General discussion and perspectives

The main aim of this thesis was to investigate the relationship between psoriasis and liver disease, with a main focus on steatosis and liver fibrosis. We determined different levels of inflammation in psoriasis (PSO), psoriatic arthritis (PsA) and rheumatoid arthritis (RA) patients; studied the prevalence and risk of steatosis and liver fibrosis irrespective of known risk factors in psoriasis patients; and finally discuss new ways to monitor liver disease during systemic treatment in these immunomodulatory inflammatory diseases (IMIDs).

SYSTEMIC INFLAMMATION

Over de past decades psoriasis has evolved from a single disease affecting only the skin, to a more systemic disease with a high disease burden. It is known that patients with psoriasis suffer more from components of the metabolic syndrome and its associated cardiovascular complications.[1] The exact role of lifestyle and disease-specific factors related to the increased prevalence of these comorbidities remains unclear. It is being hypothesized that the causal link could be the systemic inflammation.[1,2] In cardiovascular disease increased pro-inflammatory markers are present, such as interleukin (Il)-6 and C-reactive protein (CRP).[3] In psoriasis patients, the effects of these increased inflammatory markers is not that clear as compared to cardiovascular disease and some other IMIDs like RA. The knowledge regarding the levels of inflammatory markers in psoriasis in the available literature remains scarce. Most research was conducted in small laboratory studies with inflammatory markers not being their primary area of interest. We have conducted a systemic review and meta-analysis on the available literature of a selected number of pro -and anti-inflammatory markers in patients with psoriasis.[4] In this study, the level of inflammation was compared to a healthy control group. We observed a 1,5 to 2-fold increased level of inflammatory markers in PSO patients as compared to healthy controls. However, the clinical relevance and their potential etiological role in comorbidities are still subject to future debate.

Nowadays, psoriasis is more and more being regarded as an IMID, such as PsA and RA. All share some common pathogenic pathways and several treatments options.[5] PsA and RA, and especially RA, are generally accepted as well-known systemic diseases, as reflected by the ACR/EULAR RA Classification Criteria. An increased prevalence of comorbid disease is observed in PsA and RA patients, that are independent of confounding lifestyle factors such as obesity and smoking. Also the levels of inflammation as reflected by TNF-α, IL-6, and CRP are higher in these diseases affecting the joints as compared to PSO.[6] A hypothesis on the role of inflammation and lifestyle factors causing comorbidities in PSO, PsA and RA is described in Figure 1. However, this knowledge is

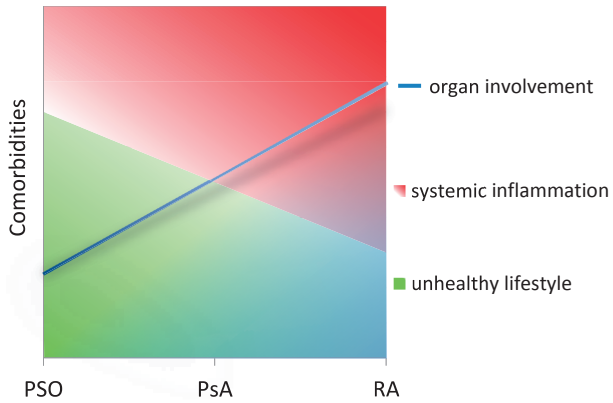

Figure 1. A hypothetical model of the etiology of the prevalence of comorbidies, systemic inflammation and organ involvement in PSO, PsA and RA
Abbreviations: PSO, psoriasis; PsA psoriatic arthritis; RA rheumatoid arthritis

mainly derived from evidence of in-between study comparisons. Studies comparing inflammation between PSO, PsA and RA within the same study were not available. We have compared levels of pro-inflammatory, and anti-inflammatory markers and different cytokines, which are important targets for new biological treatments, and tried to correct for known confounders like disease severity and medication use in PSO, PsA and RA patients within the same study. We have demonstrated that RA patients have the highest level of systemic inflammation followed by PsA and PsO.[6]

Although psoriasis is nowadays being seen as an IMID and does seem to some extent comparable to RA regarding its etiology, observed inflammatory markers and available treatment options, there are still clear differences between these two IMIDs.

HEPATO-PSORIATICA VS METABOLIC SYNDROME

In PSO patients, the prevalence of the metabolic syndrome is around 40% compared to 15-25% in the general population.[7-9] Although, numerous studies are published on this association, there is still no consensus whether PSO is an independent risk-factor for the metabolic syndrome and development of cardiovascular disease.[10,11]

Non-alcoholic fatty liver disease (NAFLD) is considered as the hepatic manifestation of the metabolic syndrome.[12] In the current epidemic of obesity, type 2 diabetes mellitus and other factors of the metabolic syndrome, NAFLD has become the most prevalent chronic liver disease in Western countries. The likelihood of having NAFLD increases

when more criteria of the metabolic syndrome are met.[13] The prevalence can be as high as 85% in obese patients.[14] Metabolic syndrome and NAFLD share insulin resistance and pathophysiological mechanisms and are bi-directionally associated.[15] With an observed increased prevalence of the metabolic syndrome in PSO patients also NAFLD is expected to be more prevalent in PSO.

In small case-control studies the prevalence of NAFLD in PSO patients varies between 46 to 59% in Western countries.[16,17] We have studied the association of NAFLD and PSO in a large population-based cohort study, The Rotterdam Study, and found that PSO is independently associated with NAFLD in patients with mild disease.[18] PSO increased the likelihood of having NAFLD by approximately 70%. In PSO patients, already having metabolic syndrome, this is the strongest predictor of concomitant NAFLD. Candia *et al.* confirmed in a recent systemic review and meta-analysis that psoriasis patients have a two-fold increase of having NAFLD as compared to controls without PSO.[19] The risk of developing NAFLD seems to be correlated with the severity of PSO, and those with PsA have an even higher risk of developing NAFLD.[19] Whilst all studies confirm this association, causality cannot be proven due to the cross-sectional design of the above mentioned studies. [16,17,20-22]

Psoriasis and NAFLD are both multifactorial diseases, in which genetic and environmental factors are involved. Figure 2 shows the complex interaction between PSO and NAFLD , which will be further explained in this paragraph. NAFLD is also believed to be associated with a state of low-grade chronic systemic inflammation, with a slightly elevated level of pro-inflammatory markers like Il-6, CRP and tumor necrosis factor-alpha (TNF-α).[14] Inflammation and cytokine-mediated mechanisms play a central role in the pathogenesis of both PSO and liver disease. They also overlap with metabolic components, which are frequently present in both PSO and NAFLD. The overlap of this "chronic inflammatory state" of PSO, metabolic syndrome and NAFLD does not prove any causal relationship between these different conditions.[23] Other overlapping mechanisms of PSO with the metabolic syndrome and NAFLD which have been proposed in the recent literature include: insulin resistance, dyslipidemia, angiogenesis, oxidative stress and endothelial dysfunction.[24] Beside these factors also (still unknown) environmental components, such as nutrition or physical exercise, and genetic factors are likely to play a role as well.

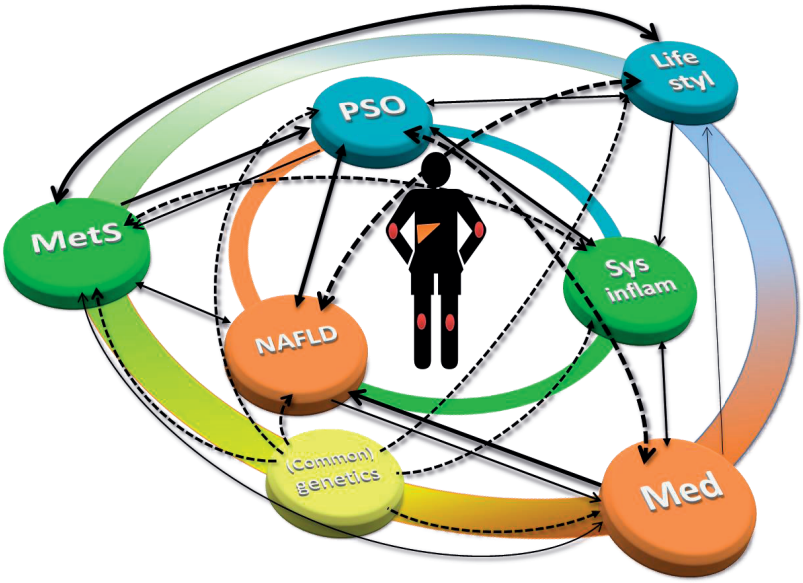

Figure 2. hepato-psoriatica; a complex interaction between psoriasis, NAFLD and co-existing factors
Psoriasis can be replaced by psoriatic arthritis or rheumatoid arthritis. Abbreviations; pso, psoriasis; MetS, metabolic syndrome; Med, medication; NAFLD, non-alcoholic fatty liver disease; sys inflam, systemic inflammation.

HEPATO-PSORIATICA AND MEDICATION

Two different meta-analyses conclude that methotrexate (MTX) is a risk factor for developing liver fibrosis in PSO patients.[25,26] However, no dose-dependent effect was observed.[25,26] Psoriasis patients receiving MTX have a higher risk of developing liver fibrosis compared to patients with PsA and RA receiving this same drug.[27] This may be explained by the higher prevalence of unfavorable lifestyle factors and components of the metabolic syndrome in PSO patients compared to PsA and RA.[2,28] In PSO patients with type 2 diabetes or pre-existing NAFLD, MTX can cause an increased risk of drug-induced hepatic fibrosis compared to patients without these metabolic comorbidities.[29] Inconsistent results were found in two meta-analysis on the association between diabetes, obesity and alcohol intake and the increased risk of liver fibrosis in PSO patients.[25,26] Furthermore, adopting a more healthy lifestyle is an effective therapeutic option in the treatment of NAFLD and also in PSO patients. It may reduce the psoriasis severity and treatment response.[29,30] The association between PSO and liver disease is important from a therapeutic point of view, since treatment may involve the use of hepatotoxic drugs, such as MTX. Although medication and the metabolic syndrome are important

risk factors for the development of liver fibrosis in PSO patients, in our study we also found an increased prevalence of liver fibrosis in PSO patients without use of hepatotoxic medication. Even after adjusting for different components of the metabolic syndrome. This implies that other more disease specific factors may play an important role as well.

MONITORING OF LIVER DAMAGE

Several international guidelines of medical societies recommend using ALT to monitor liver toxicity. ALT is indeed a good marker for acute medication induced hepatitis. However, for the detection of NAFLD and liver fibrosis, ALT appears to be unresponsive.[31,32] Even in patients with NAFLD, it's found that half of the NAFLD patients have normal ALT levels.[33] In elderly patients with NAFLD this marker is even normal in up to 88%.[34] In our studies, ALT levels were within the normal range in almost all of the participants. Furthermore, median ALT levels were normal in the total study population as well as in the NAFLD population. Neither did any of the participants with advanced fibrosis show elevated ALT levels.[35] However, ALT is still being recommended in the Dutch dermatology and rheumatology guidelines to monitor liver disease in patients receiving hepatotoxic drugs.[36]

Use of amino terminal type III procollagen peptide (P3NP), additional to ALT, has also been recommended in the European Dermatology and British guidelines to monitor liver toxicity.[37,38] However, P3NP has been abandoned by hepatologists a while ago because of several limitations. P3NP is not specific for fibrosis in the liver, is hampered by frequent presence of hepatic steatosis. P3NP can only be interpreted serially, has not been properly validated as a diagnostic test and is quite expensive.[39] Although, P3NP is being mentioned in the Dutch guidelines, it is only scarcely being used in daily dermatological practice, related to the above mentioned limitations.[40] The updated Dutch psoriasis guideline, that still needs to be approved by the Netherlands Society of Dermatology and Venereology will therefore probably omit P3NP measurements.

A new non-invasive diagnostic test, the Enhanced Liver Fibrosis (ELF) Score, has recently become available. This ELF score has been proposed to be more reliable than P3NP and also interpretable as a single measurement.[39] We have investigated the ELF Score compared to P3NP in detecting liver fibrosis in PSO, PsA and RA patients.[41] The ELF score has a smaller range and is less influenced by inflammatory markers compared to a single P3NP measurement. Overall the ELF score showed better results in PSO and RA patients.

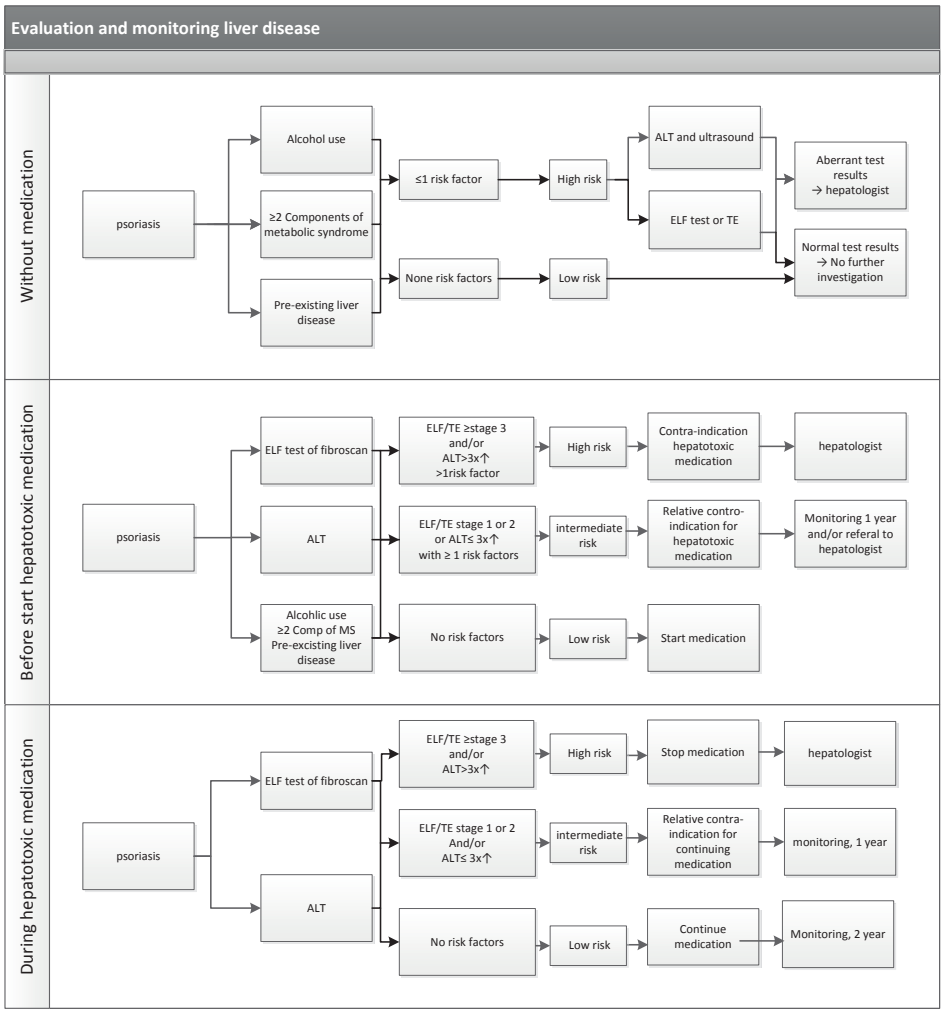

Figure 3. Flowchart on evaluation and monitoring liver disease

Without medication:
High risk: When one or more risk factors are present further investigations are needed to exclude/confirm diagnose of NAFLD or liver fibrosis. Patients can be referred to a hepatologist. A three years evaluation is recommended
Low risk: When risk factors of liver disease absent, no further investigations are needed.
Before start hepatotoxic medication:
High risk: ALT >3 times normal value, TE or ELF test indicating severe liver fibrosis (≥ stage 3), with or without further risk factors of liver disease, referring the patient to a hepatologist. It is not recommended to start hepatotoxic medication in consultation with the hepatologist..
Intermediate risk: ALT ≤3 times normal value and one or more risk factors for liver disease are present or TE or ELF test indicating mild liver fibrosis (stage 1 or 2) referral to a hepatologist is recommended. When ALT ≤3 times normal value and no risk factors are available an intense monitoring program can be followed with yearly TE or ELF test.
Low risk: No risk factors for liver disease, ALT and Fibroscan or ELF test within the normal range

During hepatotoxic medication:
High risk: ALT >3 times normal value, TE or ELF test indicating severe liver fibrosis (≥ stage 3) referring the patient to a hepatologist and stop the treatment is recommended in consultation with the hepatologist.
Intermediate risk: ALT ≤3 times normal value, or TE or ELF test indicating mild liver fibrosis (stage 1 or 2); new investigation is recommended ones yearly if the patient continuous with hepatotoxic medication.
Low risk: ALT and TE or ELF test within the normal range
Abbreviations; LF, liver function; ELF, Enhanced Liver Fibrosis.

Transient elastography (TE) is another non-invasive test that is especially reliable in identifying more advanced stages of liver fibrosis.[42,43] We have used ultrasound to detect steatohepatitis and TE to diagnose liver fibrosis in participants of the Rotterdam Study with and without psoriasis.[35] We found a two-fold increased risk of liver fibrosis in PSO patients compared to the reference population. This risk increased even four times in the NAFLD subgroup. In field of hepatology, it has now been demonstrated that the diagnostic accuracy for liver fibrosis/cirrhosis improves when biomarkers or TE are used. This accuracy further increases by combining both measurements. In two recently published hepatological guidelines (NICE and EASL) this has led to the recommendation to use the Fibroscan and/or the ELF test as first line diagnostic test to detect liver fibrosis.[32,44,45]

For now, TE is the preferred method for monitoring liver fibrosis is psoriasis patients. However, it is less readily available because of the requirement of a dedicated device and operator. When TE is not available, the ELF test seems the second best option in monitoring liver fibrosis. In clinical practice, the ELF test has a high level of applicability (>95%), good inter-laboratory reproducibility, and has the clear advantage of widespread availability.[45] In the current absence of validated ELF cut-off points for inflammatory diseases yet, we suggest to use the cut-off point for healthy people. Although, the use of the healthy cut-off values would lead to false positive cases, a negative test is sufficiently reliable to exclude those with liver conditions. Altogether if the ELF value is above the 9.8 additional investigations such as transient elastography or referral to a hepatologist seems warranted.

Other diagnostic tests for liver fibrosis are the Fibrotest[46] and Hepatoscore[47] with a higher diagnostic accuracy compared to P3NP or APRI (asparate aminotransferase to platelet ratio index). [31,48] A more advanced, but promising imaging method for the evaluation of chronic liver disease is gadoxetic acid enhanced-MRI which is currently under investigation.[32,49]

Based upon these findings, we therefore propose the following flowchart (Figure 3) to evaluate and monitor liver disease in psoriasis patients

CLINICAL RELEVANCE AND FUTURE RESEARCH

As our knowledge evolves on the relationship between NAFLD and liver fibrosis in PSO patients, future investigation is necessary for better understanding of the pathophysiology. It is important to obtain more reliable results before drawing strong conclusions. Therefore, it is necessary to use different datasets and study designs, assessing both the primary outcome and its risk factors, and to include genetic epidemiology as well. Besides epidemiological and clinical studies, translational and genetics studies are required in better understanding the possible association and to riddle its underlying mechanisms. Longitudinal studies are needed to confirm a possible causal relationship between PSO and NALFD over time.

It is important that clinicians realize that ALT is not a good marker to monitor for NAFLD and liver fibrosis in patients on hepatotoxic drugs. New diagnostic tests have been developed with better test performance to diagnose these liver diseases. It is important to validate, further develop and improve the accuracy of these existing tools for non-invasive diagnoses of liver steatosis, NASH and fibrosis, especially in IMIDs. These tools can help us to better investigate the role of disease-related liver comorbidities and to improve monitoring of hepatic side-effects during treatment. Although, these non-invasive tests are not perfect and need further validation before clinical implementation, some of them are already available in clinical practice like TE. The ELF test is a potential candidate test, but before this test is adapted in clinical practice for patients with IMIDs, further external validation is mandatory.

In the upcoming updated Dutch psoriasis guideline, it is proposed to drop P3NP measurements in PSO patients that are considered for hepatotoxic drugs. Instead it is advised to screen for known risk factors of liver disease. It can be discussed that in the near future, other candidate diagnostic methods, for example TE or ELF will be adopted by this same guideline. However, the ELF test first needs reassuring results from further validation studies in patients with IMIDs.

We recommend, before the start of any hepatotoxic medication, to evaluate the risk of concomitant liver disease in PSO, PsA and RA patients. These risk factors include alcohol use, hepatitis, other liver diseases and components of the metabolic syndrome such as hypertension, insulin resistance, dyslipidemia and obesity. If one or more risk factors are present, further investigation of the liver is recommended (Figure 3), for which the newer serum panel marker (e.g. ELF) or imaging (e.g. TE) can be recommended.

There is no clear evidence or consensus on the monitoring frequency during use of hepatotoxic medication. In the EASL guideline it is recommended for patients with NAFLD to perform a follow-up assessment by either a serum biomarker or TE at three year intervals.[45] The timeframe for NALFD to develop to steatosis and even cirrhosis can be as short as two years even without use of hepatotoxic medication.[50] Based on these data, it seems reasonable that annual evaluation of liver fibrosis is reasonable for patients at risk using potential hepatotoxic drugs and biannual evaluation for those patients without further risk factors of liver disease. For patients without medication, but with risk factors (like NAFLD) an evaluation based on a three year interval seems sufficient.

Increasing the awareness of the risk of developing liver diseases in patients with IMIDs, especially during treatment with hepatotoxic drugs by dermatologists, rheumatologists, general practitioners and hepatologists and ways to diagnose liver toxicity is of utmost importance. Furthermore, the additional comorbidities in both IMIDs and NAFLD and the potential impact on possible treatment choices should be taken in account.

Based on the results of this thesis, we conclude that NAFLD and liver fibrosis is more prevalent than expected in PSO but also in PsA and RA patients. In psoriasis this risk is not only related to traditional risk factors, but also psoriasis itself seems to be an independent risk factor for liver disease, with a modest role for systemic inflammation. New validated biomarkers or non-invasive diagnostic tests are therefore needed to evaluate and monitor for liver diseases in patients with IMIDs.

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