Summary

Psoriasis vulgaris (psoriasis) is an autoimmune disease that primarily affects the skin. The pathogenesis of psoriasis involves a combination of genetic and epigenetic modifications with a significant influence of environmental factors. The disease is characterized by papulosquamous lesions with hyperproliferation of keratinocytes, angiogenesis and dysregulation of the normal immune response leading to chronic inflammation. Excessive activation of parts of the adaptive immune system is thought to be a central factor in the pathogenesis of psoriasis. More severe forms of psoriasis tend to be associated with other diseases (comorbidities). These include metabolic and cardiovascular diseases, psoriatic arthritis, Crohn's disease and psychiatric disorders or uveitis. Many of these comorbidities show a significant association with age (the biological process of human aging).

Aging is a process of gradual decline in the body's abilities and functional capabilities. It is a universal process with a considerable degree of variability that is characteristic of all higher animals. Among the theories describing aging, the theory of accumulation of damage, which integrates the previously known mechanisms of aging, is currently dominant. The theory is based on the fact that during pathophysiological processes, undesirable changes occur in the human body that can be understood as damage. Due to the continuous accumulation of these damages, the whole system is subsequently deteriorated.

Issue addressed. Literature data suggest that people with psoriasis have shorter lifespan and an increased likelihood of developing associated diseases (comorbidities). However, the possible links between dysfunctional chronic inflammation induced by the aging process (inflammaging) and the autoimmune disease process (psoriasis) have not yet been further elucidated.

The aims of this dissertation were (1) to assess the suitability (applicability) of selected aging indicators for a model system of psoriasis and its comorbidities and (2) to use appropriate aging indicators to analyze the relationships between psoriasis, aging, and the development of comorbidities.

Three independent studies were conducted to fulfill the objectives of this study. The indicators were selected from a group of simple molecular indicators of aging and a group of composite indicators of aging. The parameters HMGB1, IL-33, S100A7, S100A12, endocan, VEGF, IL-17 and CRP were selected to assess altered intercellular communication. To assess genomic instability, we measured the level of oxidative DNA/RNA damage. To quantify

epigenetic alterations, the level of global methylation and the epigenetic clock method were selected. The length of telomeres was selected to assess the telomere attrition. Biological sampling (whole blood) was performed between 2016 and 2020. A total of 132 individuals with psoriasis (patients) and 167 randomly selected healthy individuals of comparable age, sex and lifestyle (controls) were blood collected. Lifestyle factors (with emphasis on smoking) were collected by questionnaire. There were 72 men and 60 women in the patient group and 85 men and 82 women in the control group.

The first study was aimed at evaluating the effect of psoriasis and comorbidities on the levels of markers of inflammation from the group of alarmins (HMGB1, IL-33, S100A7, S100A12). 63 patients (34 men, 29 women) and 95 controls (49 men and 46 women) participated in the study. The levels of all alarmins studied were significantly elevated in the patient group. There was a significant relationship between HMGB1 and S100A7 in the patient group and a significant relationship between HMGB1 and IL-33 in the control group.

The second study was 1) to evaluate the effect of psoriasis and its comorbidities on the levels of inflammatory markers IL-17, VEGF, endocan and CRP and 2) to analyze the relationship between epigenetic and calendar age of psoriasis patients and comorbidities (epigenetic clock; computerized evaluation of methylation of more than 500 age-related DNA gene loci). Twenty-eight patients (17 men and 11 women) and 42 controls (21 men and 21 women) participated in the study.

In the patient group (as a whole), we found significantly increased IL-17 levels and significantly decreased endocan levels. The situation was the same in the subgroup of men (patients). In the subgroup of women (patients), we found only significantly elevated IL-17 levels. In the group of patients (as a whole), we found significantly higher CRP levels. CRP levels showed a significant relationship with chronological age.

Analysis of the relationship between epigenetic age and calendar age showed no statistically significant difference between controls and patients (as a whole). However, a significant difference between epigenetic age and calendar age was found in a subgroup of women (patients). The median difference was 3.2 years for women with psoriasis, while the median difference for healthy women (controls) was -1.3 years.

The third study was designed to assess the effect of psoriasis and its comorbidities on 1) levels of global DNA methylation, 2) levels of oxidative DNA/RNA damage, and 3) changes

in telomere length. Forty-one patients (21 men and 20 women) and 30 controls (15 men and 15 women) participated in the study.

The level of global DNA methylation was higher in the patients, but the difference did not reach statistical significance. A significant relationship was found between the level of global methylation and BMI.

Patients with psoriasis had significantly higher levels of oxidative DNA/RNA damage, both in terms of the whole group and when divided into men and women. We found significantly higher levels of oxidative DNA/RNA damage in non-smoking patients than in non-smoking controls. Levels of oxidative DNA/RNA damage in patients with metabolic syndrome (MetS) comorbidity were not significantly different from those without MetS. However, patients without MetS had significantly higher levels of oxidative DNA/RNA damage compared with controls without MetS.

Significantly higher mean telomere length per chromosome was found in the patient group (as a whole) and in the subgroup of female patients (but not in the subgroup of male patients) compared to controls. Telomeres were significantly longer in non-smoking patients than in smoking patients. Telomeres were significantly longer in patients without MetS than in patients with MetS. There was a significant negative relationship between telomere length and calendar age of controls.

Conclusions of the first objective. The suitability (applicability) of selected indicators of biological aging for a model system of psoriasis and its comorbidities was assessed. Alarmins are indicators of the aging process describing altered intercellular communication and were significantly influenced by the disease model system. They can therefore be considered appropriate for this system. Another of the selected indicators of altered intercellular communication, VEGF, was not influenced by the model system and probably cannot be considered a suitable indicator. Altered intercellular communication is also indicated by other selected IL-17, endocan and CRP markers. Significant changes were observed in the disease model system. However, both indicators may be significantly influenced by environmental/work and lifestyle factors. Their use as indicators of aging in a model disease system is therefore more appropriate at the population level than at the individual level.

Of the proxies for aging indicators describing epigenetic changes, the epigenetic clock method (as opposed to the global methylation method) has proven to be preferable, as it allows detailed characterization of individual methylation sites on the epigenome.

Measurement of genomic instability by RNA/DNA oxidative damage appears to be a promising method for quantifying the rate of aging in a disease model system. However, here again, the significant influence of environmental/occupational and lifestyle factors (e.g. smoking) must be taken into account.

Measurement of telomere length has produced unexpected findings that do not allow an objective assessment of the suitability of this method as an indicator of the aging process in a model system of the disease.

Conclusions of the second objective. Using appropriate indicators of the aging process, an analysis of the relationship between psoriasis, aging, and the development of comorbidities was performed. We have demonstrated (probably for the first time according to the literature data) that patients with psoriasis (disease model system) have significant changes in parameters related to the process of aging. The most significant evidence is the finding of higher epigenetic (biological age) in women with psoriasis.

In summary, we have shown that psoriasis qualitatively affects the aging process and significantly increases the onset and development of comorbidities. All these interpretations and conclusions are burdened with a certain degree of uncertainty.