

ACE kinetic

Clinical Applications in Routine and Research

IVD
Settings for
Clinical Chemistry
Analyzers

ACE-Monitoring is contributory to
diagnose Sarcoidosis

ACE-Monitoring of Sarcoidosis
allows therapy adjustments

ACE-Monitoring of hypertensive
patients allows surveillance of
treatment efficacy

Genotype-corrected normal ranges
increase the clinical sensitivity of
ACE activity

ACE-Monitoring allows therapy
adjustments of patients under
nephroprotective ACE-inhibitor
therapy

ACE

In vivo, Angiotensin-Converting Enzyme (ACE) catalyses the conversion of Angiotensin I to Angiotensin II and inactivates bradykinin during regulating blood pressure via Renin-Angiotensin-System.

Elevated levels of serum ACE associated with the ACE-I/D-gene polymorphism have been measured in patients suffering from various disorders. They often indicate a poor prognosis or rapid progression of the disease.

- Granulomatous-inflammatory diseases such as Sarcoidosis and Mixed-Connective-Tissue Disease (MCTD)*⁹
- Nephropathies associated with Diabetes and Glomerulonephritis*^{10,12}
- Cardiovascular diseases such as left ventricular hypertrophy, brain and myocardial infarction*¹²

Sarcoidosis

Sarcoidosis is an inflammatory disease of unknown origin characterised by the formation of granuloma. The prevalence of this multisystem granulomatous disorder, which activates the immune system, varies between ethnic groups and geographic regions. Worldwide, the incidence of Sarcoidosis ranges from 10-80 cases per 100.000 inhabitants. The average age at onset is between 20 and 40 years in both men and women. Sarcoidosis may occur as acute or chronic form. The onset of the chronic type is slowly and without clear symptoms.

In about 20% of the cases especially multi-organ involvement may become life-threatening. The main symptoms are: enlargement of lymph nodes, fever, chest pain and cough and painful nodules under the skin. Symptoms may be associated with a specific organ or with several organs*⁶:

Organ	Patients %
Lymph nodes	90
Lung	90
Liver	60-90
Eyes (Uveitis)	25
Skin/Skeleton	25
Heart	5

Diagnosis

Sarcoidosis patients exhibit no distinct clinical signs. Therefore, Sarcoidosis remains a diagnosis of exclusion. In this context, **the measurement of ACE may contribute to confirm Sarcoidosis***^{3,6}. The following criteria for the diagnosis of Sarcoidosis have been established:

Identification of the typical clinical and/or radiologic picture closely related to Sarcoidosis, mainly supported by the non-caseating granulomas and exclusion of all other sarcoidosis-like diseases. Diagnosis is supported by bronchoalveolar lavage which indicates a proliferation of T-Lymphocytes and a shift of the CD4/CD8 composition towards CD4-cells.

Monitoring disease activity

Monitoring of disease activity is essential to predict disease progression. A clinical investigation, the assessment of lung capacity and a radiologic examination are routinely performed. Spontaneous and therapy-induced changes of the inflammatory activity predicting a deterioration are reflected better by serum parameters such as sIL-2R, neopterin and **especially ACE activity in serum**.

Therapy options

In most cases of acute Sarcoidosis the administration of NSAIDs is sufficient. In cases of chronic-progressive courses a therapy with corticosteroids is recommended. According to the severity of the disease and the response to the drug an initial dose is established and gradually reduced later on. A life-long treatment with a low dose of corticosteroids may be necessary. In cases of corticoid-resistance an immunosuppressive therapy using combinations of Cyclosporine A, Azathioprine, Methotrexate or Cyclophosphamide are being used.

Monitoring disease activity of Sarcoidosis with ACE

The chronic forms can last several years or even a life time. Consequently, diagnostic tools are essential to closely monitor the disease activity and to predict disease progression. ACE is valuable to assess the disease activity, especially in

systemic Sarcoidosis. It is released by epitheloid cells and its serum level correlates significantly with the granuloma burden of the patient.

The **positive predictive value** of elevated ACE activity is estimated between 75-90%, **the negative predicted value** between 70-80%*¹⁷. An initial low ACE activity indicates a good prognosis. Elevated levels significantly correlate with the granuloma burden of the individual. If only one organ is affected ACE activity often shows values within the normal range. Examples of individual chronic disease courses are presented below (Case 1 and 2). Important: **An increase in ACE activity within the normal range may indicate a disease progression**.

Genotyping

A deletion-/insertion-polymorphism in intron 16 of the angiotensin-converting enzyme (ACE) gene located on chromosome 17 has been detected. A sequence of 287 base pairs is either present (insertion, I-allele) or absent (deletion, D-allele).

Studies of the D/I-polymorphism have shown the D-allele to be associated with an enhanced ACE activity, and the I-allele with a lower one. The assessment of the gene polymorphism and the establishment of genotype-corrected values is thus helpful to improve the clinical value of ACE. It has been shown that ACE genotyping and genotype-corrected reference ranges have improved the clinical sensitivity of ACE activity in Sarcoidosis, which is still the main application of ACE in serum*¹.

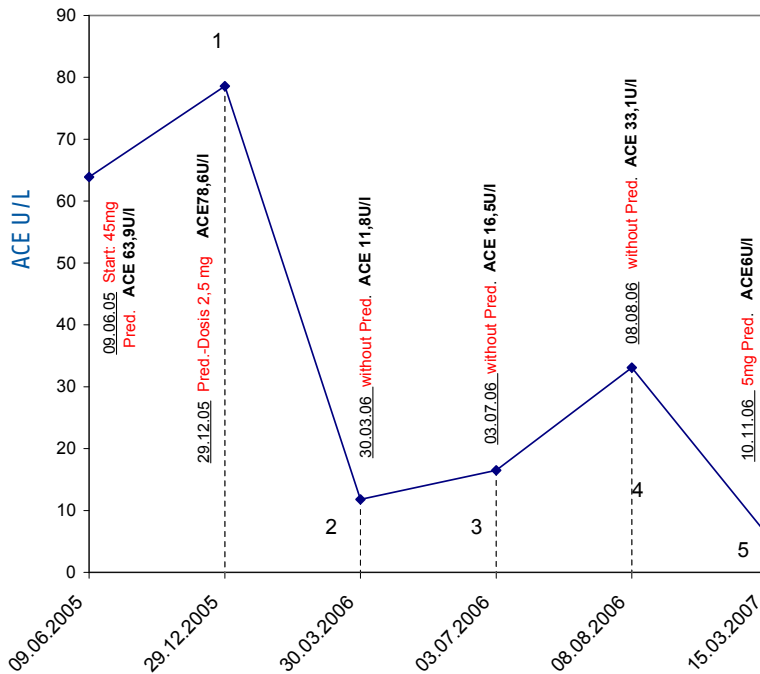
Other Areas of application

Chronic Berylliosis

Berylliosis is induced by Berylliumoxide exposure at the work place. The clinical picture and symptoms are identical to what is reported with Sarcoidosis and has to be excluded in order to diagnose correctly*^{6,7}. Differential diagnosis can be made if a skin test is used.

Disease Monitoring with ACE activity – examples

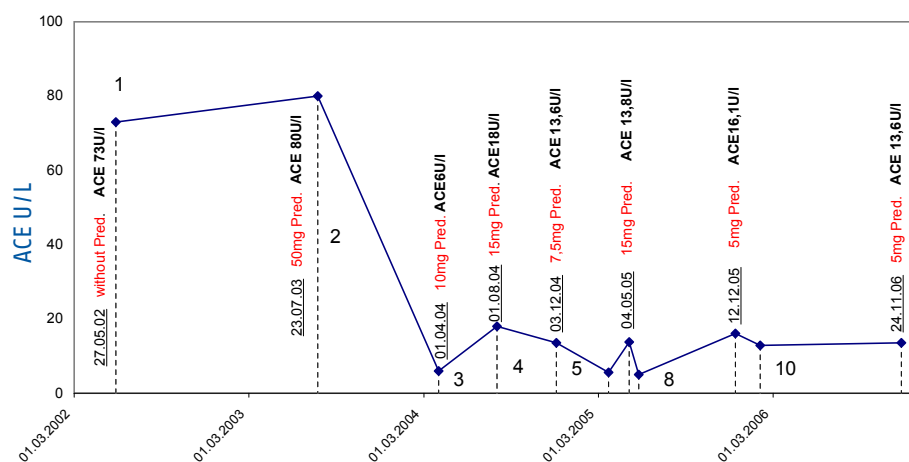
Therapy monitoring is performed according to the disease activity in intervals between 3 months and one year. Examples for typical therapy follow-up under therapy with Prednisolone:



Case 1

60-year old patient with ACE I/D-Gene Polymorphism: Genotyp ID under therapy with Prednisolone. Prednisolone and Delix (ACE-inhibitor, contains Ramipril).

Follow-Up: 1. Prednisolone-reduction; 2. Prednisolone discontinued; 3. without Prednisolone; 4. without Prednisolone; 5. Prednisolone-restart



Case 2

41-year old patient with ACE I/D-Gene Polymorphism: Genotype II. Long-term treatment with a low dosis of prednisolone. ACE levels have been classified as elevated only by using genotype-corrected normal ranges.

Follow-Up: 1. Without Prednisolone; 2. Prednisolone-increase; 3. Pred.-reduction; 4. Pred.-increase; 5. Pred.-reduction; 7. Pred.-increase; 8. Pred.-reduction; 9. low Dose

These data have been provided by Professor Dr. med J. Müller-Quernheim, University of Freiburg, Germany

Monitoring of Cardiovascular diseases/ Hypertension

The value of the ACE-I/D-polymorphism as a prognostic marker of disease progression is discussed controversially. Some groups use ACE activity measurements for therapy monitoring under ACE inhibitors*¹⁰.

Nephroprotection under ACE inhibitor therapy

A variety of diseases is associated with chronic progressive renal failure.

ACE-I/D-Polymorphism is used as a prognostic marker of disease progression. The DD- and the ID-genotype benefit from a therapy with ACE inhibitors*¹⁰. The efficacy of ACE inhibitors and thus the individual need of drugs can be determined using ACE activity testing. The treatment with ACE inhibitors is most effective in the following diseases.

- Diabetes mellitus ACE inhibitors show nephroprotective action. Furthermore, ACE activity can be elevated in cases of proliferative Retinopathy*⁸.
- Focal and segmental Glomerulosclerosis, IgA Nephropathy Patients with DD- and ID-genotype are treated with ACE inhibitors to reduce the risk of renal failure. The efficacy of ACE inhibitors is assessed by measuring ACE activity*¹⁰.

Mixed-Connective-Tissue Disease

- Many patients are at risk of developing pulmonary hypertension, which is indicated by increasing levels of ACE activity*⁹.

Summary

Serum ACE is a highly specific marker for the disease activity monitoring of Sarcoidosis patients.

Genotype-corrected normal ranges should be used to increase the clinical sensitivity of the parameter.

Serum ACE is a valuable marker for efficacy monitoring of ACE inhibitor therapy in diseases associated with ACE-I/D-Gene-Polymorphism.

Genotype-corrected reference values for serum ACE

Adults

Genotype corrected reference values using ACE kinetic have been established by Prof. Müller-Quernheim, University Clinic of Freiburg, Germany*1.

	Mean	2SD-Range
	U/L	U/L
DD-Genotype	59.3	30.1 - 89.5
DI-Genotype	45.5	15.1 - 75.9
II-Genotype	34.8	7.4 - 62.2
Total	47.0	12.4 - 81.6

Normal Ranges

Children

Serum levels in children are substantially higher and more variable than in adults. No differences have been observed related to age and gender. ACE activity levels in newborns are very low. 84 children were included in the evaluation of normal ranges.

Age	Median	2.5-97.5 th
years	U/L	Percentile U/L
0.5 - 18	66.9	29.3 - 112.2

Sarcoidosis

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Other Applications

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Methodical Background

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