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LIIS ILVES

Metabolomic profiling of chronic inflammatory skin diseases

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Metabolomic profiling of chronic inflammatory skin diseases

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Department of Dermatology and Venereology, University of Tartu, Tartu, Estonia

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Paper II **Ilves, L.**, Ottas, A., Kaldvee, B., Abram, K., Soomets, U., Zilmer, M., Jaks, V., Kingo, K. Metabolomic analysis of skin biopsies from patients with atopic dermatitis reveals hallmarks of inflammation, disrupted barrier function and oxidative stress. Acta Derm Venereol. 2021 Feb 24;101(2):adv00407. https://doi.org/10.2340/00015555-3766.

Paper III **Ilves, L.**, Ottas, A., Kaldvee, B., Abram, K., Soomets, U., Zilmer, M., Jaks, V., Kingo, K. Metabolomic Differences between the Skin and Blood Sera of Atopic Dermatitis and Psoriasis. Int J Mol Sci. 2022 Oct 27;23(21):13001. https://doi.org/10.3390/ijms232113001.

Paper IV **Ilves, L.**, Ottas, A., Raam, L., Zilmer, M., Traks, T., Jaks, V., Kingo, K. Changes in Lipoprotein Particles in the Blood Serum of Patients with Lichen Planus. Metabolites. 2023 Jan 6;13(1):91. https://doi.org/10.3390/metabo13010091.

The author of the current dissertation contributed to the publications as follows: Papers I, II, III and IV: the author participated in designing the studies, interpreted the results and wrote the papers.

2. ABBREVIATIONS

12-HETE	12-Hydroxyeicosatetraenoic acid
-L	total lipids
a	acyl
aa	diacyl
ae	acyl-alkyl
AA	amino acid
AD	atopic dermatitis
AD-L	atopic dermatitis lesional
AD-NL	atopic dermatitis non-lesional
ADMA	asymmetric dimethylarginine
Ala	alanine
AMD1	S--adenosyl--L--methionine decarboxylase 1
Arg	arginine
Asn	asparagine
Asp	aspartic acid
BCAA	branched chain amino acid
C	cholesterol
C0	free carnitine
C2	acetylcarnitine
C5	valeryl-L-carnitine
C16	hexadecanoyl-L-carnitine
C18	octadecanoyl-L-carnitine
C18.1	octadecenoyl-L-carnitine
C18.2	octadecadienyl-L-carnitine
CD4+	cluster of differentiation 4
CE	cholesteryl esters
CHD	coronary heart disease
CISD	chronic inflammatory skin diseases
Cit	citrulline
COX	cyclooxygenase
DC	dendritic cell
CVD	cardiovascular disease
DNA	deoxyribonucleic acid
FC	free cholesterol
FDR	false discovery rate
Gln	glutamine
Glu	glutamic acid

HC	healthy controls
HDL	high-density lipoprotein
HLA	human leukocyte antigen
IDL	intermediate-density lipoprotein
IFN-γ	interferon gamma
IgE	immunoglobulin E
IL	interleukin
Ile	isoleucine
L	large
LDL	low-density lipoprotein
Leu	leucine
LTB4	leukotriene B4
LP	lichen planus
Lys	lysine
LysoPC	lysophosphatidylcholine
Met	methionine
Met.SO	methionine sulfoxide
MS	metabolic syndrome
NMR	nuclear magnetic resonance
NOS	nitric oxide synthase
OLP	oral lichen planus
Orn	ornithine
PA	phosphatidic acid
PASI	Psoriasis Area Severity Index
PC	phosphatidylcholine
PCA	principal component analysis
PGE2	prostaglandin E2
PLS-DA	partial least squares discriminant analysis
Phe	phenylalanine
PL	phospholipids
Pro	proline
PS	psoriasis
PS-L	psoriasis lesional
PS-NL	psoriasis non-lesional
PsA	psoriatic arthritis
PUVA	psoralen and UVA
SDMA	symmetric dimethylarginine
SM	sphingomyelin
T2D	type 2 diabetes

Tau	taurine
TC	total cholesterol
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
TG	triglyceride
Th1	T-helper 1
Thr	threonine
TNF-α	tumour necrosis factor alpha
total DMA	total dimethylarginine
UVB	ultraviolet B
Val	valine
X.C2.C3....C0	ratio of short chain acylcarnitines to free carnitine

3. INTRODUCTION

In the present research, we investigated the metabolomic profile of three chronic inflammatory skin diseases: psoriasis (PS), atopic dermatitis (AD) and lichen planus (LP). All of them have a strong negative impact on the quality of life of the patients (Finlay & Coles, 1995; Langley et al., 2005; Beattie & Lewis-Jones, 2006; Silverberg et al., 2018; Fiocco et al. 2021). PS is characterized by erythematous-squamous plaques on the skin and is frequently accompanied by nail changes and psoriatic arthritis (Armstrong & Read, 2020; Griffiths & Barker, 2007). AD patients have pruritic dry skin with typical locations on the body depending on the age of the patient. AD is frequently associated with allergic rhinoconjunctivitis and asthma (Paller et al., 2018). Typical lesions of LP are flat polygonal pruritic papules located preferably on the sacral area, shins and flexural areas of the wrists (Boch et al., 2021). Common comorbidities of LP are hepatitis C infection (Alaizari et al., 2016) and thyroid disease (Amato-Cuartas et al., 2019; Robledo-Sierra et al., 2018). The disorders have several subtypes with different prognoses. Moreover, PS, AD and LP share several comorbidities, e.g. metabolic syndrome (MS) (Sommer et al., 2006; Daye et al., 2021; Saleh et al., 2014) and an increased risk for cardiovascular disease (CVD) (Henseler & Christophers, 1995; Neimann et al., 2006; Paller et al., 2018; Saleh et al., 2014; Silverberg & Greenland, 2015; Sommer et al., 2006).

Currently, the diagnosis of the above diseases is based on the clinical picture and pathohistology of the skin biopsy, while specific biomarkers have not been detected in the blood serum or skin.

The treatment of PS, especially biologic therapy, is effective and widely used, but even using biologics, some patients require multiple switches due to primary or secondary inefficacy (Honda et al., 2017). Compared to PS, management of AD and LP offers less treatment options.

Metabolomic studies can give us more detailed information about the development of these diseases and their comorbidities. In addition, a better understanding of the pathogenesis of chronic inflammatory skin diseases (CISD) could lead to finding disease-specific biomarkers and more precise treatment choices and modalities.

4. REVIEW OF THE LITERATURE

4.1. Chronic inflammatory skin diseases

The term chronic inflammatory skin diseases (CISD) involves a wide range of dermatoses, among which some have relatively high prevalence, like atopic dermatitis (AD), psoriasis (PS) and acne vulgaris, while others are encountered less often, like hidradenitis suppurativa and lichen planus (LP). Usually, a dermatose is considered chronic, if it has lasted at least 6 (Kolkhir et al., 2022) to 12 weeks (Pickett et al., 2015). All CISDs share skin inflammation, but the degree and cause of the inflammation, pathophysiological aspects, clinical picture and course of the disease are different. If the diagnosis is unclear, pathohistological analysis of skin biopsy is often essential.

In the present study, we focused on three CISD: PS, AD and LP. All three above-mentioned CISDs have a strong impact on the quality of the patients' life causing depression and anxiety, and affecting their ability to work (Carroll et al., 2005; Jalenques et al., 2020; Langley et al., 2005). Hence it is important to determine the metabolomic biomarkers of these diseases to fill in gaps in the knowledge of metabolomics in PS, AD and LP, as the metabolomic aspects of these diseases have not yet been thoroughly clarified.

4.2. Metabolomics

Metabolomics is an "omics" study among others, e.g. genomics, transcriptomics and proteomics, and it reflects the biological processes taking place in the organism. Metabolomics research concentrates on profiling metabolites – metabolism substrates, intermediates and products in cells and tissues, e.g. amino acids (AAs), nucleotides, sugars, biogenic amines, lipids (which can be subcategorized under the term lipidomics (Wang et al., 2020)) e.t.c.

Metabolites have different functions and are continuously affected by different intrinsic and extrinsic factors, reflecting the current state of the organism and ongoing processes (Rinschen et al., 2019). For example, phosphatidylcholines (PCs) have anti-inflammatory properties (Treede et al., 2007) and fatty acids and other lipids regulate insulin sensitivity (Yang et al., 2018). Metabolomic studies have been carried out in various diseases to elucidate their pathogenesis, e.g. in colorectal cancer (Gu et al., 2019), non-muscle invasive bladder cancer (Cheng et al., 2018), heart failure (Hunter et al., 2016) and coronary artery disease (Shah et al., 2010). Classically, the purpose of metabolomic research is to find biomarker(s) which, according to definition, is "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention". Therefore, biomarkers can be used to diagnose or monitor a disease, to prognosticate disease outcome or to predict responsiveness to the therapy, but also to evaluate treatment safety (FDA-NIH Biomarker Working Group, 2016). Positioned the farthest "downstream"

among the other "omics" (genomics, transcriptomics) studies, quite few metabolomic studies of PS, AD and LP have been published to date. In the present study, we aimed to add knowledge about the metabolomic aspects of the skin and blood sera of the above diseases.

4.3. Overview of psoriasis

4.3.1. Clinical manifestations of psoriasis

Psoriasis is a chronic inflammatory papulosquamous dermatose that affects approximately 2–3% of the adult population (Armstrong et al., 2021; Kurd & Gelfand, 2009; Stern et al., 2004), the incidence being higher in countries at higher latitudes (Parisi et al., 2013). The mean onset of PS has two peaks – 15 to 20 years of age and 55 to 60 years of age (Langley et al., 2005) – and the course of the disease varies from some aggravations during lifetime to an undulating and persistent disease. PS can be divided into different subtypes, among which the most common is chronic plaque psoriasis. Clinically, well-demarcated erythematous and scaly plaques appear preferably symmetrically on the extensor surfaces of the knees and elbows, lumbosacral area, umbilicus and scalp. Another characteristic feature is the Koebner phenomenon, in which the site of skin trauma is more prone to develop new lesions. Other, less common forms of PS are guttate, flexural, palmoplantar plaque psoriasis, erythrodermic psoriasis, generalized pustular psoriasis, pustulosis of the palms and soles and acrodermatitis continua of Hallopeau (Armstrong & Read, 2020; Bolognia et al., 2018; Griffiths & Barker, 2007). Nail involvement, which clinically manifests itself as onycholysis, pitting, oil spots and dystrophy, can be seen in 50–90% of PS patients and is frequently associated with the more severe disease and psoriatic arthritis (PsA) (Griffiths & Barker, 2007; Thomas et al., 2021). 20–30% of PS patients develop PsA (Ocampo & Gladman, 2019). Common comorbidities are hyperlipidaemia, hypertension (Neimann et al., 2006), obesity, diabetes, heart insufficiency (Henseler & Christophers, 1995), coronary heart disease (CHD), MS (Sommer et al., 2006), cancer (Vaengebjerg et al., 2020) and inflammatory bowel disease (Fu et al., 2018). PS has a strong impact on the patients' lives, decreasing their quality of life and affecting the ability to work (Finlay & Coles, 1995; Langley et al., 2005).

Depending on the severity of the disease, PS is often categorized into mild, moderate and severe forms, based on Psoriasis Area Severity Index (PASI), Body Surface Area and Dermatology Life Quality Index (Mrowietz et al., 2011).

4.3.2. Etiopathogenesis of psoriasis

PS is a multifactorial disease, which develops due to the interaction of environmental factors and genetic predispositions, but the precise cause of the disease still remains unclear. The immune system has a pivotal role in the onset and persistence of PS, especially the T-helper-1/T-helper-17 (Th1/Th17) axis and the dysregulation between the innate and the adaptive immune systems (Alwan &

Nestle, 2015; Armstrong & Read, 2020; Griffiths & Barker, 2007). It is known that PS can be triggered by infections (Leung et al., 1995; Zhu et al., 2017), stress (Griffiths & Richards, 2001; Yang & Zheng, 2020), some medications like beta-blockers, lithium and terbinafine (Balak & Hajdarbegovic, 2017; Kim & del Rosso, 2010), and trauma (Rendon & Schäkel, 2019). As patients with the first- and second-degree relatives with PS have elevated risk for PS (Farber & Nall, 1974), a number of studies address the genetic basis of the disease. The most widely known chromosomal locus that is related to PS susceptibility is PSORS1 on chromosome 6, HLA-C locus (Alwan & Nestle, 2015).

The process of inflammation is thought to start from epidermal injury that induces keratinocytes to generate an excess amount of chemokine ligand 20, which recruits myeloid dendritic cells (DC-s) and Th17-lymphocytes to the site of skin injury (Kennedy-Crispin et al., 2012), or from skin infection or other triggers that stimulate and activate keratinocytes and other innate immune cells (Armstrong & Read, 2020; Kim & Krueger, 2015). There have also been described some psoriasis autoantigens, e.g. LL37 (Lande et al., 2014), ADAMTSL5 (Arakawa et al., 2015) and PLA2G4D-generated neolipid antigens (Cheung et al., 2016), which are presented by DC-s. More specifically, LL37-specific T-lymphocytes produce interferon-γ (IFN-γ); they have been found to infiltrate psoriatic plaques and their presence in the blood serum correlates positively with severity of the disease (Lande et al., 2014).

Myeloid DC-s are activated by cytokines secreted by keratinocytes, natural killer T-lymphocytes, macrophages and plasmacytoid DC-s (Afshar et al., 2013; Alwan & Nestle, 2015; Armstrong & Read, 2020). Activated myeloid DC-s induce naïve T-cells to differentiate into Th1-lymphocytes, Th17-lymphocytes and Th22-lymphocytes via releasing interleukin-23 (IL-23) and IL-12. Th1-lymphocytes produce IFN-γ and tumor necrosis factor alpha (TNF-α); Th17-lymphocytes produce TNF-α, IL-22, IL-17A and IL-17F; and Th22-lymphocytes produce IL-22, which maintain inflammation (Armstrong & Read, 2020; Kim & Krueger, 2015). Nograles et al. have shown that IL-17 is more pro-inflammatory, inducing keratinocytes to express specific chemokines that attract neutrophils, memory T-cells and DC-s, while IL-22 impairs keratinocyte differentiation. Additionally, the psoriasis-related, antimicrobial gene S100A7 was upregulated both by IL-17 and IL-22 (Nograles et al., 2008). S100A7 and S100A15 are also chemoattractants and induce keratinocytes to produce cytokines that keep inflammation going (Hegyi et al., 2012). As a positive feedback loop, keratinocytes proliferate and produce pro-inflammatory cytokines, chemokines and anti-microbial peptides as they are activated by IL-17A, IL-17F and IL-22 produced by Th17-lymphocytes, and TNF-α and IFN-γ produced by Th1-lymphocytes (Alwan & Nestle, 2015). These signalling pathways lead to an inflammatory cascade, which in turn induces angiogenesis and attracts immune cells into the psoriatic skin (Rosenberger et al., 2007; Schön et al., 2003). Inflammatory mediators involved in the development and maintenance of PS also have an effect on insulin signalling, lipid metabolism and adipogenesis (Davidovici et al., 2010), which explains concomitant diseases like diabetes, dyslipidaemia and obesity.

4.3.3. Diagnosis of psoriasis

The diagnosis of PS is based on the clinical picture and pathohistology of the skin biopsy, if needed. Pathohistologically, epidermal hyperplasia, dilatation of dermal blood vessels and predominantly dermal inflammatory infiltrate can be seen. Additional characteristic features are parakeratosis, loss of *stratum granulosum*, elongation of *rete ridges* and existence of neutrophil-consisting microabscesses of Munro and micropustules of Kogoj (Griffiths & Barker, 2007).

4.3.4. Management of psoriasis

With the current knowledge, PS cannot be cured, but there exist various effective treatment modalities. In the management of mild to moderate PS, topical medications (glucocorticosteroids, vitamin D analogues, keratolytic agents and topical calcineurin inhibitors) are used. To reduce scaling and to increase hydration of *stratum corneum*, emollients and moisturizers should be applied (Armstrong & Read, 2020; Fluhr et al., 2008). Classical systemic treatment agents of PS include the calcineurin inhibitor cyclosporin, the synthetic retinoid acitretin and the dihydrofolate reductase inhibitor methotrexate; a recent medication is the phosphodiesterase-4 inhibitor apremilast (Armstrong & Read, 2020). Most, but not all topical and systemic medications can be used concomitantly with ultraviolet B (UVB) or psoralen and UVA (PUVA), if the treatment effect is insufficient. More frequently used and safer narrow-band UVB (311 nm) stimulates the apoptosis of pathogenic T-lymphocytes and keratinocytes (Zhang & Wu, 2018). The biologic treatment of PS – "engineered monoclonal antibodies and fusion proteins that exert their therapeutic actions by blocking specific cytokines or cytokine receptors critical to psoriatic inflammation" (Menter et al., 2019) – is used in patients with moderate-to-severe PS, whose treatment response to conventional systemic treatment is lacking or they are contraindicated. According to the pathogenesis of PS, four classes of biologics are currently in the market: TNF-α inhibitors (infliximab, adalimumab, etanercept, certolizumab), IL-12/23 inhibitor (ustekinumab), IL-17A inhibitors (secukinumab, ixekizumab, brodalumab) and IL-23 inhibitors (guselkumab, risankizumab, tildrakizumab) (Menter et al., 2019), among which infliximab, adalimumab, etanercept, ustekinumab, secukinumab, ixekizumab, guselkumab and risankizumab are available in Estonia. Biologics are usually well tolerated and effective, although it still needs to be clarified, which patient benefits the most from which biologics and how switching between biologics affects outcome.

4.3.5. Metabolomics of psoriasis

The omics studies have been increasingly more widely used to specify the pathogenetic mechanisms of diseases. Regarding PS, some studies that analyse the metabolomics of the blood of PS patients have been published. Elevated alpha ketoglutaric acid (Armstrong et al., 2014), asparagine (Asn), aspartic acid (Asp),

isoleucine (Ile), phenylalanine (Phe), ornithine (Orn), proline (Pro), lactic acid and urea levels (Kang et al., 2017) and decreased asparagine, glutamine (Gln) (Armstrong et al., 2014), crotonic acid, azelaic acid, ethanolamine and cholesterol (C) levels (Kang et al., 2017) have been found in PS patients compared to healthy controls (HC-s). Additionally, the levels of platelet-activating factor, leukotriene B4 (LTB4) (Izaki et al., 1996) and dihomogammalinolenic acid (Grattan et al., 1990) have been found to be elevated, while the levels of arachidonic acid and docosapentaenoic acid (Grattan et al., 1990) have been decreased in PS patients compared to controls. Bilgiç et al. found elevated asymmetric dimethylarginine (ADMA) and homocysteine levels, and diminished citrulline (Cit) and L-arginine/ADMA levels in PS compared to HC-s. Additionally, ADMA level and L-arginine/ADMA ratio were correlated with PASI scores (Bilgic et al., 2015). The concentrations of various amino acids and carnitines have also been shown to be altered in PS patients (Chen et al., 2021). Analysing the effect of etanercept on the plasma of PS patients, Kamleh et al. found that treatment reduced the levels of threonine (Thr), Orn and methionine (Met). Among the metabolites analysed, Thr, Cit and Orn were highly positively correlated with PASI scores (Kamleh et al., 2015). A lipidomics study has reported an increase in lysophosphatidic acid, lysophosphatidylcholine (LysoPC) and phosphatidic acid (PA) levels and a decrease in phosphatidylcholine (PC) and phosphatidylinositol levels in PS patients' blood serum (Lei et al., 2017).

The lesional skin of PS patients differs from the skin of HC-s in terms of amino acids, arachidonic acid derivates and other metabolites. An analysis with hydrogel micropatches showed elevated choline, Glu and Phe concentrations, and decreased Cit, lactic acid and urocanic acid concentrations in PS skin (Dutkiewicz et al., 2016). Additionally, the levels of choline, Phe, glutamic acid (Glu) (Dutkiewicz et al., 2016), arachidonic acid and 12-Hydroxyeicosatetraenoic acid (12-HETE) (Barr et al., 1984) were elevated and the levels of Cit, urocanic acid and lactic acid (Dutkiewicz et al., 2016) were decreased in PS lesional skin.

Comparison of PS lesional skin and PS non-lesional skin showed that the concentrations of choline, Phe, Glu (Dutkiewicz et al., 2016), taurine (Tau) (Sitter et al., 2013), arachidonic acid, 12-HETE (Barr et al., 1984), prostaglandin E2 (PGE2), PGF2α (Hammarström et al., 1975) and LTB4 (Brain et al., 1984) were elevated and the levels of Cit, urocanic acid, lactic acid (Dutkiewicz et al., 2016), myo-inositol and glucose (Sitter et al., 2013) were decreased in PS lesional skin. The ratios of Glu:Ser, creatine:Gly and Tau:alanine (Ala) were increased in PS lesional skin compared to both non-lesional skin and normal skin (Kim et al., 1989).

Less studies have been conducted to investigate the urine metabolome of PS patients. Alonso et al. analysed the urine of different immune-mediated inflammatory diseases and found that in PS patients the levels of citrate, methylsuccinate and Ala were decreased, compared to HC-s (Alonso et al., 2016).

Even though studies investigating the concentrations of specific metabolite classes are available, then to our knowledge, no systematic metabolomic analysis of the PS patients' skin has been undertaken.

4.4. Overview of atopic dermatitis

4.4.1. Clinical manifestations of atopic dermatitis

Another chronic inflammatory skin disease, atopic dermatitis, affects up to 20% of children and 1–3% of adults, and has increased in recent decades in developed countries (Asher et al., 2006; Nutten, 2015). AD usually starts in childhood and can persist during adulthood (Weidinger & Novak 2016), but the onset of the disease can also occur in adulthood. Patients with AD have dry skin and pruritic eczematous lesions, which have typical age-related locations on the body and can be divided into acute, subacute and chronic phases. Frequently, AD is accompanied by other atopic diseases like asthma and allergic rhinoconjunctivitis, and also atopic stigmata like Dennie-Morgan lines, pityriasis alba and periorbital hyperpigmentation can be seen (Weidinger & Novak, 2016). Hanifin and Rajka published the criteria for AD in 1980, which include the minor and major diagnostic features of the disease (Hanifin & Rajka, 1980). AD patients tend to more frequently have skin infections, especially those caused by herpes simplex virus and *Staphylococcus aureus*, which may cause a more severe and widespread disease (Barnetson & Rogers, 2002). In addition to atopic comorbidities, AD patients have an increased risk for anxiety, depression, suicidality, obesity and CVD (Paller et al., 2018; Silverberg, 2019; Silverberg & Greenland, 2015; Thyssen et al., 2018). The quality of life is severely impaired in both pediatric and adult AD patients, especially in the moderate and severe disease (Beattie & Lewis-Jones, 2006; Silverberg et al., 2018). To evaluate the severity of AD, various scores can be used, among which Eczema Area and Severity Index and SCORing Atopic Dermatitis are the most widely employed (Schmitt et al., 2013).

4.4.2. Etiopathogenesis of atopic dermatitis

The pathogenesis of AD is multifactorial. A wide range of factors can trigger AD, e.g. mechanical irritants, chemicals, biologic allergens and air pollutants (Wollenberg et al., 2018). Skin barrier dysfunction is one of the most important factors that contribute to the development of AD. The best known genetic defects in AD are filaggrin mutations, which can be found in up to 60% of European AD patients (Elias & Schmuth, 2009) and which lead to loss of (namely, loss-of-function genetic variants R510X and 2282del4) or decrease in filaggrin products (Boothe et al., 2017; Palmer et al., 2006). Another physical mechanism leading to skin barrier defect and AD can be the impairment of the function of tight junctions (Yuki et al., 2016). The defective skin barrier increases water loss through the skin, raises the likelihood of skin infections and colonization with *S. aureus*, and increases skin pH (Boothe et al., 2017; Čepelak et al., 2019; Edslev et al., 2020). AD can be defined as a disease that manifests itself as both immediate and Immunoglobulin E mediated (IgE-mediated), delayed-type hypersensitivity reaction of the skin, which can be induced by numerous triggers (Schmid et al., 2001;

Wollenberg et al., 2020). Serum IgE levels have been found to correlate with severity of AD (Laske & Niggemann, 2004).

Inflammation in AD skin has two phases: the Th2-mediated acute phase and the Th1-mediated chronic phase (Boothe et al., 2017). Innate immune cells activate as a result of scratching, microbial toxins or allergens (Leung, 2013) and keratinocytes start producing pro-inflammatory cytokines and chemokines, recruiting inflammatory cells (Li et al., 2021; Glatz et al., 2015; Tsakok et al., 2019). Active AD lesions consist of mainly Th2-lymphocytes that release IL-4, IL-5 and IL-13 (Leung, 2013). Additionally, Th17-lymphocyte-produced IL-17 and IL-22 have an important role in AD initiation and maintenance (Boothe et al., 2017; Koga et al., 2008; Sugaya, 2020). Of note, IL-22 causes profilaggrin/filaggrin expression's downregulation (Gutowska-Owsiak et al., 2011). Th2-biased inflammation leads to the accumulation of other immune cells, e.g. eosinophils and mast cells (Tsakok et al., 2019). In chronic AD lesions, there is a deviation towards the Th1 profile with IL-12 and IFN-γ (Leung, 2013). IL-31 is another important cytokine in AD, as its overexpression brings about clinical features of AD and induces pruritus (Saleem et al., 2017).

4.4.3. Diagnosis of atopic dermatitis

The histopathology of AD is non-specific, therefore, the diagnosis is based on the clinical picture and medical history (Weidinger & Novak, 2016).

4.4.4. Management of atopic dermatitis

The cornerstone of the management of AD is the usage of emollients to prevent excess water loss and to achieve hydration of the skin. Patients should also avoid triggering factors. In the case of an active disease, topical or systemic medications should be used. Commonly used topical therapies consist of corticosteroids (TCS) and calcineurin inhibitors (TCI). TCS-s are available in various strengths and formulations, which should be used according to the age of the patient, location of rash and severity of the disease. TCI-s tacrolimus and pimecrolimus have good anti-inflammatory and anti-pruritic effects, but they do not have the potential to make skin atrophic, which can be seen in the case of TCS-s (Wollenberg et al., 2020, 2018). Phototherapy can be used in conjunction with TCS-s or selected systemic therapy and emollients, and nb-UVB and medium-dose UVA1 are found to be similarly effective in reducing clinical signs and symptoms (Garritsen et al., 2014; Wollenberg et al., 2020). If topical therapy and phototherapy lack the effectiveness in controlling the disease, systemic therapy should be used. Briefly, in adult patients, cyclosporine A, a short course of oral glucocorticosteroids or dupilumab can be used; methotrexate, azathioprine and mycophenolate mofetil are off-label treatment options. In children, dupilumab is a licenced indication for AD treatment; cyclosporine A, methotrexate, azathioprine and mycophenolate

mofetil are used as off-label treatment options (Napolitano et al., 2022; Wollenberg et al., 2018). Dupilumab is the first biologic that can be used in the treatment of AD and it acts by blocking IL-4/IL-13 signalling (Seegräber et al., 2018). Janus kinase inhibitors have also been recently approved for treating AD (among which upadacitinib and baricitinib are currently available in Estonia – upadacitinib both in adults and children, and baricitinib in adults (EMA, 2018, 2019)).

4.4.5. Metabolomics of atopic dermatitis

The metabolomic analysis of the blood serum of AD patients revealed differences in PC-s and acylcarnitines, and in the carnitine ratios, compared to the blood serum of HC-s. Changes in metabolite levels point to defective β-oxidation and impairment in lipid signalling (Ottas et al., 2017). Another study on AD serum metabolomics reported decreased glycine and Tau conjugated bile acids and increased unsaturated fatty acids, LTB4, PG-s, 8-, 9-, 11- and 12-HETE, and 9- and 13-Hydroxyoctadecadienoic acid in paediatric AD patients compared to HC-s. The metabolites of the cyclooxygenase (COX) and lipoxygenase pathways were increased in the patients' groups, which implies increased inflammation in AD. Patients with high IgE levels had also elevated free fatty acids and carnitines, which reflects a decrease in and/or dysfunction of fatty acid β-oxidation; elevated citric acid and lactic acid, which indicates energy metabolism disorder; and some elevated SM-s, which shows a decrease in sphingomyelinase activity, which has been described before (Huang et al., 2014; Jensen et al., 2004). Hotze et al. measured the metabolite levels of AD patients' blood sera before and after treatment with the monoclonal antibody omalizumab which targets IgE. They found that the patients who responded to therapy – and who did not have filaggrin mutations – had higher baseline levels of certain PC-s compared to the non-responders. Also, during treatment the levels of glycerophospholipids, acylcarnitines, sphingomyelins (SM-s), amino acids and carbohydrates decreased significantly. The researchers suggested that omalizumab might alter the levels or acting of inflammation-promoting lipids (Hotze et al., 2014). Connection has also been established between dimethylamine and isopropanol, which are microbial-derived and IgE-related metabolites, and filaggrin mutations in AD patients (Chiu et al., 2021).

The urine analysis of AD children revealed an increase in creatinine, creatine, citrate, formate, 2-hydroxybutyrate, dimethylglycine and lactate levels and a decrease in Ala, glycine and betaine levels in an AD patient compared to HC-s (Assfalg et al., 2012).

As in PS, a few studies investigating metabolites in different body fluids and tissues of the AD patients' are published, but no systematic metabolomic analysis of the AD patients' skin has been done yet.

4.5. Overview of lichen planus

4.5.1. Clinical manifestations of lichen planus

Lichen planus is an inflammatory papulosquamous disease which, in addition to the skin, can affect the mucous membranes, nails and hair (Fox & Odom, 1985; Le Cleach & Chosidow, 2012). Classically, flat polygonal violaceous papules that are covered with Wickham striae are extremely pruritic and locate on the shins, in the sacral area and the flexural area of the wrists, but can disseminate all over the body and have various clinical subtypes, e.g. hypertrophic LP, bullous LP and LP pigmentosus (Boch et al., 2021; Bolognia et al., 2018). Cutaneous hypertrophic LP and mucosal LP are considered to be potentially premalignant or potentially malignant conditions (oral LP (OLP) is grouped under a potentially malignant disorders (Warnakulasuriya et al., 2021)), since the incidence of squamous cell carcinoma is ~1% for these conditions (Friedl et al., 2011; Giuliani et al., 2019; Ioannides et al., 2020). The prevalence of cutaneous LP disease is 0.2–1% and that of OLP is approximately 1–4% in the adult population (Bolognia et al., 2018; Lukács et al., 2015). The peak incidence occurs between the ages of 40 and 60 years (Carbone et al., 2009; Irvine et al., 1991). The classical cutaneous form of LP resolves in 6–18 months (Ioannides et al. 2020).

The most frequently described comorbidities are hepatitis C infection (Alaizari et al., 2016), thyroid disease (Amato-Cuartas et al., 2019; Robledo-Sierra et al., 2018), MS (Daye et al., 2021; Saleh et al., 2014), dyslipidaemia (Kumar et al., 2019) and diabetes mellitus (Kumar et al., 2019; Sun et al., 2022). Moreover, patients with LP have an increased risk for CVD (Aksu et al., 2016; Conrotto et al., 2018; Leasure et al., 2021; Saleh et al., 2014), alopecia areata, vitiligo, lichen sclerosus, myasthenia gravis and ulcerative colitis (Ioannides et al., 2020).

4.5.2. Etiopathogenesis of lichen planus

The exact etiopathogenesis of LP is still unclear, but it is widely recognized as a T-cell mediated autoimmune disease. The pathogenesis of the disease involves the migration of cluster of differentiation 4 (CD4+) and CD8+ T-lymphocytes to the dermoepidermal junction, cytotoxic activity towards epidermal keratinocytes and the apoptosis of basal keratinocytes (Boch et al., 2021; Lehman et al., 2009; Sugerman et al., 2000). Mast cells (Ramalingam et al., 2018) and DC-s (Santoro et al., 2005) have also been found in the inflammatory infiltrate of LP lesions and may be involved in the pathogenesis of LP. In addition to TNF-α (Chen JF et al., 2022), IFN-γ, IL-6 (Fayyazi et al., 1999) and IL-8 (Mozaffari et al., 2018; Kaur & Jacobs, 2015), other cytokines, e.g. IL-4 (Mehrbani et al., 2020), IL-17 (Husein-ElAhmed & Steinhoff, 2022; Miteva et al., 2022), IL-23 (Mardani et al., 2021), IL-12A and IL-21 (Pietschke et al., 2021) have been found to take part in the development of the disease.

Various external factors, e.g. stress, medications and infections have a role in the development and exacerbations of the disease (Alaizari et al., 2016; Ioannides

et al., 2020; Lukács et al., 2015). Patients with specific HLA haplotypes, including human leukocyte antigen Bw57 (HLA-Bw57), HLA-B27 and HLA-DR also have a higher risk for developing LP (Boch et al., 2021; Carrozzo et al., 2001; Porter et al., 1993).

4.5.3. Diagnosis of lichen planus

In addition to the clinical picture, a pathohistologic analysis of the skin can be carried out in order to confirm the diagnosis of LP. Pathohistologically, a band-like lymphohistiocytic inflammatory infiltrate, irregular saw-tooth-patterned acanthosis, Civatte bodies (apoptotic basal keratinocytes), increased granular layer (which clinically correlate with Wickham striae) and pigment incontinence are characteristic of LP skin lesions (Marshman, 1998). Additionally, Hussein et al. have found an increase in dermal microvessel density, which reflects local angiogenesis in the LP skin (Hussein, 2007).

4.5.4. Management of lichen planus

The treatment goal of cutaneous LP is to diminish itching and reduce the duration of active lesions. According to the European S1 guidelines on the management of LP, the first-line treatment options are TCS-s, followed by off-label options like intralesional triamcinolone injections, systemic corticosteroids, acitretin or isotretinoin and oral cyclosporine. To reduce itching, oral antihistamines and topical antipruritic agents can be used. There exist also second- and third-line treatment options, however, as cutaneous LP is usually self-limited and resolves in 1–2 years, possible side effects must be kept in mind when prescribing various medications (Ioannides et al., 2020).

In the case of oral LP, a good treatment response can be more difficult to achieve. The aim of the treatment should be to reduce the risk for malignant transformation and suppress symptoms. Avoidance of possible aggravating factors (smoking, dental amalgam, certain drugs) is suggested, and the patient needs to take good oral care. First-line treatment options are the same as in the case of cutaneous LP: TCS-s, intralesional corticosteroid injections, systemic corticosteroids, systemic retinoids and oral cyclosporine, as well as topical retinoids (Ioannides et al., 2020).

In the management of genital LP, the main treatment goal is to prevent scarring in the erosive form of LP. The treatment options are principally the same as in OLP, with TCI-s and topical anaesthetic gel being also suggested. In most cases, using emollients and TCS-s for some weeks is sufficient (Ioannides et al., 2020).

For the treatment of lichen planopilaris, TCS-s, intralesional corticosteroid injections and systemic corticosteroids are used, also, oral cyclosporine can be effective. LP affecting the nails is usually challenging to treat, the first-line treatment is triamcinolone acetonide injections (Ioannides et al., 2020).

Biologic treatment and Janus kinase inhibitors inhibitors are not available in the treatment of LP as there are no corresponding clinical studies.

4.5.5. Metabolomics of lichen planus

To date, there has been only a few metabolomic studies conducted on LP, the research has mostly focused on OLP. In one of the oral potentially malignant disorders, erosive LP, alterations in certain blood serum metabolite levels like lysophosphatidylethanolamine (0:0/18:0), prostaglandin G1, leukotriene D4 and protoporphyrinogen IX have been found, which are evidence of inflammation, apoptosis, neutrophil dysfunction and increased oxidative stress (Warnakulasuriya et al., 2021; Yang et al., 2017). Gouveia-Figueira et al. found that the ratio of linoleic acid-derived oxylipins, 9-hydroxyoctadecadienoic acid to 13-hydroxyoctadecadienoic acid, was altered in mucosal biopsies of OLP, indicating activation of COX-2 and related cyclooxygenases. This might contribute to the burning sensation and pain associated with OLP (Gouveia-Figueira et al., 2019). Increased COX-2 expression has also previously been found in mucosal biopsies of OLP, which is suggested to support autoimmunity as a cause of the disease (Danielsson et al., 2012). Additionally, expression of COX-2 in OLP epithelium correlates positively with severity of the disease (Chankong et al., 2016). In the urine of reticular oral LP patients, 13 metabolites were found to be up-regulated and 17 metabolites down-regulated, compared to controls, which indicated various pathological processes like inflammation, oxidative stress injury, apoptosis and the deoxyribonucleic acid (DNA) damage and repair disorder (Yang et al., 2020). The serum level of calprotectin, which is a marker for neutrophil activation, has been found to be elevated in patients with cutaneous LP, compared to HC-s, and is suggested to be a marker for severity and progression of LP (Khattab et al., 2022).

Dyslipidaemia, e.g. increased low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) values and decreased high-density lipoprotein cholesterol (HDL-C) values, have previously been described in LP patients (Panchal et al., 2015; Lai et al., 2016), however, changes in the composition of lipoprotein particles have not yet been evaluated in this case.

4.6. Metabolomics in the comorbid diseases of psoriasis, atopic dermatitis and lichen planus

The metabolomics of certain chronic inflammatory dermatoses – PS, AD and LP – are discussed above. The metabolomics of a number of their comorbidities have also been previously investigated. In PsA, which can be seen in ~30% of PS patients (Ritchlin et al., 2017), Coras et al. found elevated trimethylamine-N-oxide levels in the patients' blood serum and it was correlated with disease activity and inflammation (Coras et al., 2019). Comparison of PsA and seronegative rheumatoid arthritis revealed that patients with PsA had higher Ala, Thr, leucine (Leu), valine (Val), acetate, creatine, lactate and choline levels and higher various lipid ratios, and lower Phe levels in their blood serum (Souto-Carneiro et al., 2020).

A number of metabolomic studies have established associations between certain metabolites and the risk for type 2 diabetes (T2D), e.g. elevated serum

levels of Phe, hexose and some diacyl-phosphatidylcholine and decreased levels of lysophosphatidylcoline C18:2, glycine, SM C16:1; some acyl-alkyl-phosphatidylcholine levels have been found to contribute to a higher risk for T2D (Floegel et al., 2013); also, higher concentrations of branched chain amino acids (BCAA-s) have been found to be associated with an increased risk for diabetes (Rebholz et al., 2018).

Furthermore, an increase in Met, Gln and histidine and a decrease in Arg, formate, acetate e.t.c. were found to be related to asthma (Jung et al., 2013); negative correlations were found between MS and plasma levels of serine and some glycerophospholipids with acyl-alkyl bonds (Carioca et al., 2021); and a range of acylcarnitines were increased and long- and medium-chain fatty acids were decreased in the serum of patients with active Crohn's disease (Lai et al., 2019).

CVD, which is a comorbidity of all three above discussed chronic inflammatory dermatoses, has been dealt with in various metabolomic studies. Vaarhorst et al. described the metabolomic profile of plasma associated with the incidence of CHD, namely myocardial infarction, unstable angina pectoris, coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, which consisted of 13 metabolites including Val, Orn and glutamate (Vaarhorst et al., 2014). Several plasma and serum lipids have been found to be associated with incident CVD, e.g. lysophosphatidylcholine 18:1 (LPC 18:1), LPC 18:2, monoglyceride 18:2, SM 28:1 (Ganna et al., 2014), species of cholesterol esters and triacylglycerols e.t.c (Stegemann et al., 2014).

4.7. Summary of the literature review

Chronic inflammatory skin diseases psoriasis, atopic dermatitis and lichen planus affect the quality of life of the patients as the rash can appear on visible sites on the body, be pruritic and the management can consume a lot of time and be expensive (Carroll et al., 2005; Jalenques et al., 2020; Langley et al., 2005). The duration of the diseases varies from several months to being lifelong, and the course is unpredictable. Psoriasis treatment involves various modalities including biologic treatment, but there is always a possibility of primary or secondary inefficacy, and it is not known which patient gains the most from which treatment. Atopic dermatitis and lichen planus have less treatment options, and there are currently no biologic treatment options in the management of lichen planus.

Metabolomic studies reflect the biological processes that take place in the organism and can be used to elucidate the pathogenesis of a disease and to find biomarker(s). Biomarkers can be used in diagnosing and monitoring a disease, prognosticating the outcome or predicting responsiveness to the treatment (FDA-NIH Biomarker Working Group, 2016). In psoriasis, atopic dermatitis and lichen planus, quite few metabolomic studies have been carried out. Therefore, we aimed to investigate the skin and/or blood sera of the above diseases to gain new knowledge about and clarify the pathogeneses of these diseases.

5. AIMS OF THE THESIS

The main aim of this study was to determine the metabolomic profiles of the skin and blood serum of chronic inflammatory skin diseases in order to clarify the pathogenetic mechanisms of PS, AD and LP, which would help find their potential disease specific biomarkers, as well as treatment targets to be used in the future.

The specific aims were the following:

1. To compare the metabolomic profiles of the skin of PS patients and HC-s and to find possible metabolomic biomarkers for PS.
2. To compare the metabolomic profiles of the skin of AD patients and HC-s and to find possible metabolomic biomarkers for AD.
3. To compare the metabolomic profiles of the skin and blood sera of AD and PS patients in order to find possible similarities and differences between these two major chronic inflammatory dermatoses.
4. To determine the metabolomic profile of the blood serum of LP patients and to compare the results with the metabolomic profile of the blood serum of HC-s.

6. SUBJECTS AND METHODS

6.1. Ethics approval

The studies were approved by the Research Ethics Committee of the University of Tartu (approvals 245/M-18, 269/T-9 and 351/M-12). The protocols of the Declaration of Helsinki were followed and all of the participants provided their informed written consent.

6.2. Recruitment of volunteers and characteristics of the study participants

Adult patients with AD and PS and their age- and sex-matched controls were recruited from the Clinic of Dermatology and the Clinic of Traumatology and Orthopaedics of Tartu University Hospital between 2013 and 2015 to analyse the skin metabolomics of AD and PS. The total number of AD patients was fifteen (four men, 11 women, aged 20–50 years), the number of PS patients was 20 (13 men, seven women, aged 23–75 years) and the number of HC-s was 36 (23 men, 13 women, aged 20–75 years, among whom 17 were age- and sex-matched AD controls and 19 were PS controls). Patients with any other concomitant chronic skin disease were excluded. All participants were East European Caucasians. The characteristics of AD and PS patients and HC-s are shown in Table 1.

Table 1. Clinical and demographic characteristics of the patient cohorts and HC-s in the comparison of AD and PS skin biopsies.

	AD skin	AD matching HC skin	PS skin	PS matching HC skin
Allergies	14 (93%)	4 (24%)	4 (20%)	7 (37%)
Food allergies	9 (60%)	3 (18%)	1 (5%)	3 (16%)
Allergies to medications	3 (20%)	2 (12%)	1 (5%)	2 (11%)
Allergies to dust mite or hair	11 (73%)	2 (12%)	2 (10%)	2 (11%)
Allergies to pollen	11 (73%)			
Allergic rhinoconjunctivitis or bronchial asthma	11 (73%)		NI	NI
Positive AD family history	7 (47%)	2 (12%)	2 (10%)	2 (11%)
Psoriatic joint involvement	NA		5 (25%)	
Psoriatic nail involvement	NA		7 (35%)	

Table 1. Continuation

	AD skin	AD matching HC skin	PS skin	PS matching HC skin
Comorbidities				
Diabetes	NI		2 (10%)	1 (5%)
Urticaria (no active rash at the time of biopsy)	NI		2 (10%)	1 (5%)
Thyroid disease	NI		1 (5%)	
Rheumatoid arthritis	NI		1 (5%)	1 (5%)
Hypertension	NI		4 (20%)	2 (11%)
Positive PS family history	NI		9 (45%)	1 (5%)

To compare the blood sera of AD and PS patients, 25 patients with AD (19 women, 6 men, aged 19–54 years) and 55 patients with PS (18 women, 37 men, aged 20–75 years) were recruited from the Clinic of Dermatology of Tartu University Hospital between 2013 and 2015. The clinical and demographic characteristics of the patient cohorts are shown in Table 2.

Table 2. Clinical and demographic characteristics of the patient cohorts.

	PS serum	AD serum
Age, mean (y) (range)	46.3 (20–75)	33.4 (19–54)
Sex, no. (%)		
Male	37 (67.3)	6 (24)
Female	18 (32.7)	19 (76)
Ethnicity	Caucasian	Caucasian
PASI score, mean (range)	9.675 (1–34)	
PS associated joint involvement (%)	15 (27.3)	
PS associated nail involvement (%)	22 (40)	
AD associated rhinitis (%)		13 (52)
AD associated asthma (%)		9 (36)
AD type, no. (%)		
Normal IgE – intrinsic		5 (20)
Elevated IgE – extrinsic		18 (72)
Unknown		2 (8)
Family history (%)		
Positive	23 (41.8)	12 (48)
Negative	24 (43.6)	10 (40)
Unknown	8 (14.6)	3 (12)
Age at onset (%)		
≥40 years (PS)	12 (21.8)	
<18 years (AD)		23 (92)

To analyse the levels of blood serum metabolites, lipoproteins and lipoprotein particles in LP patients and HC-s: 32 patients with cutaneous LP (22 women, 10 men, aged 19–80 years) and 32 HC-s (22 women, 10 men, aged 21–80 years) were recruited in 2021 from the Clinic of Dermatology of Tartu University Hospital. The diagnosed cardiovascular, metabolic and infectious comorbidities of the patients and controls are shown in Table 3. All the participants were Caucasians of East European descent.

Table 3. Diagnosed cardiovascular, metabolic and infectious comorbidities of the LP patients and HC-s.

	No. of LP patients (%)	No. of HC (%)
Cardiovascular		
Hypertension	16 (50)	13 (40.6)
Atherosclerosis	2 (6.3)	1 (3.1)
Stenocardia	1 (3.1)	
Congestive heart failure	1 (3.1)	1 (3.1)
Atrial fibrillation	1 (3.1)	
Metabolic		
Type 2 diabetes	2 (6.3)	3 (9.4)
Hypothyroidism	4 (12.5)	
Pure or familial hypercholesterolemia		1 (3.1)
Infectious		
Chronic hepatitis C infection	2 (6.3)	

6.3. Skin biopsy collection protocol

The 3 mm punch biopsies were taken from the lesional and adjacent, visually non-lesional skin not exposed to the sun, of the patients suffering from PS and AD, as well as from similar locations of the non-sun-exposed skin of HC-s (Papers I, II and III). The biopsies were taken in the morning, before breakfast, and were immediately frozen in liquid nitrogen. They were kept at –80 °C until needed. The skin biopsies were collected over a period of 3 years, after which the extraction of the metabolites and the lyophilization of the samples were done, and stored until analysis at –80 °C as described earlier (Álvarez-Sánchez et al., 2010). The biopsies were weighed and a solution composed of 12 mg/g methanol and chloroform and 6 ml/g water was added pursuant to the sample's weight to separate polar and non-polar metabolites. A BulletBlender (NextAdvance) was used for milling after inserting 12 mm steel balls into the tube. After incubating for 1 hour on ice, the supernatant was transferred into a clean tube, centrifuged at 16000 x g, and incubated at 4 °C for 15 minutes. The methanol/water and chloroform phases were transferred into separate tubes and lyophilized.

6.4. Serum collection protocol

The blood sera of PS, AD and LP patients and their matching HC-s (Papers III and IV) were collected before breakfast using 5 ml Vacutainer (REF 367614) tubes containing micronized silica particles to accelerate the process of clotting. Further, the samples were left to clot at room temperature for an hour and were centrifuged thereafter at 1300 x g for 20 minutes. 300 µl aliquots of the serum were pipetted and stored at –80 °C until needed.

6.5. Analysis of metabolites and particles

To determine the nature of the metabolites, two approaches can be used in metabolomic studies: targeted and untargeted metabolomics. Untargeted metabolomics allows to discover new, chemically yet unknown metabolites, in addition to already known ones. This technique usually generates large amounts of data and analytes which can be difficult to identify. In targeted metabolomics, pre-defined metabolites are sought for and can be analysed quantitatively or semi-quantitatively (Roberts et al., 2012). In the present study, we used targeted metabolomics, which has a high sensitivity and selectivity, to determine and quantify the metabolites. This method enabled us to determine 188 pre-defined metabolites in the skin and blood sera of PS and AD patients and HC-s and 248 metabolites and particles in the blood sera of LP patients and its corresponding HC-s.

For the targeted analysis of 188 metabolites of the lesional and non-lesional skin of PS and AD and the skin of HC (Paper I, II and III), Absolute*IDQ* p180 kit (Biocrates Life Sciences AG, Innsbruck, Austria) was used. We used 3.0 × 100 mm, 3.5 µm C18 column (Agilent Zorbax Eclipse XDB), with 4 × 3 mm column protection system (Pre-Column SecurityGueard, Phenomenex, C18) on a 1260 series HPLC (Agilent, Santa Clara, CA, USA) in tandem with a QTRAP 4500 (ABSciex, Framing- ham, MA, USA) mass-spectrometer. The user's manual of the *AbsoluteIDQ p180* kit provides the full protocol. Briefly, after thawing the lyophilized samples on ice, the two lyophilized phases were dissolved in 85% methanol/15% water in compliance with their previous weight (15–25 µl of added solvent). Both phases were added to the kit's filter plate and 10 µl internal standards were added. Phenylisothiocyanate was used to derive the samples, the samples were dried and the metabolites were extracted using 40% methanol in water. Chloroform, formic acid, acetonitrile, methanol and water were all HPLC grade and were purchased from Sigma-Aldrich (Darmstadt, Germany).

The blood serum samples of AD and PS, and of the corresponding HC-s (Paper III) were thawed on ice and pipetted onto a 96-well plate (10 µl per sample). Subsequently, phenylisothiocyanate was used to derive the samples. To determine the concentrations of metabolites, a combination of flow injection analysis and liquid chromatography through a C18 column was used.

The blood serum samples of LP patients and of the corresponding HC-s (Paper IV) were analysed by Nightingale OYJ using high-throughput nuclear

magnetic resonance (NMR) spectroscopy, which allowed to quantify 248 metabolites and particles including various lipoproteins, fatty acids, lipids and multiple low-molecular-weight metabolites as ketone bodies and amino acids. Molar units were used for quantification of the concentrations. An article by Soininen et al. gives a more detailed overview of the measurement (Soininen et al., 2015).

6.6. Statistical data analysis

The R version 3.5.1 was used for data analysis in Papers I and II (R Core Team (2018)). The non-parametric Kruskal-Wallis rank-sum test and the Wilcoxon rank-sum test were used to find the metabolites differing between the phenotypic groups. A False discovery rate (FDR) of 5% was employed to adjust probabilities and a corrected p-value of <0.05 was considered statistically significant.

The R version 3.5.1 was also used for data analysis in Paper III. To compare the metabolite levels of the skin and serum, the concentration of each metabolite was normalized to values between 0 and 1. For statistical analysis, the non-parametric Kruskal-Wallis rank-sum test and the Wilcoxon rank-sum-test were used. A FDR 5% corrected p-value of <0.05 was considered statistically significant.

In Paper IV, the R version 4.1.3 was used for data analysis (R Core Team (2018)). After scaling the dataset and removing outliers with SD > 4 from the mean metabolite concentrations, the Wilcoxon–Mann–Whitney test was used to find the metabolites and particles differing significantly between LP and HC. A total of 19 principal components that explained >95% of variability in the data was shown with the principal component analysis. The threshold for multiple testing was set according to $p < 0.05 / 19$ principal components; i.e. $p < 0.0029$.

7. RESULTS

7.1. Metabolomic profile of plaque psoriasis skin (Paper I)

The metabolomic studies of PS have concentrated mostly on serum or plasma samples, much less research has been performed on the metabolomics of PS skin (Dutkiewicz et al., 2016; Kim et al., 1989; Sitter et al., 2013). We compared the metabolomic profile of PS lesional (PS-L) skin to the visually non-lesional (PS-NL) skin and to control the skin samples obtained from HC-s.

The concentrations of 29 metabolites differed significantly in PS-L skin samples when all three sample groups were analysed (Kruskal-Wallis rank-sum test, FDR 5% corrected p-value <0.05; Table 4).

Comparison of PS-L skin to the skin of HC-s revealed that the concentrations of 17 metabolites, including amino acids (glutamate, Glu, p=0.002); methionine, Met, p=0.0027; arginine, Arg, p=0.0049), biogenic amines (spermidine, p=0.000002; putrescine, p=0.00001), acylcarnitines (valeryl-L-carnitine, C5, p=0.000002; octadecadienyl-L-carnitine, C18.2, p=0.0211; hexadecanoyl-L-carnitine, C16, p=0.0459; octadecanoyl-L-carnitine, C18, p=0.0347), phosphatidylcholines (PC.ae.C36.0, p=0.0021; PC.ae.C38.0, p=0.0307; PC.ae.C34.0, p=0.0347; PC.ae.C38.1, p=0.0418; PC.aa.C40.4, p=0.0439; a – acyl; aa – diacyl; ae – acyl-alkyl), asymmetric dimethylarginine (ADMA, p=0.0027), total dimethylarginine (total DMA, p=0.0052) and histamine (p=0.0072) were increased, while two metabolite ratios (Cit to Orn, p=0.013, and Orn to Arg, p=0.003) were decreased in PS-L skin.

The concentrations of 14 metabolites were increased in PS-L skin compared to both PS-NL skin and HC skin (C5, spermidine, Glu, Met, ADMA, putrescine, total DMA, PC.ae.C36.0, Arg, C18.2, PC.ae.C38.0, C16, PC.ae.C34.0 and PC.ae.C38.1), and the levels of 9 metabolites were elevated only in PS-L skin compared to PS-NL skin (acetylcarnitine, C2, p=0.001; lysine, Lys, p=0.0017; lysophosphatidylcholine acyl C16:1, lysoPC.a.C16.1, p=0.0017; leucine, Leu, p=0.0008; octadecenoyl-L-carnitine, C18.1, p=0.0107; Fisher ratio, p=0.0097; PC.aa.C42.4, p=0.0196, methionine sulfoxide, Met.SO, p=0.0068; phenylalanine, Phe, p=0.0114). A single metabolite ratio (Cit to Orn, p=0.0023) was also decreased in PS-L skin compared to PS-NL skin. The comparison of PS-NL and HC skin did not reveal any metabolites with statistically significant differences in their concentrations between the groups.

According to the data, the metabolomic profile of PS-L skin is different from the metabolomic profile of PS-NL skin and HC skin, which is evident in principal component analysis of statistically significantly changed metabolites (Figure 1). We also attempted to find out if there is relationship between PASI and the measured metabolites in PS-L skin, but did not find statistically significant correlations.

Table 4. Metabolites and their ratios with statistically significant differences in their concentrations between samples obtained from plaque psoriasis lesional (PS-L) skin and non-lesional (PS-NL) skin and from the skin of healthy controls (HC-s).

Metabolite	HC-s mean (μM)	PS-L mean (μM)	PS-NL mean (μM)	KW p-value FDR 5% corrected
Amino acids				
Glu	139.444	342.85	139.52	0.0001
Met	7.828	20.142	7.852	0.0002
Arg	49.728	136.455	60.55	0.0042
Lys	50.179	83.16	38.261	0.0063
Leu	50.924	90.3	31.96	0.0079
Met.SO	1.559	1.255	0.435	0.0323
Phe	31.434	49.705	22.78	0.0329
Dimethylarginines				
ADMA	0.571	1.419	0.475	0.0002
total.DMA	0.068	0.519	0.034	0.0002
Biogenic amines				
Spermidine	1.782	6.234	4.178	<0.0001
Putrescine	0.889	2.383	1.31	0.0002
Histamine				
Histamine	11.195	21.197	14.976	0.0138
Carnitines				
C5	0.359	1.52	0.372	<0.0001
C2	3.636	4.32	3.041	0.0063
C18.2	0.026	0.041	0.025	0.0063
C16	0.066	0.096	0.061	0.02
C18.1	0.059	0.075	0.044	0.0207
C18	1.589	3.265	1.93	0.0368
Metabolite ratios				
Cit...Orn	4.914	2.526	8.168	0.0018
Orn...Arg	0.763	0.193	0.378	0.0048
Fisher.ratio	1.847	2.025	1.698	0.0237
X.C2.C3....C0	0.35	0.306	0.289	0.0339
Glycerophospholipids				
PC.ae.C36.0	0.364	1.643	0.358	0.0003
lysoPC.a.C16.1	0.585	0.76	0.335	0.0064
PC.ae.C38.0	0.196	0.392	0.189	0.0125
PC.ae.C34.0	0.402	0.85	0.4	0.0244
PC.aa.C42.4	0.024	0.038	0.02	0.0248
PC.ae.C38.1	0.177	0.423	0.219	0.0323
PC.aa.C40.4	0.233	0.37	0.239	0.0386

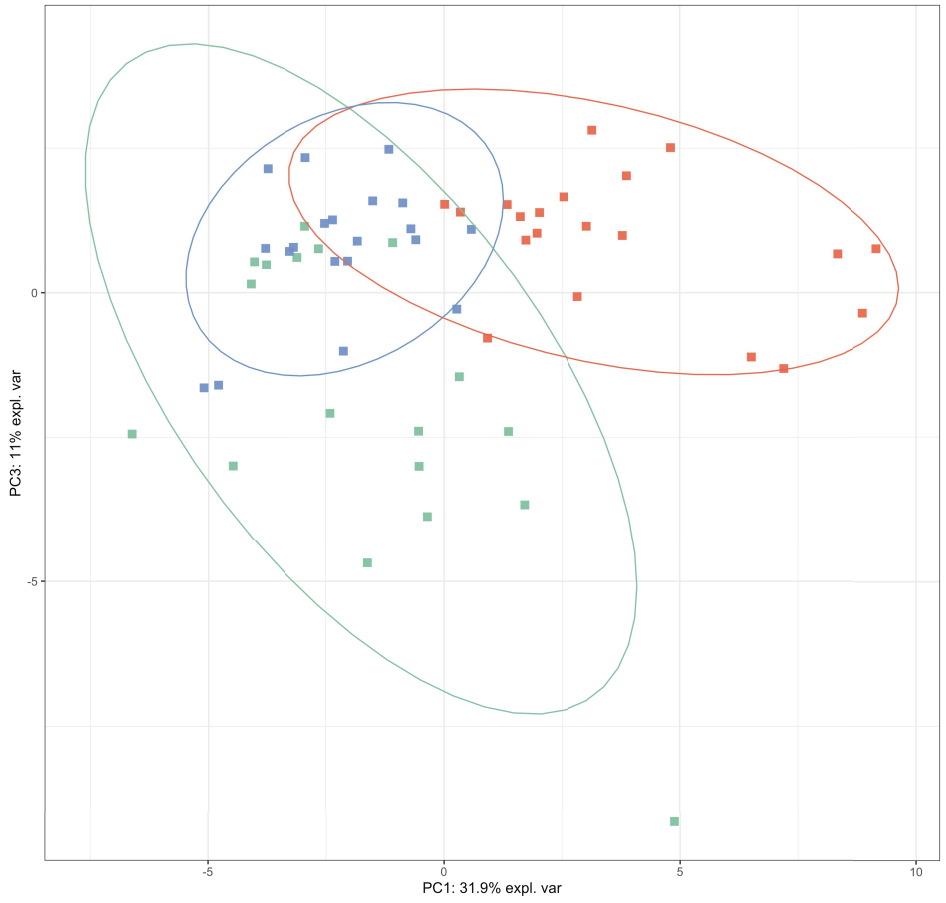

Figure 1. PCA plot of targeted analysis. PS-L skin – red squares; PS-NL skin – blue squares; HC skin samples – green squares. X and Y axes represent the percentage of variability explained by principal components one and two. The data includes statistically significantly changed metabolites in the Kruskal-Wallis test.

7.2. Metabolomic profile of atopic dermatitis skin (Paper II)

To analyse the metabolomic profile of the skin of AD patients, samples from AD lesional (AD-L) skin, AD non-lesional (AD-NL) skin and the skin of controls (HC) were examined. The levels of 77 metabolites and their ratios differed statistically significantly between the three phenotypic groups in targeted analysis (Kruskal-Wallis rank-sum test, FDR 5% corrected p-value <0.05; Table 5). Statistically significant differences were found in the groups of biogenic amines, amino acids, acylcarnitines, phosphatidylcholines and sphingomyelins.

Table 5. Metabolites and their ratios differing statistically significantly between atopic dermatitis lesional (AD-L) skin, non-lesional (AD-NL) skin and the skin of healthy controls (HC). MWW: Mann-Whitney-Wilcoxon test.

Metabolite	HC-s median (µM)	AD-L median (µM)	AD-NL median (µM)	Kruskal-Wallis rank sum test, Benjamini and Hochberg (FDR 5%) corrected p-value <0.05	MWW HC-s vs. AD-L FDR corrected	Median fold change (AD-L vs. HC-s)	MWW AD-L vs. AD-NL FDR corrected	Median fold change (AD-L vs. AD-NL)
Amino acids								
Glu	120	293	134.3	0.0033	0.0252	2.44	0.0002	2.18
Met	6.075	17.2	9.41	0.0037	0.0244	2.83	0.0007	1.83
Gln	148	233	118	0.0073	0.0815	1.57	0.0008	1.97
Asn	22.35	29.2	13	0.0103	0.8701	1.31	0.0013	2.25
Arg	41.1	74	38.5	0.023	0.0597	1.8	0.0112	1.92
Lys	43.9	73.4	43.4	0.0252	0.1754	1.67	0.003	1.69
Biogenic amines								
Putrescine	0.876	2.79	0.76	0.0003	0.0004	3.18	0.0005	3.67
ADMA	0.699	0.519	0.262	0.0044	0.9957	0.74	0.0007	1.98
Acylcarnitines								
C2	3.1	3.01	2.43	0.0019	0.733	0.97	0.0008	1.24
Glycerophospholipids								
PC.aa.C32.0	4.15	5.54	2.79	0.0011	0.0676	1.33	0.0002	1.99
PC.aa.C40.5	0.41	0.658	0.283	0.0011	0.0263	1.6	0.0003	2.33
PC.aa.C42.5	0.032	0.067	0.029	0.0011	0.0024	2.09	0.0007	2.31
PC.aa.C40.4	0.228	0.372	0.199	0.0012	0.0107	1.63	0.0002	1.87
PC.aa.C40.3	0.089	0.15	0.08	0.0019	0.0136	1.69	0.0007	1.88
PC.aa.C38.4	6.64	9.52	4.73	0.003	0.0527	1.43	0.0007	2.01
PC.ae.C36.0	0.296	0.567	0.247	0.0033	0.0252	1.92	0.0007	2.3
PC.aa.C30.0	1.385	1.64	0.977	0.0035	0.3864	1.18	0.0002	1.68

Table 5. Continue

Metabolite	HC-s median (µM)	AD-L median (µM)	AD-NL median (µM)	Kruskal-Wallis rank sum test, Benjamini and Hochberg (FDR 5%) corrected p-value <0.05	MWW HC-s vs. AD-L FDR corrected	Median fold change (AD-L vs. HC-s)	MWW AD-L vs. AD-NL FDR corrected	Median fold change (AD-L vs. AD-NL)
PC.aa.C38.5	2.88	4.27	2.12	0.0035	0.1097	1.48	0.0007	2.01
PC.aa.C36.4	7.485	9.48	5.02	0.0035	0.3019	1.27	0.0007	1.89
PC.ae.C34.0	0.376	0.455	0.234	0.0037	0.1933	1.21	0.0007	1.94
PC.ae.C38.4	0.511	0.687	0.38	0.0039	0.3556	1.34	0.0003	1.81
PC.aa.C38.3	1.9	2.64	1.49	0.0044	0.1624	1.39	0.0005	1.77
lysoPC.a.C18.0	1.615	1.38	0.944	0.0051	0.4618	0.85	0.003	1.46
PC.aa.C40.6	0.842	1.16	0.715	0.0058	0.3019	1.38	0.0002	1.62
PC.aa.C36.3	7.085	9.02	5.01	0.0064	0.3649	1.27	0.0002	1.8
PC.aa.C36.5	0.855	0.831	0.415	0.0064	0.7773	0.97	0.001	2
PC.ae.C40.1	0.147	0.184	0.112	0.007	0.0592	1.25	0.0009	1.64
PC.ae.C42.3	0.051	0.066	0.031	0.007	0.0676	1.29	0.0019	2.13
PC.ae.C38.5	0.989	1.7	0.727	0.0073	0.3528	1.71	0.0011	2.34
PC.ae.C40.5	0.144	0.178	0.106	0.0082	0.4076	1.23	0.0007	1.68
PC.ae.C36.1	0.889	0.868	0.496	0.0085	0.8701	0.97	0.0011	1.75
PC.aa.C34.4	0.099	0.095	0.058	0.009	0.958	0.96	0.0013	1.64
PC.aa.C42.4	0.021	0.033	0.021	0.009	0.0252	1.57	0.0068	1.57
PC.ae.C40.6	0.152	0.191	0.117	0.0096	0.4618	1.26	0.0007	1.63
lysoPC.a.C16.1	0.53	0.404	0.303	0.0103	0.2551	0.76	0.0461	1.33
PC.aa.C34.1	31.25	38.2	26.8	0.0103	0.4618	1.22	0.0011	1.43
PC.aa.C36.6	0.049	0.038	0.027	0.0103	0.3019	0.78	0.0316	1.41
PC.ae.C34.1	1.66	1.56	0.903	0.0103	0.8701	0.94	0.0015	1.73
PC.ae.C42.2	0.059	0.094	0.053	0.0103	0.0506	1.59	0.0039	1.77
PC.aa.C38.6	1.28	1.8	0.939	0.0107	0.647	1.41	0.0007	1.92

Table 5. Continue

Metabolite	HC-s median (µM)	AD-L median (µM)	AD-NL median (µM)	Kruskal-Wallis rank sum test, Benjamini and Hochberg (FDR 5%) corrected p-value <0.05	MWW HC-s vs. AD-L FDR corrected	Median fold change (AD-L vs. HC-s)	MWW AD-L vs. AD-NL FDR corrected	Median fold change (AD-L vs. AD-NL)
PC.aa.C34.2	15.1	16	10.6	0.0119	0.9269	1.06	0.001	1.51
PC.aa.C34.3	0.877	0.827	0.503	0.0138	0.9957	0.94	0.0019	1.64
PC.aa.C36.1	4.825	4.85	3.31	0.0138	0.8499	1.01	0.003	1.47
PC.aa.C36.2	15.5	17.7	11.2	0.0138	0.5917	1.14	0.0007	1.58
PC.aa.C28.1	0.665	0.616	0.433	0.0145	0.7087	0.93	0.0029	1.42
PC.aa.C32.1	3.22	3.09	1.42	0.0178	0.733	0.96	0.0057	2.18
PC.ae.C36.4	0.862	0.991	0.612	0.0178	0.8701	1.15	0.006	1.62
PC.aa.C38.0	0.245	0.255	0.149	0.0186	0.9954	1.04	0.0031	1.71
PC.ae.C40.4	0.139	0.167	0.119	0.0194	0.3019	1.2	0.0029	1.4
PC.ae.C36.2	1.023	0.861	0.618	0.0252	0.7087	0.84	0.0075	1.39
PC.ae.C38.0	0.192	0.214	0.147	0.0252	0.647	1.11	0.0031	1.46
PC.aa.C32.2	0.404	0.306	0.158	0.0257	0.8701	0.76	0.0031	1.94
lysoPC.a.C20.4	2.26	1.68	1.43	0.0281	0.303	0.74	0.1575	1.17
PC.ae.C36.5	1.45	2.12	1.1	0.0368	0.6773	1.46	0.0061	1.93
lysoPC.a.C16.0	6.485	7.88	5.33	0.0381	0.659	1.22	0.0055	1.48
lysoPC.a.C18.1	2.525	2.07	1.91	0.0381	0.3556	0.82	0.1469	1.08
PC.aa.C32.3	0.04	0.037	0.026	0.0381	0.958	0.93	0.0061	1.42
PC.ae.C38.6	0.567	0.858	0.444	0.0381	0.8499	1.51	0.0082	1.93
PC.ae.C32.1	0.756	0.806	0.472	0.0413	0.958	1.07	0.0056	1.71
PC.ae.C34.2	1.085	1.1	0.773	0.0456	0.7043	1.01	0.0241	1.42
lysoPC.a.C17.0	0.253	0.273	0.183	0.0472	0.9957	1.08	0.0132	1.49

Table 5. Continue

Metabolite	HC-s median (µM)	AD-L median (µM)	AD-NL median (µM)	Kruskal-Wallis rank sum test, Benjamini and Hochberg (FDR 5%) corrected p-value <0.05	MWW HC-s vs. AD-L FDR corrected	Median fold change (AD-L vs. HC-s)	MWW AD-L vs. AD-NL FDR corrected	Median fold change (AD-L vs. AD-NL)
Sphingolipids								
SM.C26.0	0.033	0.086	0.069	0.0003	0.0004	2.61	0.005	1.25
SM.C26.1	0.054	0.146	0.079	0.0003	0.0004	2.7	0.0029	1.85
SM..OH..C24.1	0.088	0.177	0.109	0.0011	0.0012	2.01	0.002	1.62
SM.C24.1	2.28	5.23	3.07	0.0014	0.0024	2.29	0.003	1.7
SM.C16.0	5.68	9.53	5.88	0.0044	0.0252	1.68	0.0008	1.62
SM..OH..C16.1	0.163	0.318	0.222	0.0082	0.0288	1.95	0.0039	1.43
Total.SM.OH	1.27	1.82	1.34	0.009	0.0252	1.43	0.0052	1.36
SM.C18.1	0.185	0.297	0.185	0.0107	0.0395	1.61	0.0047	1.61
SM..OH..C14.1	0.372	0.49	0.339	0.0135	0.0374	1.32	0.0072	1.45
SM..OH..C22.2	0.24	0.348	0.261	0.0135	0.0274	1.45	0.0145	1.33
SM.C24.0	1.035	1.97	1.3	0.0138	0.0274	1.9	0.0252	1.52
SM.C16.1	0.431	0.58	0.491	0.0269	0.0873	1.35	0.0082	1.18
SM.C18.0	4.12	6.64	3.75	0.0308	0.3019	1.61	0.0075	1.77
SM..OH..C22.1	0.353	0.519	0.331	0.0309	0.0374	1.47	0.0459	1.57
Metabolite ratios								
Cit…Arg	2.632	0.487	1.27	0.0037	0.007	0.19	0.0118	0.38
Cit…Orn	3.685	0.848	2.74	0.0263	0.0372	0.23	0.0423	0.31

In the comparison of AD-L skin and HC skin, the concentrations of 21 metabolites (putrescine, p=0.0004; SM.C26.0, p=0.0004; SM.C26.1, p=0.0004; PC.aa.C40.5, p=0.0263; PC.aa.C42.5, p=0.0024; SM..OH..C24.1, p=0.0012; PC.aa.C40.4, p=0.0107; SM.C24.1, p=0.0024; PC.aa.C40.3, p=0.0136; Glu, p=0.0252; PC.ae.C36.0, p=0.0252; Met, p=0.0244; SM.C16.0, p=0.0252; SM..OH..C16.1, p=0.0288; PC.aa.C42.4, p=0.0252; total SM.OH, p=0.0252; SM.C18.1, p=0.0395; SM..OH..C14.1, p=0.0374; SM..OH..C22.2, p=0.0274; SM.C24.0, p=0.0274; SM..OH..C22.1, p=0.0374) were elevated in AD-L skin and two metabolite ratios (Cit to Arg, p=0.007; Cit to Orn, p=0.0372) were decreased in AD-L skin.

In the comparison of AD-L skin and AD-NL skin, the concentrations of 73 metabolites including AAs, biogenic amines, acylcarnitines, PC-s and SM-s were elevated in AD-L skin. Like in the comparison of AD-L skin and HC skin, the ratios of Cit to Arg (p=0.0118) and Cit to Orn (p=0.0423) were decreased in AD-L skin. We did not find any statistically significant differences between the concentrations of metabolites in AD-NL skin and HC skin.

The findings showed that the metabolomic profile of AD-L skin differs from the metabolomic profile of AD-NL skin and HC skin, based on the principal component analysis of statistically significantly changed metabolites (Figure 2).

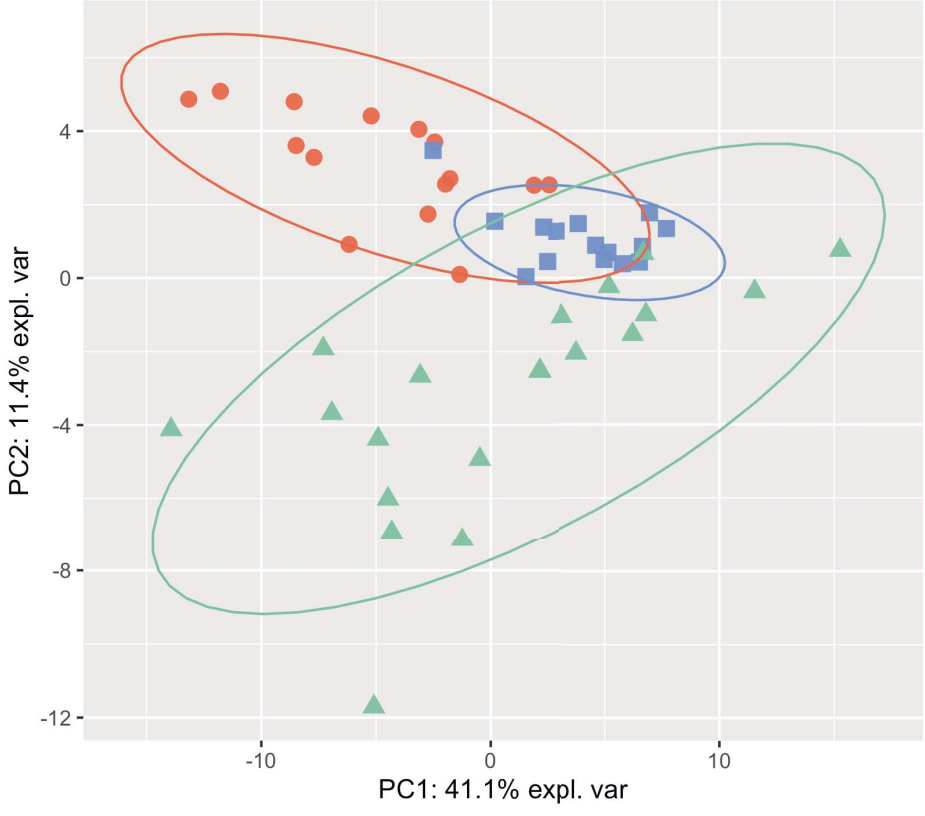

Figure 2. PCA plot based on the whole dataset of targeted analysis. AD-L skin – red circles; AD-NL skin – blue squares; HC skin – green triangles. X and Y axes represent the percentage of variability explained by principal components one and two.

7.3. Comparative analysis of metabolite levels in skin and serum of patients with PS and AD (Paper III)

We also compared the metabolomic profiles of the skin of PS and AD patients and the sera of PS and AD patients to find possible similarities and differences between the two chronic inflammatory skin diseases (Figure 3).

Comparing the lesional skin of PS (PS-L) and the lesional skin of AD (AD-L) we found 19 metabolites and their ratios with statistically significant differences in their concentrations between the two groups (Table 6). In AD-L skin, the median levels of SM-s (SM.C26.0, p=0.0028; SM.C26.1, p=0.0035; hydroxysphingomyeline C22.1, SM.OH.C22.1, p=0.0095; SM.C18.1, p=0.0095; SM.C24.1, p=0.0095; SM.C24.0, p=0.0294; hydroxysphingomyeline C22.2, SM.OH.C22.2, p=0.0328; SM.C16.1, p=0.044; SM.C16.0, p=0.044) and the ratio of Orn to Arg (p=0.0285) were elevated when compared to PS-L skin. The median concentrations of ADMA (p=0.0043), C2 (p=0.0086), C18.2 (p=0.0318) and glycerophospholipids (PC.ae.C38.1, p=0.0095; PC.ae.C36.0, p=0.0184; lysoPC.a.C16.1, p=0.0274; PC.ae.C38.0, p=0.0365; PC.ae.C36.1, p=0.044; PC.ae.C38.2, p=0.044) were increased in PS-L skin when compared to AD-L skin.

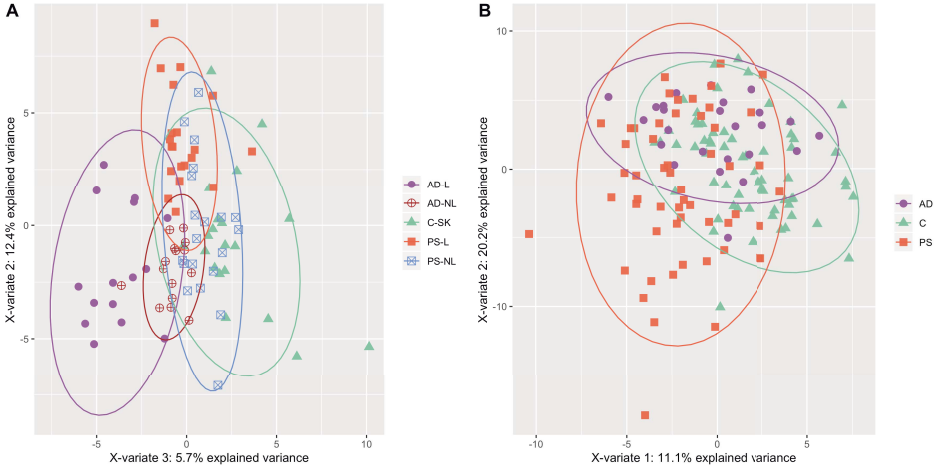

Figure 3. (A) PLS-DA plot of the samples of AD-L (filled violet circles), AD-NL (empty violet circles), PS-L (filled red squares), PS-NL (empty blue squares) and HC (filled green triangles) skin. (B) PLS-DA plot of the samples of PS (red squares), AD (violet circles) and HC (green triangles) sera. Data is based on statistically significantly changed metabolites in the Kruskal-Wallis test.

Table 6. Metabolites and their ratios differing statistically significantly between atopic dermatitis lesional (AD-L) skin and psoriasis lesional (PS-L) skin.

Metabolite	AD-L median value	PS-L median value	AD-L vs PS-L MWW p-value FDR 5% corrected	Median fold change (AD-L over PS-L)	Median fold change (PS-L over AD-L)
Biogenic amines					
ADMA	0.1622	**0.4483**	0.0043		2.8
Acylcarnitines					
C2	0.1504	**0.2529**	0.0086		1.7
C18.2	0.2241	**0.4397**	0.0318		2
Sphingolipids					
SM.C26.0	**0.5119**	0.2083	0.0028	2.5	
SM.C26.1	**0.4966**	0.2109	0.0035	2.4	
SM.OH.C22.1	**0.6539**	0.3365	0.0095	1.9	
SM.C18.1	**0.5165**	0.2443	0.0095	2.1	
SM.C24.1	**0.6115**	0.3218	0.0095	1.9	
SM.C24.0	**0.6181**	0.3434	0.0294	1.8	
SM.OH.C22.2	**0.5429**	0.3222	0.0328	1.7	
SM.C16.1	**0.4554**	0.3275	0.044	1.4	
SM.C16.0	**0.5086**	0.3374	0.044	1.5	
Glycerophospholipids					
PC.ae.C38.1	0.1106	**0.241**	0.0095		2.2
PC.ae.C36.0	0.0722	**0.1618**	0.0184		2.2
lysoPC.a.C16.1	0.1331	**0.2108**	0.0274		1.6
PC.ae.C38.0	0.1751	**0.3319**	0.0365		1.9
PC.ae.C38.2	0.1615	**0.2585**	0.044		1.6
PC.ae.C36.1	0.1518	**0.2338**	0.044		1.5
Metabolite ratios					
Orn…Arg	**0.0063**	0.0025	0.0285	2.5	

Comparison of AD-NL and PS-NL skin revealed that the median concentration of only one metabolite, i.e. C2 (p=0.0481), differed significantly between the groups and was represented at higher concentrations in the samples of PS-NL skin (the median value was 0.0985 in AD-NL skin and 0.1455 in PS-NL skin, i.e. 1.5-fold change).

When comparing the blood sera of PS and AD patients, we found 5 metabolites that had statistically significantly higher median values in PS sera (Table 7): Cit (p=0.0392), Glu (p=0.0392), Pro (p=0.0392), carnitine (C0, p=0.0184) and C18.1 (p=0.0392).

Table 7. Metabolites with median values differing statistically significantly between the sera of AD and PS patients.

Metabolite	AD serum median value	PS serum median value	AD serum vs PS serum MWW p-value FDR 5% corrected	Median increase (PS vs AD, times)
Amino acids				
Cit	0.1843	**0.2806**	0.0392	1.5
Glu	0.1146	**0.2282**	0.0392	2
Pro	0.1793	**0.3073**	0.0392	1.7
Acylcarnitines				
C0	0.154	**0.4292**	0.0184	2.8
C18.1	0.2312	**0.3417**	0.0392	1.5

7.4. Changes in metabolites, lipoproteins and lipoprotein particles in the blood serum of lichen planus patients (Paper IV)

In Paper IV, we analysed the metabolomic profile of the blood serum of LP patients and compared it to the serum of HC-s. In this study, we found 16 markers regarding lipoproteins that differed statistically significantly between the two groups. The levels of lipoprotein components were altered in intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL) and large LDL in the blood serum of LP patients.

The levels of phospholipids (PL), cholesteryl esters (CE), total cholesterol (TC) and free cholesterol (FC) were increased in IDL particles in LP patients compared to HC. In L-LDL, the levels of total lipids, TC, FC, CE and PL were increased in LP patients. The concentrations of FC, TC and total lipids were elevated in LDL particles in LP patients compared to HC. In addition to this, the levels of TC, total FC, total CE and clinical value of LDL cholesterol (calculated as LDL-C + IDL-C + cholesterol in very small very-low-density lipoproteins × 0.15) were increased in patients suffering from LP (Table 8, Figure 4 and Figures S1-S3).

Table 8. Lipoprotein particles and metabolites with statistically significant differences between the blood serum samples of LP patients and HC-s.

Composition of lipoprotein particles and metabolites	Mean for LP	Mean for HC	Wilcox-test LP vs. HC, $p < 0.0029$
Large LDL			
L-LDL-L	0.4	–0.39	0.0007
L-LDL-C	0.41	–0.4	0.0008
L-LDL-FC	0.41	–0.39	0.0008
L-LDL-CE	0.4	–0.39	0.001
L-LDL-PL	0.4	–0.38	0.0011
LDL			
LDL-FC	0.39	–0.38	0.0008
LDL-C	0.38	–0.37	0.0024
LDL-L	0.38	–0.37	0.0027
IDL			
IDL-PL	0.4	–0.39	0.0013
IDL-CE	0.4	–0.39	0.0021
IDL-C	0.4	–0.39	0.0023
IDL-FC	0.39	–0.38	0.0027
Clinical LDL cholesterol and its values			
Clinical LDL-C*	0.39	–0.38	0.0014
Total C	0.41	–0.4	0.0016
Cholesteryl esters			
Total CE	0.41	–0.39	0.0013
Free cholesterol			
Total FC	0.4	–0.39	0.0028

C – cholesterol; CE – cholesteryl esters; FC – free cholesterol; HC – healthy controls; IDL – intermediate-density lipoprotein; L – large; -L – total lipids; LDL – low-density lipoprotein; LP – lichen planus; PL – phospholipids. * Clinical LDL-C can be obtained from the NMR-based measures using the equation: clinical LDL-C = LDL-C + IDL-C + XS-VLDL × 0.15.

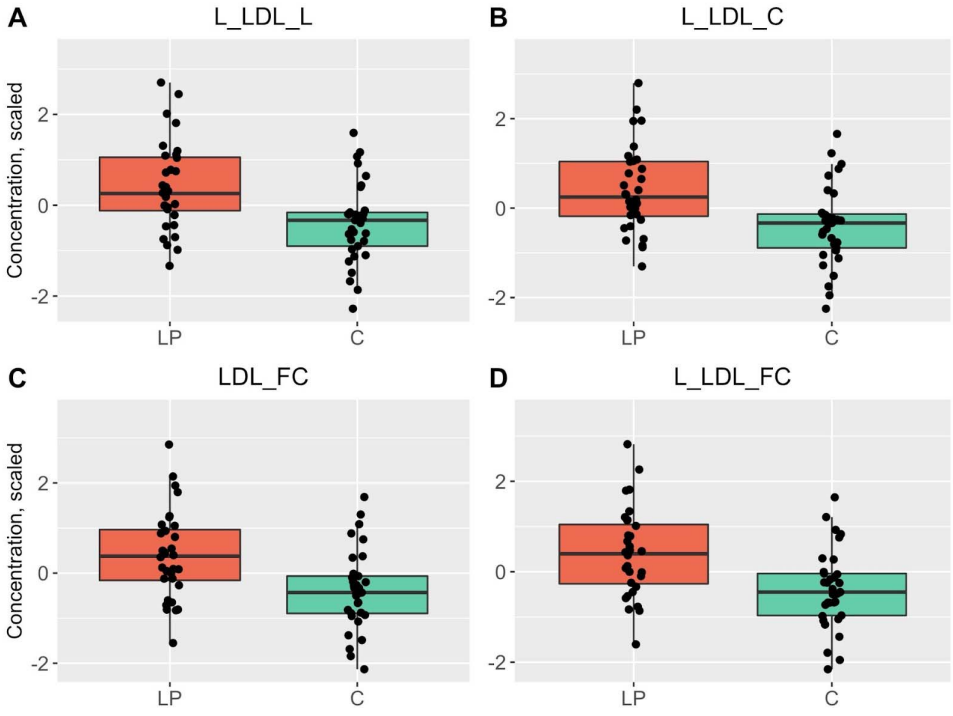

Figure 4. Boxplots of the top four statistically significant results that differed between the blood serum samples of LP patients (red) and HC-s (green). $p<0.0029$ is considered statistically significant.

Additionally, even though the changes were not statistically significant, smaller alterations were detected in the composition of high-density lipoproteins (HDL) and VLDL, as well as in the concentrations of non-HDL cholesterol, SM-s, linoleic acid, polyunsaturated fatty acids, omega-6 fatty acids and Leu.

We also analysed the ratios related to cardiovascular diseases and T2D – known comorbidities of LP. However, when comparing LP patients and HC, we did not find changes in the ratios of HDL-C to apolipoprotein A1, LDL-C to HDL-C, total triglycerides (TG) to HDL-C, total FC to HDL-C, non-HDL-C to HDL-C or LDL-C to apolipoprotein B.

Also, we analysed other metabolites including ketone bodies, glycolysis related metabolites, other apolipoproteins and amino acids, but there were no alterations in their levels between HC and LP patients.

8. DISCUSSION

We analysed three chronic skin diseases: PS, AD and LP, among which PS and LP belong to the group of papulosquamous diseases. At first, AD may seem to be an opposite disease, regarding its etiopathogenesis and comorbidities, however, the pathogenesis and comorbidities in adult AD patients are more similar to those of PS and LP than would be expected. For example, all three diseases share an increased risk for obesity, CVD, depression and anxiety. To date, it is not clear what the exact factors that distinguish the diseases are, as they have similar pathways and comorbidities in the chronic phase.

8.1. Metabolomic profile of plaque psoriasis

Paper I is focused on the metabolomic profile of the skin of PS patients. In the comparison of PS-L skin, PS-NL skin and HC skin, 29 metabolites and their ratios differed statistically significantly between the three phenotypic groups.

AAs Glu, Met and Arg had all elevated concentrations in PS-L skin compared to HC skin and, additionally, Lys, Leu and Phe levels were also elevated in PS-L skin compared to PS-NL skin. As shown previously, the increase in Glu levels might potentially be the expression of higher demand for glutamine in the characteristic pathophysiological aspects of PS, like cellular hyperproliferation, increased activity of immune cells and accelerated synthesis of proteins (Armstrong et al., 2014; Yan et al., 2017). Higher Phe levels can reflect the decrease in its turnover to tyrosine, which can be seen in chronic inflammatory disorders (Neurauter et al., 2008). Both Phe and Glu have been previously found increased in the blood serum of patients with PS (Ottas et al., 2017). Elevated Lys levels can be related to greater collagen production (Koivukangas et al., 1995) and increased L-carnitine synthesis in PS (Pekala et al., 2011).

The Fisher ratio reflects the molar ratio of BCAA-s Leu, Val and Ile to aromatic AAs Phe and Tyr. BCAAs have an important role in the maturation of DC-s and are needed for lymphocyte proliferation (Tajiri & Shimizu, 2018). Additionally, the catabolism of glycoketogenic BCAAs might be intensified in PS, which leads to an increase in Glu and short-chain acylcarnitines (e.g. predominantly Val- and Ile-derived C3, and Leu- and Ile-derived C5 (Mednova et al., 2022), the latter of which was found to be increased in our study).

Among AAs, the levels of Met were also elevated in PS-L skin. Met can be oxidized to Met.SO, which is evidence of oxidative stress (Mashima et al., 2003). However, we did not find increased Met.SO levels in PS lesional skin, which implies that there is no excess oxidative stress in psoriatic lesions, which is protein-related. Polyamines, among which putrescine and spermidine were elevated in psoriatic lesions, also help to protect against oxidative damage (Pegg, 2014). They have an important role in various processes, like cellular growth, differentiation and proliferation, and are produced extensively during cell division (Bae

et al., 2018; Broshtilova et al., 2012, 2013), which complies with the hyperproliferative state of PS.

We also found alterations in the levels and ratios of metabolites that are related to the urea cycle, namely Cit, Orn and Arg. Cit can be synthesized from Arg and proteins that contain Cit derive primarily from keratin K1. Protein citrullination is found to be dysfunctional or diminished in PS lesional skin (Curis et al., 2005; Ishida-Yamamoto et al., 2000). The decreased ratio of Cit to Orn is concordant with the previously found declined activity of Orn carbamoyltransferase (Ottas et al., 2017). However, the levels of neither Cit or Orn differed statistically significantly between the groups. Arg and ADMA are metabolically closely related and levels of both of them were elevated in PS-L skin. Higher ADMA concentrations have also been described previously in the blood of PS patients, and are positively correlated with severity of the disease (Bilgic et al., 2015; Pina et al., 2016).

Up to 80% of PS patients complain about pruritus and histamine is a well-known mediator of itch (Szepietowski et al., 2002). We found elevated histamine levels in PS-L skin, which is consistent with previous findings (Krogstad et al., 1997) and may, at least in part, be responsible for the itch sensation.

The changes in acylcarnitine levels are evidence of increased cellular stress and pro-inflammatory state in psoriatic plaques (McCoin et al., 2015). Elevated C2 concentration signifies the metabolic status of skin cells by modulating the homeostasis of intracellular coenzyme A (Longo et al., 2016).

Elevation of glycerophospholipid concentrations in PS-L skin is in good concordance with the hyperproliferative state of psoriatic lesions as glycerophospholipids are important components of cell membranes. Additionally, lysophosphatidylcholines have been found to induce and maintain chronic inflammation via provoking T-lymphocyte chemotaxis (Ryborg et al., 1994).

All in all, the metabolomic profile of psoriatic lesional skin is mainly characterized by features of increased cellular proliferation expressed by an increase in phosphatidylcholine and carnitine levels, and inflammation, which manifests itself via elevated concentrations of Phe, long-chain acylcarnitines and lysophospatidylcholine.

8.2. Metabolomic profile of atopic dermatitis

In Paper II, the aim was to characterize the metabolomic profile of the lesional skin of AD patients and to compare it to that of the non-lesional skin of AD patients and the skin of HC-s. Comparing the three phenotypic groups, we found 77 metabolites and their ratios with statistically significant differences, which belonged to AAs, biogenic amines, acylcarnitines, SM-s and PC-s.

As in PS-L skin, the levels of putrescine were elevated in AD-L skin. In addition to being involved in cell growth and proliferation, DNA protection from oxidative damage and regulation of immune cells, biogenic amines are involved in inflammatory processes and probably have both pro- and anti-inflammatory

properties (Bae et al., 2018; Lagishetty & Naik, 2008; Minois, 2014). Considering the pathway of *de novo* synthesis of the biogenic amines putrescine, spermidine and spermine (Janne et al., 2005), we suggested that the increase in putrescine and Met levels were due to the continuous synthesis of putrescine by ornithine decarboxylase I and the possible downregulation of S--adenosyl--L--methionine decarboxylase 1 (AMD1) in the lesional skin of AD patients. However, as AD causes severe pruritus and it has previously been found that AMD1 is upregulated in wound-edge cells in scratch assays (Lim et al., 2018), we would have expected to find elevated spermine and spermidine levels in AD-L skin.

Increased dimethylarginine concentrations may reflect inflammation and metabolic imbalance. ADMA levels were elevated in AD-L skin samples; we have also found increased ADMA and total DMA levels in PS-L skin samples (Pohla et al., 2020). Both ADMA and symmetric dimethylarginine (SDMA) take part in inflammatory processes and their higher levels have been found in several diseases, e.g. atherosclerosis and chronic kidney disease (Franceschelli et al., 2013; Schepers et al., 2011). As ADMA inhibits nitric oxide synthase (NOS) (Vallance & Leone, 1992), biosynthesis of Cit from Arg is decreased. This leads to an increase in Arg levels and a decrease in the ratio of Cit to Arg. Dimitriades et al. have also found decreased arginase 1 activity and an increase in Arg levels in the plasma of children suffering from AD (Dimitriades et al., 2014).

Changes in AA levels in AD-L skin involve alterations in non-essential AAs like Asn and Glu. Both are needed in protein synthesis; additionally, Asn has an important role in the development of the brain (PubChem; Ruzzo et al., 2013) and Glu is an essential neurotransmitter that can also be linked to inflammation (Cui et al., 2019; Haroon et al., 2016). Increased Glu levels are found in other conditions like rheumatoid arthritis and obesity, which have an inflammatory component as does AD (J. (Li et al., 2018; Liu et al., 2017). An increase in Met levels, besides elevation of Glu levels and undetectable Met.SO levels in AD-L skin lesions, might reflect the defective synthesis of anti-oxidative compounds, as the oxidation of Met to Met.SO and conversion to cysteine would protect against oxygen radicals (Bin et al., 2017; Vogt, 1995).

Met and Lys, whose levels were also elevated in AD-L skin, are required in the synthesis of carnitine. Carnitine is known to have a substantial role in fatty acid metabolism, making the transport of long-chain fatty acids through the inner mitochondrial membrane possible and thereby enabling β-oxidation (Longo et al., 2016; Pekala et al., 2011). C2, whose levels we found to be increased in AD-L skin and previously in PS-L skin (Pohla et al., 2020), also regulates the homeostasis of intracellular Coenzyme A and gives information about the energetic state and the metabolic state of the skin cells (Longo et al., 2016).

AD is a disease with reduced skin barrier and the impaired synthesis of ceramides, which is in concordance with the finding of SM-s being elevated in AD-L skin compared to AD-NL skin and HC skin. This indicates decreased activity of sphingomyelinase, which synthesizes ceramides from SM-s (Jensen et al., 2004). SM-s, as well as PC-s are both structural components and sources of bioactive compounds (Wanner et al., 2004). Increased PC levels can be explained

by defective or lacking phosphatidylcholine-sphingomyelin transacylase in AD skin, which was detected by Peiser et al (Peiser et al., 2007). The chemoattractant properties of lysoPC-s, whose concentrations were elevated in AD-L skin (as was in PS-L skin), might reflect one of their roles in AD as lysoPC-s are able to induce the migration of T-lymphocytes into the epidermis (Ryborg et al., 1994).

In conclusion, metabolomic shifts in atopic skin is a sign of susceptibility to oxidative stress, which is characterized by increased Met and Glu levels, inflammation, which is expressed by increased putrescine and ADMA levels, and disruption of skin barrier function, which is supported by elevated concentrations of SM.

8.3. Differences between the metabolomic profiles of psoriasis and atopic dermatitis

To systematically analyse differences at the level of metabolism in the two common inflammatory dermatoses, AD and PS, we compared the metabolomic profiles of the blood serum, and the lesional and non-lesional skin of AD and PS patients.

Comparison between AD-L skin and PS-L skin revealed differences in the levels of 19 metabolites and their ratios. The lesional skin of AD was characterized by increased SM levels and elevation of a group of PC-s in PS-L skin. Both are structural components, i.e. lipid constituents of membranes, acting also as sources of bioactive derivates, whose signalling can be linked to various processes including differentiation, proliferation or either induction or inhibition of apoptosis (Wanner et al., 2004). As shown before, an increase in SM levels may be related to reduced sphingomyelinase activity that subsequently leads to decreased ceramide levels (Imokawa et al., 1991; Jensen et al., 2004). The latter is also affected by increased expression of SM deacylase in the epidermis of AD patients (Hara et al., 2000). These changes might be influenced by Th2-mediated inflammation which is characteristic of AD skin (Berdyshev et al., 2018; Sawada et al., 2012).

The levels of PC-s, on the other hand, were elevated in PS-L skin. One important signalling molecule that can be synthesized from PC-s is arachidonic acid. This can subsequently be metabolized into prostaglandins and leukotriens (Furse & de Kroon, 2015; Gibellini & Smith, 2010), among which several have been found to be elevated in PS-L skin (Barr et al., 1984; Brain et al., 1984; Hammarström et al., 1975).

Regarding AAs, the ratio of Orn to Arg was lower and ADMA levels were higher in PS-L skin compared to AD-L skin. As ADMA inhibits NOS, it prevents the synthesis of Cit from Arg. We have previously found elevated Arg concentrations in both PS-L skin and AD-L skin when compared to HC skin (Ilves et al., 2021; Pohla et al., 2020). Additionally, higher ADMA levels have also been found in the blood of PS patients (Bilgic et al., 2015), which is in accordance with

elevated ADMA levels also in its common comorbidity CVD, including atherosclerosis (Dowsett et al., 2020; Mangiacapra et al., 2016; Mehta et al., 2010).

Carnitines C2 and C18.2 showed increased concentrations in PS-L skin when compared to AD-L skin, and C2 was also elevated in PS-NL skin when compared to AD-NL skin. This can be explained by the higher need for energy in psoriatic hyperproliferative epidermis, which can be met by fatty acid β-oxidation in mitochondria (Reuter & Evans, 2012).

Carnitines (C0 and C18.1) were also elevated in PS serum when compared to AD serum. Alterations in lipid metabolism have previously been suggested to occur in PS and AD as the decrease in the ratio C2 to free carnitine (C0) has been found in the blood of both diseases' patients (Ottas et al., 2017; Ottas et al., 2017).

Three AAs, Glu, Pro and Cit, were found to be elevated in PS patients' blood compared to AD patients' blood. Glu has an important role in AA metabolism and in stabilizing protein structure (Brosnan & Brosnan, 2013). Besides PS (Dutkiewicz et al., 2016), increased levels of Glu have been found in the blood of patients with other inflammatory diseases, e.g. atherosclerosis (Lehn-Stefan et al., 2021) and non-alcoholic fatty liver disease (Gaggini et al., 2018), which are also comorbid conditions of PS. Pro can be metabolized into Orn and subsequently into putrescine or Cit (*KEGG PATHWAY: Arginine and Proline Metabolism*). Both Pro and Cit have been found to be elevated in PS patients' blood (Kamleh et al., 2015; Kang et al., 2017). Also, it has recently been found that IL-17, one of the most important cytokines in PS, can influence the balance between the urea cycle metabolites (Lou et al., 2020).

To sum up, the metabolomic profiles of the skin and sera of AD and PS show distinct patterns which are in concordance with the pathogenetic mechanisms of both diseases. Clear differences were brought out, e.g. barrier defect in AD, which was expressed by increased SM levels, and hyperproliferation in PS, which was characterized by elevated concentrations of carnitines and phosphatidylcholines.

8.4. Metabolomic profile and changes in lipoproteins and their particles in the blood serum of lichen planus patients

To find out changes in the blood serum of LP patients and HC-s, we used NMR spectroscopy to measure the levels of blood serum metabolites, lipoproteins and lipoprotein particles. Regarding lipoproteins, we found 16 markers that differed statistically significantly between the two groups. MS and one of its components, dyslipidaemia, are comorbidities of LP, and chronic inflammatory skin diseases increase the likelihood of MS and dyslipidaemia (Daye et al., 2021; Panchal et al., 2015). Dyslipidaemia is characterized by various alterations in lipid levels, e.g., decreased levels of HDL-C and increased levels of LDL-C and TG (Kopin & Lowenstein, 2017). As described above, we found alterations in the levels of cholesterol (C), cholesteryl esters (CE), free cholesterol (FC), total lipids (L) and phospholipids (PL) in L-LDL, LDL and IDL particles. We would have expected

to find laboratory-confirmed dyslipidaemia more frequently in LP patients (Table S1), based on the results and previously published articles, which indicates the need for routine screening of LP patients for dyslipidaemia.

Lipoproteins consist mainly of apoproteins, TG-s, CE-s, FC-s and PL-s, and are divided into subclasses based on their composition and density (Feingold, 2000). It has previously been shown that there exist alterations in lipid and lipoprotein levels in the blood of LP patients, as well as an increase in C-reactive protein levels (Panchal et al., 2015) and Castelli's atherogenic index (Lopez-Jornet et al., 2012), but specific changes in lipoprotein composition have not been established. We suggest that alterations in lipoprotein composition may change the manifestation and course of comorbidities, as L-LDL, LDL and IDL are related to lipid transport and are pro-atherogenic (dependending also on particle size). Patients with elevated L-LDL and small-LDL levels have been shown to have higher risk for all-cause mortality, including cardiovascular mortality, compared to intermediate-size LDL levels. Higher C-reactive protein and IL-6 levels were also found in patients with increased L-LDL levels (Grammer et al., 2015), which are increased in LP patients as well. The risk for cardiovascular death is higher for patients whose LDL particles consist of more sphingolipids and less phosphatidylcholines – these changes increase the aggregation of LDL (Ruuth et al., 2018).

In our study, we found small, statistically insignificant changes in the composition of HDL particles. Qualitative and quantitative molecular alterations in HDL have been described in various diseases like coronary artery disease (Annema & von Eckardstein, 2016), rheumatic diseases, MS and diabetes mellitus (Annema & von Eckardstein, 2013). Irrespective of the normal levels of HDL, patients with type 1 diabetes have increased cardiovascular risk (Ganjali et al., 2017). Normally, HDL has anti-inflammatory, anti-apoptotic, anti-thrombotic and antioxidative properties and protects against CVD (Feingold, 2000). Changes in its composition are thought to have an impact on its functional properties (Annema & von Eckardstein, 2016; Cardner et al., 2020; Ganjali et al., 2017). Cardner et al. have reported alterations in the composition of HDL particles in CHD as well as in T2D (Cardner et al., 2020).

In conclusion, we found an altered composition of lipoproteins in the blood serum of LP patients compared to controls. As previous studies have shown that the composition of lipoproteins may affect their function, we suggest that changes in it could lead to a higher risk for specific comorbidities like MS and dyslipidaemia, and vice versa. In cases where LDL and IDL particles are altered/modified, the turnover and hepatic uptake are disturbed, which can result in an increased cardiovascular risk. Screening for dyslipidaemia in patients suffering from LP is also supported by the results of our study.

9. CONCLUSIONS

1. We found that the metabolomic profile of PS lesional skin involve cellular hyperproliferation and inflammation. The lesional skin of PS patients was clearly different from visually non-lesional skin and the skin of HC-s. We suggest that local inflammatory processes induce cellular hyperproliferation and may be the main cause of metabolomic shifts.
2. The metabolomic profile of AD lesional skin was characterized by ongoing inflammation, increased susceptibility to oxidative stress and disrupted skin barrier function. The lesional skin of AD patients differed from the non-lesional skin and the skin of HC-s; there were no statistically significant differences in metabolite levels between AD-NL skin and the skin of HC-s.
3. Comparison of the metabolomic profiles of the skin of PS and AD patients revealed that the lesional skin of PS showed characteristics of increased cell proliferation, while changes in AD lesional skin suggested impaired barrier function. The blood serum of PS patients indicated cellular hyperproliferation. Metabolomic profiles of the studied diseases are well correlated with differences in their pathogenetic mechanisms.
4. Metabolomic analysis of the blood serum of LP patients revealed alterations in the composition of lipoproteins, specifically in the composition in IDL, LDL and L-LDL. These changes might lead to an increased risk for comorbidities like MS and dyslipidaemia, and vice versa.

9.1. Strengths and limitations

To date, the research conducted in the area of the metabolomics of the skin of AD and PS patients has been limited. Moreover, no comparative study has been performed on the skin and blood metabolomics of PS and AD patients. Considering this, the present study is the first using the comparative approach in the research of the skin and blood metabolomics of PS and AD. Additionally, to our knowledge, this is the first study of the metabolomics of LP blood serum.

The main limitation of our study is the relatively small number of participants. Also, with such a study design, it is difficult to prove causality, specifically whether the change in the metabolite levels was the cause or the consequence of the disease.

9.2. Contributions to the field

Our findings contribute to the unraveling and clarification of the pathogenetic mechanisms of PS, AD and LP. Alterations in lipoprotein particles in LP patients should encourage clinicians to routinely screen for dyslipidaemia.

9.3. Future directions

We are continuously collecting new blood and skin samples from new patients in order to obtain larger cohort sizes for subsequent studies. Additionally, we are carrying out research into PS, AD and LP proteomics and into validation of their possible disease specific biomarkers.

Further studies are needed to specify the relationships between metabolomic changes in PS, AD and LP, and their comorbidities.

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11. SUPPLEMENTARY MATERIALS

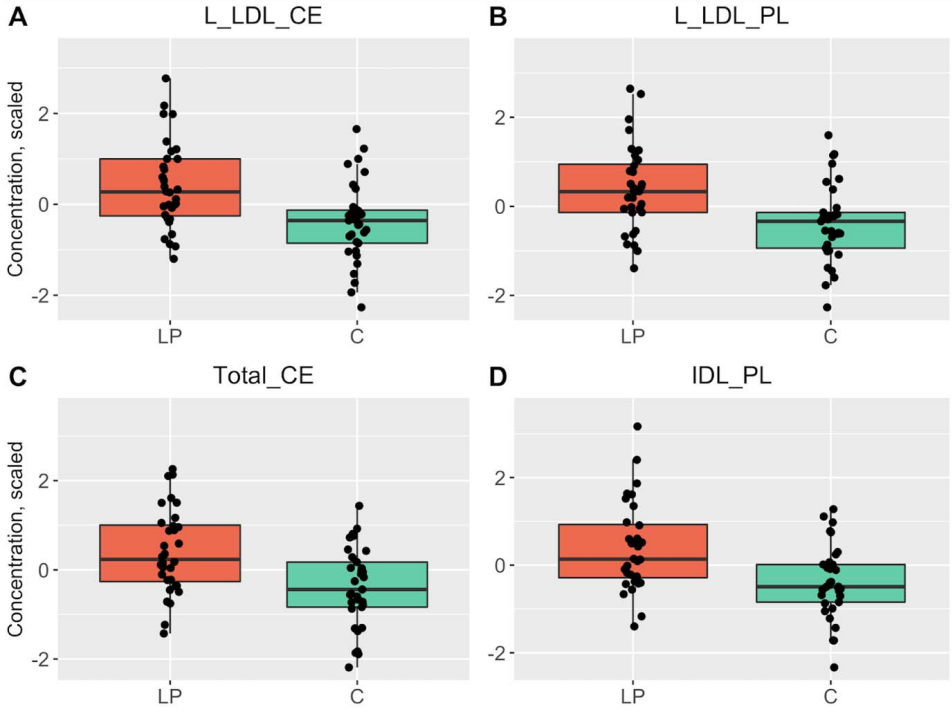

Figure S1. Boxplots of the metabolites and lipoprotein particles that had statistically significant differences between the blood samples of LP patients and HC.

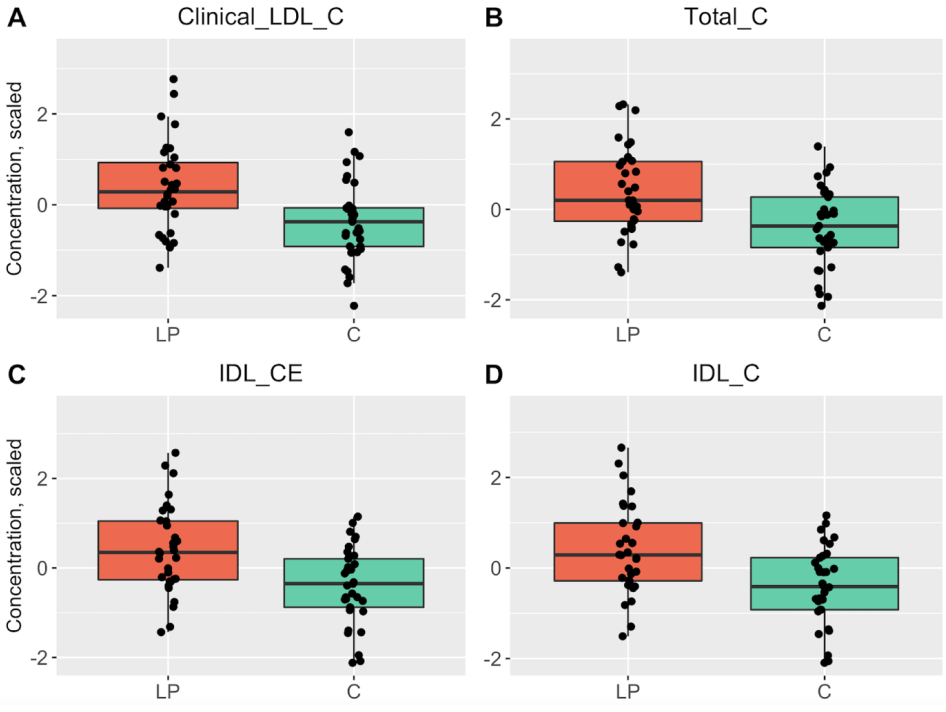

Figure S2. Boxplots of the metabolites and lipoprotein particles that had statistically significant differences between the blood samples of LP patients and HC.

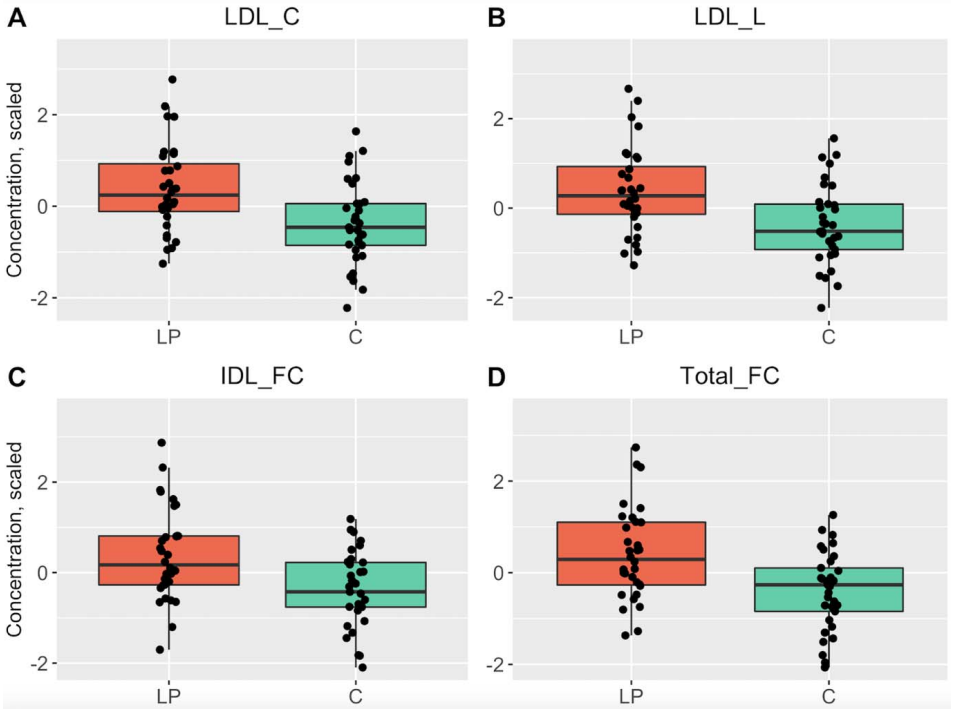

Figure S3. Boxplots of the metabolites and lipoprotein particles that had statistically significant differences between the blood samples of LP patients and HC.

Table S1. Diagnosed metabolic and cardiovascular comorbidities of LP patients and HC.

Diagnosis	Number of LP patients (%)	Number of HC (%)
Cardiovascular		
Hypertension	16 (50)	13 (40.6)
Atherosclerosis	2 (6.3)	1 (3.1)
Stenocardia	1 (3.1)	
Congestive heart failure	1 (3.1)	1 (3.1)
Atrial fibrillation	1 (3.1)	
Metabolic		
Type 2 diabetes	2 (6.3)	3 (9.4)
Hypothyroidism	4 (12.5)	
Pure hypercholesterolemia		1 (3.1)
Infectious		
Chronic hepatitis C infection	2 (6.3)	

12. SUMMARY IN ESTONIAN

Krooniliste põletikuliste dermatooside metaboloomiline profileerimine

12.1. Üldteoreetiline taust

Käesoleva uuringu raames uurisime kolme kroonilise põletikulise nahahaiguse – psoriaasi, atoopilise dermatiidi ja lameda lihheni – metaboloomilist profiili.

Psoriaasi iseloomustab erütematoos-skvamoossete naastude teke nahale ning sageli kaasneb küünte ja liigeste haaratus, samuti on psoriaasi korral tõusnud risk haigestuda mitmesse teisesesse haigusesse, näiteks kardiovaskulaarhaigustesse, diabeeti ja põletikulisse soolehaigusesse. Psoriaasil on tugev negatiivne mõju patsientide elukvaliteedile. Haiguse patogeneesis on olulisel kohal Th1/Th17 raja haaratus ning kaasasündinud ja omandatud immuunsuse düsregulatsioon. Kuigi bioloogiline ravi on efektiivne ja aina laialdasemalt kasutatavam, vajab osa patsiente primaarse või sekundaarse ebaefektiivsuse tõttu mitmeid ravimi vahetusi. Uuringud metaboloomika vallas annavad haiguse patogeneesist ja organismis toimuvatest muutustest täpsema ülevaate, tänu millele võiks tulevikus saada teha suunitletumaid ravivalikuid.

Atoopiline dermatiit on samuti sageli esinev krooniline põletikuline dermatoos, millele on iseloomulik kuiv ja sügelev nahk ning lööbe teke eelistatud kehapiirkondadesse vastavalt patsiendi eale. Tihti kaasuvad allergiline rinokonjunktiviit ja astma, kuid neil on suurem risk ka depressiooni, ärevuse ja kardiovaskulaarhaiguste tekkeks ning patsientide elukvaliteet on langenud. Atoopilise dermatiidi puhune põletik on kahefaasiline, olles ägedas faasis kallutatud Th2 suunas ning kroonilises faasis Th1 suunas. Võrreldes psoriaasiga on atoopilise dermatiidi raviks vähem ravivõimalusi ning metaboloomilistest muutustest arusaamine aitab loodetavasti tulevikus enam ravivõimalusi välja töötada.

Lameda lihheni puhul tekivad väga sügelevad polügonaalsed lillakad paapulid eelistatult randmete painutuspindadele, säärtele ja sakraalpiirkonda, kuid lööve võib paikneda ka dissemineerunult üle keha. Kaasuvatest haigustest esineb neil patsientidel sagedamini näiteks hepatiit C infektsiooni, metaboolset sündroomi ja düslipideemiat, samuti on tõusnud risk haigestuda kardiovaskulaarhaigustesse. Meile teadaolevalt ei ole varasemalt lameda lihheni puhuseid muutusi lipoproteiinide koostises uuritud, küll aga võivad nimetatud muutused häirida nende funktsiooni ning mõjutada nii lameda lihheni kui kaasuvate haiguste väljakujunemist.

Metaboloomika on üks „oomika“ harudest, mis tegeleb metaboliitide, näiteks aminohapete, lipiidide ja biogeensete amiinide profileerimisega, peegeldades selle kaudu organismis toimuvaid bioloogilisi protsesse. Metaboloomikat kasutatakse tihti erinevate seisundite biomarkerite leidmiseks, et iseloomustada ja täpsustada normaalsete või patoloogiliste protsesside mehhanisme.

12.2. Uurimuse põhieesmärgid

Antud doktoritöö eesmärgiks oli kindlaks määrata krooniliste põletikuliste dermatooside – psoriaasi, atoopilise dermatiidi ja lameda lihheni – naha ja vere metaboloomiline profiil, et täpsustada antud haiguste patogeneetilisi mehhanisme.

Täpsemalt oli eesmärkideks:

1. Võrrelda psoriaasiga patsientide ja tervete kontrollide naha metaboloomilist profiili leidmaks psoriaasile iseloomulikke metaboloomilisi biomarkereid.
2. Võrrelda atoopilise dermatiidiga patsientide ja tervete kontrollide naha metaboloomilist profiili leidmaks atoopilisele dermatiidile iseloomulikke metaboloomilisi biomarkereid.
3. Võrrelda psoriaasi ja atoopilise dermatiidiga patsientide naha ja vereseerumi metaboloomilisi profiile, et leida nimetatud kahe sagedase kroonilise põletikulise dermatoosi vahel võimalikke sarnasusi ja erinevusi.
4. Selgitada välja lameda lihheniga patsientide vereseerumi metaboloomiline profiil ja võrrelda seda tervete kontrollide vereseerumiga.

12.3. Uuritavate grupid ja metoodika

Psoriaasi naha metaboloomilise profiili uuringusse kaasasime 20 psoriaasiga patsienti ja 19 vanuse ja soo osas vastavat kontrolli. Atoopilise dermatiidi naha metaboloomilise profiili uuringusse kaasasime 15 atoopilise dermatiidiga patsienti ja 17 kontrolli. Võrdlemaks psoriaasi ja atoopilise dermatiidiga patsientide vereseerumite metaboloomikat, kaasasime 55 psoriaasiga patsienti ja 25 atoopilise dermatiidiga patsienti. Lameda lihheni vereseerumi metaboliitide, lipoproteiinide ja lipoproteiinide partiklite uurimiseks kaasasime 32 lameda lihheniga patsienti ja 32 kontrolli. Kõik patsiendid ja kontrollgrupi liikmed allkirjastasid informeeritud nõusoleku vormi.

Psoriaasi ja atoopilise dermatiidi patsientide naha uurimiseks võeti enne hommikusööki 3 mm puuriga biopsiad nii haiguskoldest kui lähedalasuvast visuaalselt tervest nahast ning kontrollide puhul sarnastest, päikesele mitteavatud piirkondadest, mille järgselt bioptaadid külmutati koheselt vedellämmastikus ja asetati –80 °C juurde hoiule. Nahabiopsiate kogumine vältas 3 aastat, seejärel toimus metaboliitide eraldamine ja suunatud määramine mass-spektromeetria abil, kasutades *AbsoluteIDQ p180* analüüsikomplekti.

Psoriaasi, atoopilise dermatiidi, lameda lihheni ning neile vanuse ja soo poolest vastavate kontrollide vereseerumi uurimiseks koguti vereanalüüs enne hommikusööki 5 ml Vacutainer (REF 367614) katsutitesse, jäeti tunniks toatemperatuurile hüübima ning seejärel tsentrifuugiti 20 minutit. Seerum jagati 300 µl alikvootideks ning hoiustati kuni analüüsimiseni –80 °C juures. Psoriaasi ja atoopilise dermatiidi patsientide vereseerumite metaboliidid määrati suunatult mass-spektromeetria abil. Lameda lihheni ja kontrollide vereseerumi metaboliitide

suunatud määramiseks kasutati suure läbilaskevõimega tuumamagnetresonants-spektroskoopiat (*high-throughput NMR spectroscopy*).

Statistilise analüüsi läbiviimiseks kasutati programmi R (I, II ja III artikli puhul versiooni 3.5.1, IV artikli puhul versiooni 4.1.3). Metaboliitide gruppide vaheliste erinevuste leidmiseks kasutati Kruskal-Wallise ja Wilcoxon–Mann–Whitney teste.

12.4. Tulemused ja arutelu

Psoriaasiga patsientide haiguskolde naha, näiliselt terve naha ja kontrollide naha metaboloomilise profiili võrdluses leidsime 29 metaboliiti, mille tase erines gruppide vahel statistiliselt oluliselt. 17 metaboliidi tase (Glu, Met, Arg, spermidiin, putrestsiin, atsüülkarnitiinid C5, C18.2, C16 ja C18, ADMA, dimetüülarginiinid, histamiin ja mitmed fosfatidüülkoliinid) oli PS-L nahas tõusnud ning kaks metaboliitide suhet (tsitrulliini suhe ornitiini ning ornitiini suhe Arg-i) langenud võrreldes kontrollgrupiga. 14 metaboliidi tase (C5, C18.2, C16, spermidiin, Glu, Met, ADMA, putrestsiin, dimetüülarginiinid, Arg ja neli fosfatidüülkoliini) oli PS-L nahas tõusnud võrreldes nii PS-NL kui kontrollgrupi nahaga. 9 metaboliidi kontsentratsioon (C2, C18.1, Lys, Leu, Fisheri suhe, Met.SO, Phe, lüsofosfatidüülkoliin atsüül C16:1 ja fosfatidüülkoliin diatsüül C42.4) oli tõusnud ja tsitrulliini suhe ornitiini langenud PS-L nahas võrrelduna PS-NL nahaga. PS-NL ja kontrollgrupi naha vahel erinevusi ei leidunud. Analüüsist nähtub, et PS-L naha metaboloomiline profiil eristub PS-NL ja kontrollgrupi naha metaboloomilisest profiilist. PASI väärtuse ja PS-L nahas leiduvate metaboliitide tasemete vahel statistiliselt olulist korrelatsiooni ei leidunud.

PS-L nahas tõusnud Glu tase võib väljendada suurenenud glutamiini nõudlust, mis tekib PS-le omase keratinotsüütide hüperproliferatsiooni, immuunrakkude suurenenud aktiivsuse ja valgusünteesi kiirenemise puhul. Nii Glu kui Phe kõrgemaid tasemeid on leitud varasemalt ka PS patsientide veres. Lys taseme tõusu saab seostada kollageeni suurenenud tootmise ja L-karnitiini sünteesi intensiivistumisega. Fisheri suhe väljendab hargnenud ahelaga aminohapete Leu, Val ja Ile molaarset suhet aromaatsetesse aminohapetesse Phe ja Tyr-i. Hargnenud ahelaga aminohapetel on oluline roll dendriitrakkude küpsemisel ja neid on vaja lümfotsüütide proliferatsioonil. PS-L nahas leidsime ka kõrgema Met taseme, kuid Met sulfoksiidi tase, mis viitaks oksüdatiivsele stressile, ei olnud tõusnud – seega ei ole psoriaasikolletes tõenäoliselt liigset valkudega seotud oksüdatiivset stressi. Lisaks aitavad polüamiinid, mille hulgas PS-L nahas leidsime putrestsiini ja spermidiini kõrgema taseme, oksüdatiivse kahjustuse vastu kaitsta. Muuhulgas on neid vaja rakkude kasvuks, diferentseerumiseks ja paljunemiseks, ning polüamiine toodetakse ulatuslikult rakkude jagunemise käigus, mis sobitub hästi PS hüperproliferatiivse staatusega. Uurea tsükliga seotud metaboliitide tasemete ja suhete muutused viitavad valkude tsitrullineerimise häirele ja ornitiini karbamoüültransferaasi vähenenud aktiivsusele. Samuti on PS patsientide veres varasemates uuringutes leitud kõrgemaid ADMA tasemeid ning positiivne korrelatsioon haiguse raskusega. PS-L nahas oli ka kõrgem histamiini tase. Histamiin

on tuntud sügeluse mediaator ning kuni 80% PS patsientidest kaebab sügeluse üle, seega võib rohkenenud histamiini hulk vähemalt osaliselt olla PS patsientidel nahasügeluse põhjuseks. Atsüülkarnitiinide taseme tõus viitab suurenenud rakulisele stressile psoriaasikolletes ja sealsele proinflammatoorsele seisundile. Hüperproliferatsiooniga korreleerub hästi ka glütserofosfolipiidide kontsentratsiooni tõus PS-L nahas, samuti on leitud, et lüsofosfatidüülkoliinid soodustavad kroonilist põletikku ja säilitavad seda T-lümfotsüütide kemotaksise kaudu. Nähtub, et PS haiguskolde naha metaboloomilist profiili iseloomustavad eelkõige intensiivistunud rakujagunemine ja põletik.

Atoopilise dermatiidiga patsientide haiguskolde ja näiliselt terve naha ning tervete kontrollide metaboloomilise profiili võrdlemisel leidsime 77 metaboliiti ja nende suhet, mis kolme grupi omavahelises võrdluses statistiliselt oluliselt erinesid. Metaboliidid kuulusid biogeensete amiinide, aminohapete, atsüülkarnitiinide, fosfatidüülkoliinide ja sfingomüeliinide gruppidesse. Võrreldes tervete kontrollide nahaga leidsime 21 metaboliiti (putrestsiin, Glu, Met, mitmed fosfatidüülkoliinid ja sfingomüeliinid), mille tasemed olid AD-L nahas kõrgemad, ja kaks metaboliitide suhet (tsitrulliini suhe arginiini ja tsitrulliini suhe ornitiini), mis olid AD-L nahas madalamad. Samad metaboliitide suhted olid madalamad ka AD-L nahas võrrelduna AD-NL nahaga. Võrreldes AD-NL nahaga, oli AD-L nahas tõusnud 73 metaboliidi tase, mille hulgas oli nii aminohappeid, biogeenseid amiine, atsüülkarnitiine, fosfatidüülkoliine kui sfingomüeliine. AD-NL ja kontrollgrupi nahkade metaboloomilise profiili vahel erinevusi ei leidunud. Seega eristub AD haiguskolde naha metaboloomiline profiil selgelt näiliselt terve naha ja kontrollgrupi naha metaboloomilisest profiilist.

Nagu ka PS haiguskolde nahas, leidsime AD haiguskolde nahas kõrgema putrestsiini taseme, mis on lisaks teistele funktsioonidele, nagu rakkude kasv ja paljunemine, kaasatud ka põletikulistesse protsessidesse. Põletikku ja häireid metaboolses tasakaalus peegeldab samuti ADMA taseme tõus ning nii ADMA kui SDMA kõrgemat taset on leitud erinevate haiguste puhul, näiteks kroonilise neeruhaiguse ja ateroskleroosi korral. Kuna ADMA inhibeerib lämmastikoksiidi süntaasi, on tsitrulliini biosüntees arginiinist vähenenud. See viib omakorda Arg taseme tõusule ning vähendab tsitrulliini suhet arginiini. Ka varasemalt on leitud AD-ga laste vereplasmas arginaas 1 aktiivsuse langust ning Arg taseme tõusu. Aminohapetest olid muutunud ka Asn ja Glu tasemed. Mõlemad on vajalikud valgu sünteesis, lisaks on Asn-l roll aju arengus ja Glu on nii oluline neurotransmitter, kui ka seotud põletikuga. Met, kuid mitte sulfoksideeritud Met taseme tõus võib viidata ka antioksüdatiivsete ühendite puudulikule sünteesile, kuna Met oksüdeerimine sulfoksideeritud Met-ks ja konversioon tsüsteiiniks kaitseks vabade hapniku radikaalide eest. Samuti läheb Met koos Lys-ga tarvis karnitiini sünteesiks, mis on vajalik rasvhapete metabolismis, võimaldades transportida pika ahelaga rasvhappeid läbi sisemise mitokondriaalse membraani, mille järgselt toimub nende β-oksüdatsioon. On teada, et AD puhul on nahabarjäär ja tseramiidide süntees häiritud. See ühtib tõusnud sfingomüeliinide tasemega AD-L nahas, peegeldades sfingomüelinaasi vähenenud aktiivsust, mis sünteesib sfingo-

müeliinidest tseramiide. Nii sfingomüeliinid kui fosfatidüülkoliinid on nii strukturaalsed komponendid kui ka bioaktiivsete ühendite allikad. Kõrgemaid fosfatidüülkoliinide tasemeid võib selgitada varasemalt leitud puuduliku fosfatidüülkoliini-sfingomüeliini transatsülaasi tasemega. Lisaks toimivad lüsofosfatidüülkoliinid kemoatraktantidena, soodustades T-lümfotsüütide epidermisesse migreerumist. Kokkuvõtvalt viitavad AD haiguskoldes olevad metaboloomilised muutused suurenenud oksüdatiivsele stressile, põletikule ja häirunud nahabarjäärile.

Psoriaasi ja atoopilise dermatiidiga patsientide haiguskollete naha metaboliitide omavahelisel võrdlusel leidsime 19 statistiliselt oluliselt erinevat metaboliiti ja nende suhet. AD-L nahas olid võrreldes PS-L nahaga kõrgemad sfingomüeliinide tasemed ning ornitiini suhe arginiini. PS-L nahas olid ADMA, C2, C18.2 ja glütserofosfolipiidide tasemed kõrgemad kui AD-L nahas. Näiliselt tervete nahkade võrdluses oli PS-NL nahas kõrgem C2 tase kui AD-NL nahas. Vereseerumite võrdluses leidsime 5 metaboliiti, mille kontsentratsioonid olid kõrgemad PS patsientide veres: tsitrulliin, Glu, proliin, C0 ja C18.1.

Sfingomüeliinid ja fosfatidüülkoliinid on membraanide struktuursed komponendid ning ühtlasi ka allikaks bioaktiivsetele ühenditele, mis osalevad erinevates protsessides diferentseerumisest kuni apoptoosi inhibeerimise või soodustamiseni. Arahhidoonhape on üks olulistest signaalmolekulidest, mida saab fosfatidüülkoliinidest sünteesida, ning mida metaboliseeritakse edasi prostaglandiinideks ja leukotrieenideks – mitmeid neist on PS-L nahas varasemalt ka kõrgemates kontsentratsioonides leitud. Kõrgemaid C2 ja C18.2 tasemeid PS-L nahas võrrelduna AD-L nahaga ning kõrgemat C2 kontsentratsiooni PS-NL nahas võrrelduna AD-NL nahaga võib selgitada psoriaasile iseloomuliku hüperproliferatiivse epidermise ja sellest johtuvalt suurema energiavajadusega, mida aitab katta mitokondrites toimuv β-oksüdatsioon. Ka PS patsientide vereseerumis olid C0 ja C18.1 tasemed kõrgemad kui AD patsientide omas. Lisaks oli PS patsientide veres aminohapete tase kõrgem. Glu kõrgemaid tasemeid on leitud ka teiste põletikuliste haiguste, näiteks ateroskleroosi ja mittealkohoolse rasvmaksa puhul – haigused, mida esineb PS-ga patsientide seas sagedamini. PS patogeneesi üks olulisemaid tsütokiine, IL-17, võib aga mõjutada uurea tsükli metaboliitide tasakaalu. Seega esinevad nii PS kui AD patsientide nahas kui veres selged, vastavate haiguste patogeneesile omased metaboloomilised mustrid.

Lameda lihheni metaboloomilise profiili analüüsimisel leidsime 16 lipoproteiinidega seotud markerit, mis eristusid statistiliselt oluliselt tervete kontrollide markeritest. Nii keskmise tihedusega lipoproteiinide (*intermediate-density lipoproteins*, IDL), madala tihedusega lipoproteiinide (*low-density lipoproteins*; LDL) kui suurte LDL partiklite komponentide hulgas esinesid muutused, näiteks fosfolipiidide, kolesterooli estrite, vaba ja kogu kolesterooli ning kogu lipiidide hulgas. Väiksemaid, statistiliselt ebaolulisi muutusi esines ka kõrge tihedusega lipoproteiinide (*high-density lipoproteins*, HDL) ja väga madala tihedusega lipoproteiinide (*very-low-density lipoproteins*, VLDL) komponentide hulgas.

Teadaolevalt on lameda lihheni kaasuvateks haigusteks metaboolne sündroom ja üks selle komponentidest, düslipideemia. Varasemalt on leitud, et kõrgema

L-LDL ja väikese-LDL (*small-LDL*, S-LDL) tasemega patsientidel on suremuse risk mistahes haigustesse, kaasa arvatud kardiovaskulaarhaigustesse, suurem kui keskmise suurusega LDL (*intermediate-size LDL*) puhul. Samuti on suurenenud risk surra kardiovaskulaarhaigustesse patsientidel, kelle LDL partiklid koosnevad rohkematest sfingolipiididest ja vähematest fosfatidüülkoliinidest, kuna taolised muutused suurendavad LDL agregatsiooni. HDL kohta tehtud uuringutes on leitud, et näiteks koronaararterite haiguse, reumaatiliste haiguste, metaboolse sündroomi ja diabeedi korral esinevad HDL partiklites muutused, mistõttu on muutunud ka HDL funktsionaalsed omadused. Seetõttu võib järeldada, et lipoproteiinide partiklites tekkivad muutused võivad põhjustada nii suuremat kaasuvate haiguste (s.h metaboolse sündroomi ja düslipideemia) riski kui ka ise neist tingitud olla. LDL ja IDL partiklite muutuste korral on nende ülesvõtmine maksa poolt häiritud, mis võib omakorda tõsta kardiovaskulaarset riski. Meie tulemused toetavad ka lameda lihheniga patsientide rutiinset skriinimist düslipideemia suhtes.

12.5. Järeldused

1. Leidsime, et psoriaasi haiguskollete nahale on iseloomulikud hüperproliferatsioonile ja põletikule omased metaboloomilised muutused. Psoriaasi haiguskolde nahk eristus selgelt näiliselt tervest nahast ja tervete kontrollide nahast. Metaboloomiliste muutuste peamiseks põhjuseks võivad olla lokaalsed põletikulised protsessid, mis soodustavad rakkude hüperproliferatsiooni.
2. Atoopilise dermatiidi haiguskollete naha metaboloomilist profiili iseloomustas põletik, suurenenud vastuvõtlikkus oksüdatiivsele stressile ja häiritud naha barjäärfunktsioon. Atoopilise dermatiidiga patsientide naha haiguskollete metaboloomiline profiil eristus näiliselt terve naha ja tervete kontrollide naha metaboloomilisest profiilist ning me ei leidnud statistiliselt olulisi erinevusi ka näiliselt terve naha ja tervete kontrollide naha metaboloomilise profiili vahel.
3. Psoriaasi ja atoopilise dermatiidiga patsientide naha metaboloomilise profiili võrdluses leidsime, et peamised erinevused seisnesid psoriaasipuhuses suurenenud rakkude paljunemises ning atoopilise dermatiidi korral esinevas häirunud naha barjäärfunktsioonis. Vereseerumite võrdluses esines samuti viiteid psoriaasile iseloomulikule rakkude hüperproliferatsioonile. Erinevused haiguste metaboloomilises profiilis korreleeruvad nende patogeneetiliste mehhanismidega.
4. Lameda lihheniga patsientide vereseerumi metaboloomiline analüüs väljendas muutusi lipoproteiinide koostises, täpsemalt IDL, LDL ja L-LDL koostises. Antud muutused võivad põhjustada kaasuvate haiguste, nagu metaboolne sündroom ja düslipideemia, suurenenud riski, ning ka ise olla neist tingitud.

Täpsustamaks psoriaasi, atoopilise dermatiidi ja lameda lihheni ning nende kaasuvate haiguste vahelisi seoseid, on selles vallas vajalikud edasised uuringud.

13. ACKNOWLEDGEMENTS

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Above all, I am truly grateful to my family for being there for me all the time: my dear husband Norman and daughter Laura, beloved parents Kaja and Asko, dear brother Karl and the rest of my family, including Sirje, Tiiu, Vello, Anneli, Tõnis, Kaili, Piret, Paul, Mihkel, Harald, Kelli and Uku. Your support and presence has always meant a lot to me.

14. PUBLICATIONS

15. CURRICULUM VITAE

Name:	Liis Ilves (Née Pohla)
E-mail:	liis.ilves@ut.ee
Mother tongue:	Estonian
Education:	MD

Education

2018–...	University of Tartu, Doctoral studies in Medicine
2017–2021	University of Tartu, Dermatovenereology residency
2011–2017	University of Tartu, Medicine
1999–2011	Tallinn School No 21
2000–2007	Tallinn Music School

Work Experience

2022 April – ...	Confido Medical Center, dermatovenereologist
2022 March – ...	Tartu University Hospital, Dermatology Clinic of Tartu University Hospital, specialist in dermatovenereology
2019 Jul – 2020 Dec	University of Tartu, Junior Research Fellow of Clinical Medicine (0.5)
2017 Sept – 2021 Nov	Tartu University Hospital, South-Estonian Hospital, East Tallinn Central Hospital, West Tallinn Central Hospital, The North Estonia Medical Centre, Tallinn Children's Hospital, resident
2015 Jan–Feb	North Estonia Medical Centre, Surgery Clinic, Orthopaedics Centre, assistant nurse

Other languages

English	speaking: good; writing: good; understanding: good
Russian	speaking: intermediate; writing: intermediate; understanding: intermediate

Associations

European Academy of Dermatology and Venereology (since 2019)
Estonian Society for Dermatovenereologists (ENSAS) (since 2018)
Estonian Junior Doctors' Association (since 2017)
Estonian Medical Students' Association (2011–2017)

Training

10.02.2023	ENSAS conference
11.11.2022	ENSAS conference
25.–26.08.2022	7th Nordic Course on Skin Surgery (Copenhagen)
16.–17.06.2022	2nd Nordic Course on Laser Dermatology (Copenhagen)
12.–14.05.2022	EADV Spring Symposium 2022 (Ljubljana)
11.02.2022	ENSAS conference
29.09–02.10.2021	EADV 2021 Congress (web)
21.05.2021	ENSAS conference (presentation)
12.02.2021	ENSAS conference
20.11.2020	ENSAS conference (web)
12.–14.10.2020	EADO 2020 Congress (web)
14.02.2020	ENSAS conference
09.–13.10.2019	EADV 2019 Congress (Madrid)
04.–07.09.2019	IUSTI Europe Congress on Sexually Transmitted Diseases (Tallinn)
07.06.2019	ENSAS conference – dermoscopy
25.05.2019	Dermoscopy Course (Warsaw)
28.–29.03.2019	Nordic Dermoscopy Course 2019 (Göteborg)
15.02.2019	ENSAS conference
14.02.2019	Conference of Biologic Treatment
20.–23.11.2019	Euroderm Excellence (Nizza)
16.11.2018	ENSAS conference (presentation)
25.05.2018	ENSAS conference – cryosurgery
03.11.2017	Internal Medicine XV conference in East Tallinn Central Hospital
04.11.2016	Internal Medicine XVI conference in East Tallinn Central Hospital

Honours and awards

2022, Liis Ilves, Michael Hornstein Memorial Scholarship

2021, Liis Ilves, Liisa Kolumbus's Memorial Scholarship

2020, Liis Ilves, „Atoopilist dermatiiti põdevate patsientide naha metaboloomilises analüüsis esineb häirunud nahabarjäärile ja oksüdatiivsele stressile iseloomulikke muutusi", The Scientific Conference of the anniversary of the Faculty of Medicine of the University of Tartu, Award of the best oral e-poster presentation among doctoral students.

2020, Liis Ilves, Aigar Ottas, Bret Kaldvee, Kristi Abram, Ursel Soomets, Mihkel Zilmer, Viljar Jaks, Külli Kingo, „Atoopilist dermatiiti põdevate patsientide naha metaboloomilises analüüsis esineb häirunud nahabarjäärile ja oksüdatiivsele stressile iseloomulikke muutusi", Award of Tartu University Hospital

Additional information

Participated in Melanoma Day in Kuressaare (2018), Tallinn (2019) and Pärnu (2023).

Publications

Ilves, L., Eisen, M. Psoriaasi ravivõimalused EuroGuiDermi juhendi põhjal Eesti oludele kohandatuna. Lege Artis, February 2023.

Ilves, L., Ottas, A., Raam, L., Zilmer, M., Traks, T., Jaks, V., Kingo, K. Changes in Lipoprotein Particles in the Blood Serum of Patients with Lichen Planus. Metabolites 2023, 13(1), 91.

Ilves, L., Ottas, A., Kaldvee, B., Abram, K., Soomets, U., Zilmer, M., Jaks, V., Kingo, K. Metabolomic Differences between the Skin and Blood Sera of Atopic Dermatitis and Psoriasis. International Journal of Molecular Sciences 2022 Oct 27;23(21):12001.

Ilves, L., Ottas, A., Kaldvee, B., Abram, K., Soomets, U., Zilmer, M., Jaks, V., Kingo, K. Metabolomic analysis of skin biopsies from patients with atopic dermatitis reveals hallmarks of inflammation, disrupted barrier function and oxidative stress. Acta Dermato-Venereologica 2021 Feb 24;101(2):adv00407.

Ilves L, Uusküla A, Juus E, Kiivet R. Bioloogilised ravimid psoriaasi ravis. TTH47. Tartu Ülikooli peremeditsiini ja rahvatervishoiu instituut; 2020.

Ilves, L. Dermatoloogilised probleemid eakatel. Pereõde, November 2020.

Pohla, L, Ottas, A., Kaldvee, B. et al. Hyperproliferation is the main driver of metabolomic changes in psoriasis lesional skin. Scientific Reports 10, 3081 (2020).

Pohla, L, Karelson, M. Pemphigus foliaceus ehk lehtketendav villtõbi. Haigus-juhu kirjeldus ja ülevaade. Eesti Arst, November 2019.

Pohla, L. Atoopiline dermatiit on sageli atoopilise marsi esmane väljendus. Lege Artis, March 2019.

Pohla, L. Atoopilisse dermatiiti haigestumus on viimaste aastakümnete jooksul suurenenud. Perearst, December 2018.

Pohla, L, Karelson, M. Urtikaariat põeb elu jooksul umbes viiendik rahvastikust. Perearst, September 2018.

Pohla, L. Naha seenhaigus. Perearst, January 2018.

Pohla, L, Pärna, E. Nodoosne erüteem on enamasti iselimiteeruv. Perearst, December 2017.

Pohla, L, Karelson, M. Mitmevärvilise kliiketendustõve ravis on eelistatavad lokaalsed ravimid. Apteeker, November 2017.

16. ELULOOKIRJELDUS

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Emakeel:	eesti
Haridustase:	kõrgharidus

Hariduskäik

2018–...	Tartu Ülikool, doktorantuur arstiteaduses
2017–2021	Tartu Ülikool, residentuur dermatoveneroloogia erialal
2011–2017	Tartu Ülikool, meditsiiniteaduste valdkond, eriala: arstiteadus
1999–2011	Tallinna 21. Kool, hõbemedal
2000–2007	Tallinna Muusikakool

Teenistuskäik

2022 aprill – ...	Confido Meditsiinikeskus, dermatoveneroloog
2022 märts – ...	SA Tartu Ülikooli Kliinikum, arst-õppejõud dermatoveneroloogia erialal
2019 juuli – 2020 dets	Tartu Ülikool, meditsiiniteaduste valdkond, Kliinilise meditsiini instituut, kliinilise meditsiini nooremteadur (0,50)
2017 sept – 2021 nov	SA Tartu Ülikooli Kliinikum, Lõuna-Eesti Haigla AS, SA Ida-Tallinna Keskhaigla, SA Põhja-Eesti Regionaalhaigla, AS Lääne-Tallinna Keskhaigla, SA Tallinna Lastehaigla, arst-resident
2015 jaan – veebr	SA Põhja-Eesti Regionaalhaigla, Kirurgiakliinik, III Ortopeedia osakond, abiõde.

Võõrkeelteoskus

Inglise keel	kõnes: hea kirjas: väga hea arusaamine: väga hea
Vene keel	kõnes: keskminekirjas: vähene arusaamine: keskmine

Kuuluvus ühendustesse

European Academy of Dermatology and Venereology (alates 2019)
Eesti Naha- ja Suguhaiguste Arstide Selts (alates 2018)
Eesti Nooremarstide Ühendus (alates 2017)
Eesti Arstiteadusüliõpilaste Selts (2011–2017)

Koolitused

10.02.2023	ENSAS konverents
11.11.2022	ENSAS konverents
25.–26.08.2022	7th Nordic Course on Skin Surgery (Kopenhaagen)
16.–17.06.2022	2nd Nordic Course on Laser Dermatology (Kopenhaagen)
12.–14.05.2022	EADV Spring Symposium 2022 (Ljubljana)
11.02.2022	ENSAS konverents
19.11.2021	ENSAS konverents
29.09–02.10.2021	EADV 2021 kongress (veebipõhine)
21.05.2021	ENSAS konverents (ettekanne)
12.02.2021	ENSAS konverents
20.11.2020	ENSAS konverents (veebipõhine)
12.–14.10.2020	EADO 2020 kongress (veebipõhine)
07.–08.09.2020	Ida-Tallinna Keskhaigla Tromboosikoolitus
14.02.2020	ENSAS konverents
09.–13.10.2019	EADV 2019 kongress (Madrid)
04.–07.09.2019	33. IUSTI Euroopa kongress (Tallinn)
07.06.2019	ENSAS konverents – dermatoskoopia
25.05.2019	Dermatoskoopia kursus (Varssavi)
28.–29.03.2019	Nordic Dermoscopy Course 2019 (Göteborg)
15.02.2019	ENSAS konverents
14.02.2019	Bioloogilise ravi konverents
20.–23.11.2018	Euroderm Excellence (Nizza)
16.11.2018	ENSAS konverents (ettekanne)
25.05.2018	ENSAS konverents – krüokirurgia
03.11.2017	Ida-Tallinna Keskhaigla Sisekliiniku XV konverents
04.11.2016	Ida-Tallinna Keskhaigla Sisekliiniku XIV konverents

Tunnustused, stipendiumid

2022, Liis Ilves, Michael Hornstein Memorial Scholarship

2021, Liis Ilves, Liisa Kolumbuse Mälestusfondi stipendium

2020, Liis Ilves, „Atoopilist dermatiiti põdevate patsientide naha metaboloomilises analüüsis esineb häirunud nahabarjäärile ja oksüdatiivsele stressile iseloomulikke muutusi“, Tartu Ülikooli Arstiteaduskonna teaduskonverentsi parim doktorantide e-postri tutvustus

2020, Liis Ilves, Aigar Ottas, Bret Kaldvee, Kristi Abram, Ursel Soomets, Mihkel Zilmer, Viljar Jaks, Külli Kingo, „Atoopilist dermatiiti põdevate patsientide naha metaboloomilises analüüsis esineb häirunud nahabarjäärile ja oksüdatiivsele stressile iseloomulikke muutusi“, Tartu Ülikooli Kliinikumi teadustöö preemia

Lisainfo

Osalenud Melanoomipäeval Saaremaal (2018), Tallinnas (2019) ja Pärnus (2023).

Publikatsioonid

Ilves, L., Eisen, M. Psoriaasi ravivõimalused EuroGuiDermi juhendi põhjal Eesti oludele kohandatuna. Lege Artis, veebruar 2023.

Ilves, L., Ottas, A., Raam, L., Zilmer, M., Traks, T., Jaks, V., Kingo, K. Changes in Lipoprotein Particles in the Blood Serum of Patients with Lichen Planus. Metabolites 2023, 13(1), 91.

Ilves, L., Ottas, A., Kaldvee, B., Abram, K., Soomets, U., Zilmer, M., Jaks, V., Kingo, K. Metabolomic Differences between the Skin and Blood Sera of Atopic Dermatitis and Psoriasis. International Journal of Molecular Sciences 2022 Oct 27;23(21):12001.

Ilves, L., Ottas, A., Kaldvee, B., Abram, K., Soomets, U., Zilmer, M., Jaks, V., Kingo, K. Metabolomic analysis of skin biopsies from patients with atopic dermatitis reveals hallmarks of inflammation, disrupted barrier function and oxidative stress. Acta Dermato-Venereologica 2021 Feb 24;101(2):adv00407.

Ilves L, Uusküla A, Juus E, Kiivet R. Bioloogilised ravimid psoriaasi ravis. TTH47. Tartu Ülikooli peremeditsiini ja rahvatervishoiu instituut; 2020.

Ilves, L. Dermatoloogilised probleemid eakatel. Pereõde, november 2020.

Pohla, L., Ottas, A., Kaldvee, B., Abram, K., Soomets, U., Zilmer, M., Jaks, V., Kingo, K. Hyperproliferation is the main driver of metabolomic changes in psoriasis lesional skin. Scientific Reports 10, 3081 (2020).

Pohla, L., Karelson, M. Pemphigus foliaceus ehk lehtketendav villtõbi. Haigusjuhu kirjeldus ja ülevaade. Eesti Arst, november 2019.

Pohla, L. Atoopiline dermatiit on sageli atoopilise marsi esmane väljendus. Lege Artis, märts 2019.

Pohla, L. Atoopilisse dermatiiti haigestumus on viimaste aastakümnete jooksul suurenenud. Perearst, detsember 2018.

Pohla, L., Karelson, M. Urtikaariat põeb elu jooksul umbes viiendik rahvastikust. Perearst, september 2018.

Pohla, L. Naha seenhaigus. Perearst, jaanuar 2018.

Pohla, L., Pärna, E. Nodoosne erüteem on enamasti iselimiteeruv. Perearst, detsember 2017.

Pohla, L., Karelson, M. Mitmevärvilise kliiketendustõve ravis on eelistatavad lokaalsed ravimid. Apteeker, november 2017.

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1. **Heidi-Ingrid Maaroos**. The natural course of gastric ulcer in connection with chronic gastritis and *Helicobacter pylori*. Tartu, 1991.
2. **Mihkel Zilmer**. Na-pump in normal and tumorous brain tissues: Structural, functional and tumorigenesis aspects. Tartu, 1991.
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20. **Tõnis Karki**. Quantitative composition of the human lactoflora and method for its examination. Tartu, 1996.
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24. **Paavo Pokk**. Stress due to sleep deprivation: focus on $GABA_A$ receptor-chloride ionophore complex. Tartu, 1996.
25. **Kristina Allikmets**. Renin system activity in essential hypertension. Associations with atherothrombogenic cardiovascular risk factors and with the efficacy of calcium antagonist treatment. Tartu, 1996.
26. **Triin Parik**. Oxidative stress in essential hypertension: Associations with metabolic disturbances and the effects of calcium antagonist treatment. Tartu, 1996.
27. **Svetlana Päi**. Factors promoting heterogeneity of the course of rheumatoid arthritis. Tartu, 1997.
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29. **Paul Naaber**. *Clostridium difficile* infection and intestinal microbial ecology. Tartu, 1997.
30. **Rein Pähkla**. Studies in pinoline pharmacology. Tartu, 1997.
31. **Andrus Juhan Voitk**. Outpatient laparoscopic cholecystectomy. Tartu, 1997.
32. **Joel Starkopf**. Oxidative stress and ischaemia-reperfusion of the heart. Tartu, 1997.
33. **Janika Kõrv**. Incidence, case-fatality and outcome of stroke. Tartu, 1998.
34. **Ülla Linnamägi**. Changes in local cerebral blood flow and lipid peroxidation following lead exposure in experiment. Tartu, 1998.
35. **Ave Minajeva**. Sarcoplasmic reticulum function: comparison of atrial and ventricular myocardium. Tartu, 1998.
36. **Oleg Milenin**. Reconstruction of cervical part of esophagus by revascularised ileal autografts in dogs. A new complex multistage method. Tartu, 1998.
37. **Sergei Pakriev**. Prevalence of depression, harmful use of alcohol and alcohol dependence among rural population in Udmurtia. Tartu, 1998.
38. **Allen Kaasik**. Thyroid hormone control over β-adrenergic signalling system in rat atria. Tartu, 1998.
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40. **Maire Vasar**. Allergic diseases and bronchial hyperreactivity in Estonian children in relation to environmental influences. Tartu, 1998.
41. **Kaja Julge**. Humoral immune responses to allergens in early childhood. Tartu, 1998.

42. **Heli Grünberg**. The cardiovascular risk of Estonian schoolchildren. A cross-sectional study of 9-, 12- and 15-year-old children. Tartu, 1998.
43. **Epp Sepp**. Formation of intestinal microbial ecosystem in children. Tartu, 1998.
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47. **Bela Adojaan**. Immune and genetic factors of childhood onset IDDM in Estonia. An epidemiological study. Tartu, 1999.
48. **Jakov Shlik**. Psychophysiological effects of cholecystokinin in humans. Tartu, 1999.
49. **Kai Kisand**. Autoantibodies against dehydrogenases of α-ketoacids. Tartu, 1999.
50. **Toomas Marandi**. Drug treatment of depression in Estonia. Tartu, 1999.
51. **Ants Kask**. Behavioural studies on neuropeptide Y. Tartu, 1999.
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53. **Tanel Laisaar**. Treatment of pleural empyema — special reference to intrapleural therapy with streptokinase and surgical treatment modalities. Tartu, 1999.
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56. **Siiri Kõljalg**. *Acinetobacter* – an important nosocomial pathogen. Tartu, 1999.
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64. **Jana Kivastik**. Lung function in Estonian schoolchildren: relationship with anthropometric indices and respiratory symptomas, reference values for dynamic spirometry. Tartu, 2000.
65. **Karin Kull**. Inflammatory bowel disease: an immunogenetic study. Tartu, 2000.
66. **Kaire Innos**. Epidemiological resources in Estonia: data sources, their quality and feasibility of cohort studies. Tartu, 2000.
67. **Tamara Vorobjova**. Immune response to *Helicobacter pylori* and its association with dynamics of chronic gastritis and epithelial cell turnover in antrum and corpus. Tartu, 2001.
68. **Ruth Kalda**. Structure and outcome of family practice quality in the changing health care system of Estonia. Tartu, 2001.
69. **Annika Krüüner**. *Mycobacterium tuberculosis* – spread and drug resistance in Estonia. Tartu, 2001.
70. **Marlit Veldi**. Obstructive Sleep Apnoea: Computerized Endopharyngeal Myotonometry of the Soft Palate and Lingual Musculature. Tartu, 2001.
71. **Anneli Uusküla**. Epidemiology of sexually transmitted diseases in Estonia in 1990–2000. Tartu, 2001.
72. **Ade Kallas**. Characterization of antibodies to coagulation factor VIII. Tartu, 2002.
73. **Heidi Annuk**. Selection of medicinal plants and intestinal lactobacilli as antimicrobil components for functional foods. Tartu, 2002.
74. **Aet Lukmann**. Early rehabilitation of patients with ischaemic heart disease after surgical revascularization of the myocardium: assessment of health-related quality of life, cardiopulmonary reserve and oxidative stress. A clinical study. Tartu, 2002.
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76. **Piret Hussar**. Histology of the post-traumatic bone repair in rats. Elaboration and use of a new standardized experimental model – bicortical perforation of tibia compared to internal fracture and resection osteotomy. Tartu, 2002.
77. **Tõnu Rätsep**. Aneurysmal subarachnoid haemorrhage: Noninvasive monitoring of cerebral haemodynamics. Tartu, 2002.
78. **Marju Herodes**. Quality of life of people with epilepsy in Estonia. Tartu, 2003.
79. **Katre Maasalu**. Changes in bone quality due to age and genetic disorders and their clinical expressions in Estonia. Tartu, 2003.
80. **Toomas Sillakivi**. Perforated peptic ulcer in Estonia: epidemiology, risk factors and relations with *Helicobacter pylori*. Tartu, 2003.
81. **Leena Puksa**. Late responses in motor nerve conduction studies. F and A waves in normal subjects and patients with neuropathies. Tartu, 2003.
82. **Krista Lõivukene**. *Helicobacter pylori* in gastric microbial ecology and its antimicrobial susceptibility pattern. Tartu, 2003.

83. **Helgi Kolk**. Dyspepsia and *Helicobacter pylori* infection: the diagnostic value of symptoms, treatment and follow-up of patients referred for upper gastrointestinal endoscopy by family physicians. Tartu, 2003.
84. **Helena Soomer**. Validation of identification and age estimation methods in forensic odontology. Tartu, 2003.
85. **Kersti Oselin**. Studies on the human MDR1, MRP1, and MRP2 ABC transporters: functional relevance of the genetic polymorphisms in the *MDR1* and *MRP1* gene. Tartu, 2003.
86. **Jaan Soplepmann**. Peptic ulcer haemorrhage in Estonia: epidemiology, prognostic factors, treatment and outcome. Tartu, 2003.
87. **Margot Peetsalu**. Long-term follow-up after vagotomy in duodenal ulcer disease: recurrent ulcer, changes in the function, morphology and *Helicobacter pylori* colonisation of the gastric mucosa. Tartu, 2003.
88. **Kersti Klaamas**. Humoral immune response to *Helicobacter pylori* a study of host-dependent and microbial factors. Tartu, 2003.
89. **Pille Taba**. Epidemiology of Parkinson's disease in Tartu, Estonia. Prevalence, incidence, clinical characteristics, and pharmacoepidemiology. Tartu, 2003.
90. **Alar Veraksitš**. Characterization of behavioural and biochemical phenotype of cholecystokinin-2 receptor deficient mice: changes in the function of the dopamine and endopioidergic system. Tartu, 2003.
91. **Ingrid Kalev**. CC-chemokine receptor 5 (CCR5) gene polymorphism in Estonians and in patients with Type I and Type II diabetes mellitus. Tartu, 2003.
92. **Lumme Kadaja**. Molecular approach to the regulation of mitochondrial function in oxidative muscle cells. Tartu, 2003.
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97. **Gunnar Tasa**. Polymorphic glutathione S-transferases – biology and role in modifying genetic susceptibility to senile cataract and primary open angle glaucoma. Tartu, 2004.
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