainly in adipose tissue and is known to have anti-inflammatory properties by reducing tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) levels. Skin cells such as sebocytes, keratinocytes and fibroblasts express receptors for adiponectin, which regulates their proliferation and sebum production [29]. Significantly reduced adiponectin serum levels were observed in several studies in both AD and NAFLD patients compared to healthy controls [30, 31]. Low adiponectin levels were observed especially in early-onset AD, which starts before 2 years of age [32].

Fatty liver is also promoted by high leptin and resistin serum levels, however there is no sufficient evidence of their elevation in AD.

Discussion

Epidemiologic studies clearly indicate that genetic factors influence both AD and NAFLD development. Animal experiments mentioned above suggest that genetics could have some contribution to AD and NAFLD coexistence, however this has not been reflected in human studies so far.

In this article we mention a few manuscripts which analysed AD and NAFLD comorbidity in humans. The results are contradictory in paediatric and adult populations. Also, there is a disproportion of both the quantity and quality of data for minors and grown-ups. Trials conducted in children were all prospective, compared AD patients to non-AD controls and confirmed a positive association between AD and NAFLD. In total 1946 subjects were enrolled. To our best knowledge, only two studies in adults have been published so far. One of them, although retrospective, used similar methodology as paediatric trials and after analysing data from 243 patients did not confirm the significant difference between AD and control groups. The second publication searched for new-onset AD in a group of adult patients already diagnosed with NAFLD. The mean age of subjects in this study was 51.23 ±15.94 years. Meanwhile, most cases of AD in adulthood are persistent disease which developed in childhood, which makes the result less credible. It is uncertain whether the age-related differences result from undiscovered factors predisposing children with AD to fatty liver or from insufficient data, especially in adults.

The gut-skin axis is a tempting hypothesis broadly investigated in recent research in regard to various diseases. Similar microbiome alterations as well as dysfunctional intestinal barrier were found in patients with AD and NAFLD. However, decreased biodiversity and increased *Enterobacteriaceae* levels are not specific for AD and NAFLD and can be found in other conditions.

A decrease of adiponectin production was observed especially in early-onset AD, which fits into the age-related epidemiologic differences between studies in paediatric and adult populations mentioned above. Adiponectin expression is also inversely correlated to obesity, which is a common comorbidity and a risk factor for AD.

Lifestyle and dietary habits should not be underestimated when considering NAFLD prevalence in patients with AD. Some studies suggest that patients with AD have a higher risk of making poor nutritional choices and avoiding physical activity [33, 34]. This could be due to both psychological and sociological burden of the disease. Exercise is also known to exacerbate cutaneous symptoms of AD, which makes patients less inclined to engage in sports.

Conclusions

Pathogeneses of both AD and NAFLD are considered multi-hit and share several points of contiguity, which makes the relationship between them plausible. All studies conducted in paediatric populations so far confirmed the association between the two entities. However, existing evidence linking AD and NAFLD is insufficient and further research in this field is needed, especially regarding adults.

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Ethical approval

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Conflict of interest

The authors declare no conflict of interest.

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