Human ALS ELISA

(Human Acid Labile Subunit)

Cat. No.: RMEE35R

TECHNICAL FEATURES+APPLICATIONS

- Quantitative determination of the acid labile subunit (ALS) of the ALS/IGF/IGFBP-3 complex
- Inter-Assay variation of ≤ 8% and Intra-Assay variation of ≤ 6.8%
- Sensitivity 0.23 mU/mL
- A single measurement is informative for diagnosis of GH deficiency or GH excess

INTENDED USE

This enzyme immunoassay kit is suited for measuring ALS in human serum or EDTA-/heparin-/citrate plasma for diagnostic and scientific purposes.

The results of this test sytem can be used as supplementary information in GH-diagnostics together with IGF-I and IGFBP-3 measurements. Thus, it is of use in evaluation of GH-deficiency and excess [14, 15].

INTRODUCTION

The Insulin-like Growth Factors (IGF) – I and II are bound to specific binding proteins in circulation (IGFBP). Until today seven different proteins have been identified IGFBP-1 to 7 [1, 2]. IGF bioavailablity, transport and storage is regulated or facilitated by these binding proteins which are expressed differentially according physiological and developmental requirements. The most abundant IGFBP in circulation is IGFBP-3. Together with IGFBP-5 it is able to form the so called ternary complex with IGF and the acid-labile subunit (ALS) [3-5]. In the circulation nearly all IGF is bound in this ternary complex and thus not able to cross the endothelial barrier. Only very small amounts of IGF or IGFBP-3 exist outside this complex [6, 7]. The acid-labile subunit is an important part of the IGF-storage mechanism in circulation. In ALS deficiency or in ALS knock-out mice the concentration of IGF and IGFBP-3 in the circulation is significantly decreased resulting in impaired growth [10].

The acid-labile Subunit, is a synthezised as propeptide of 605 amino acids. The signal peptide, necessary for ALS secretion (AA 1-27) cleaved off enduring the transport process (Swiss-Prot P35858 Version 82). The mature protein consists of 578 amino acids and contains about 20 leucin rich sequence repeats. Beside the leucin-rich repeats several potential N-linked glycosylation sides have been described. Miller BS et al. were able to demonstrate that incomplete glycolsylation of IGFs, ALS and IGFBP-3 results in a decreased serum concentration of these proteins. Oral mannose therapy resulted in a partial normalization of the glycosylation pattern and went along with improved growth [8]. Mutations in or the complete knock out of the ALS gene result in IGF / IGFBP-3 deficiency and therewith in disturbation of growth [9,10]. Beside growth also other endocrine axes may be involved. In primary ALS deficiency hyperinsulinemia could be observed [11, 12]. Further, the HGH-IGF-IGFBP-system seems to be of relevance in coronary disease [13].

The first ALS immunoassay was described by Baxter RC in 1990 [6]. By this in-house radioimmunoassay it was shown that ALS is present in high concentrations in serum (50µg/mL) of healthy humans. But not detectable in other body fluids like amniotic fluid, cerebrospinal fluid or seminal plasma – in spite of the fact that these body fluids contain high level IGFBP-3.

SPECIMEN COLLECTION, PREPARATION AND STORAGE

Serum samples are suitable. Further. 30 IE/mL Heparin. 6.8 mM EDTA or 0.015M Sodium Citrate did not interfere with ALS measurement.

Serum Samples can be stored and transported at room temperature (20-25°C) for 3 days. 3 freeze thaw cycles do not influence the ALS determination.

Samples should be handled as recommended in general: chilled as soon as possible. In case there will be a longer period between the sample withdrawal and determination store the undiluted samples frozen -20°C or below in tightly closable plastic tubes. Avoid on principal repeated freeze-thaw cycles of serum/plasma (if required. please subaliquote).

In most determinations (e.g. Serum- or Plasma samples and no extreme values expected) the dilution of **1:100 with Sample Buffer PP is suitable**. respectively the assay covers the range from 0 - 4000 mU/ mL. If required. the dilution with **Sample Buffer PP** can be higher or lower.

Suggestion for dilution protocol:
Pipette **990 µL Sample Buffer PP** (red colored) in PE-/PP-Tubes (application of a multi-stepper is recommended in larger series). add **10 µL Serum**- or **Plasma** (dilution 1:100) and mix each tube **immediately**. After mixing use **50 µL** of this solution within 1 hour **per determination** in the assay (pipetting control = red coloring of the solution in the wells).

REAGENTS PROVIDED

1)	MTP	**Microtiter plate.** ready for use: Microtiter plate with 96 wells. divided up in 12 strips with 8 wells separately breakable. coated with anti-human ALS Antibody. packed in a laminate bag.
2)	CAL	**Standards A-F**. lyophilised. contain human ALS. Standard values are 0. 1.5. 6.25. 12.5. 25. 40 mU/mL ALS . Standards are **reconstituted with 1000 µL Sample Buffer PP each**. Use 50 µL pro well in the assay. Standards can be stored at 4°C overnight or at -20°C for up to three weeks after reconstitution. Avoid repeated freeze thaw cycles.
3)	BUF PP	**Sample Buffer PP**. 125 mL. ready for use. red colored. please use for the reconstitution of **Standards A-F** and **Controls KS1/KS2** and for the dilution of **Samples** and **Controls KS1/KS2**
4)	Control	**Control Sera KS1 and KS2**. 250 µL. lyophilised. contain human Serum and should be **reconstituted in 250 µL Sample Buffer PP each**. The ALS target values and the respective ranges are given on the vial labels. The dilutions should be according to the dilution of the respected samples.
5)	Ab	**Antibody Conjugate AK**. 7mL. ready-to-use. contains biotinylated anti-human ALS Antibody.
	CONJ	**Enzyme Conjugate EK**. 12mL. ready-to-use.. contains HRP (Horseradish-Peroxidase)-labelled Streptavidin.
6)	WASHBUF 20x	**Washing Buffer (WP).** 50 mL. 20 X concentrated solution.
7)	SUBST	**Substrate (S).** 12 mL. ready for use. horseradish-peroxidase-(HRP)-substrate. stabilised H_2O_2 Tetramethylbencidine.
8)	H_2SO_4	**Stopping Solution (SL).** 12 mL. ready for use. 0.2 M sulphuric acid. Caution acid!
9)		Sealing tape for covering of the microtiter plate. 2 x. adhesive.

MATERIALS REQUIRED BUT NOT PROVIDED

Precision pipettes (100 and 200µL) Micropipettes and multichannel pipettes with disposable plastic tips
Distilled or Deionized water for dilution of the Washing Buffer (WP)
Vortex-mixer
Device to aspirate the standards and the samples from the wells (recommended because of the potential danger of infection by human samples)
Timer (120 min. range)
Reservoirs (disposable)
Plate washer and plate shaker (recommended)
Calibrated Micro plate reader ("ELISA-Reader") with filter for 450 and 620nm (or ≥590 nm)
Foil welding device for laminate bags (recommended)

REAGENT PREPARATION

In conducting the assay. follow strictly the test protocol. Room temperature incubation means: Incubation at 20 - 25°C.

Reagents with different lot numbers should not be mixed. The microtiter plate and all reagents are stable unopened until the expiry date. if stored in the dark at 2° - 8°C (see label).

The Standards **A – F** and **Control Sera KS1/KS2** are reconstituted with the **Sample Buffer PP** provided in the Kit. It is recommended to keep the reconstituted reagents at room temperature for 15 minutes and then to mix them thoroughly but gently (no foam should result) with a Vortex mixer.

The shelf life of the components after opening is not affected. if used appropriately. Store the unused seal stripes of the microtiter plate together with the desiccant at 2-8°C. Reconstituted Components (**Standards A – F** and **Control Sera KS1/KS2**) should be stored at -20°C (or below) for not longer than 3 months. When using the standards anew. please thaw them rapidly but gently (no temperature rise over the room temperature and no powerful vortexing.

The 1:20 diluted Washing Buffer **WP** is only limited stable. Please dilute only according to daily requirements.

Before use. all kit components should be brought to room temperature. **Precipitates. possible in buffers. should be dissolved before use through mixing and warming**.

The **Substrate Solution S**. stabilised H_2O_2-Tetramethylbencidine. is photosensitive – store and incubate in the dark.

When performing the assay. the Standards **A-F.** Control Sera **KS1/KS2** and the samples should be pipetted as fast as possible (e.g.. 15 minutes). To avoid distortions due to differences in incubation times the antibodies **AK** and **EK** as well as the succeeding **Substrate Solution S** should be added to the plate in the same order and in the same time interval as the samples. **Stop Solution SL** should be added to the plate in the same order as the Substrate Solution **S**

STORAGE CONDITIONS

The microtiter plate wells and all undiluted reagents are stable until the expiry date if stored in the dark at 2-8°C.
Store the unused seal strips and microtiter wells together with the desiccant at 2° to 8°C.

The Substrate Solution (S). stabilised H_2O_2-Tetramethylbencidine. is photosensitive – store and incubate in the dark.

Reconstituted Components (**Standards A – F** and **Control Sera KS1/KS2**) can be stored for up to 3 weeks at -20°C (or below). Avoid repeated freeze-thaw cycles. In case you plan to perform multiple independent determinations over a longer period with one kit. you should aliquot the components prior to freezing into suitable smaller volumes. This is strongly recommended.

WARNINGS AND PRECAUTIONS

For in-vitro diagnostic use only. For professional use only.
Before starting the assay. read the instructions completely and carefully. Use the valid version of the package insert provided with the kit. Be sure that everything is understood. The mediagnost GmbH is not liable for any loss or harm caused by non-observance of the instructions. as far as no law withstands.

Before use. all kit components should be brought **to room temperature at 20 - 25°C**. Precipitates in buffers should be dissolved before use by thorough mixing and warming. **Temperature WILL affect the absorbance** readings of the assay. However. values for the patient samples will not be affected.

Do not mix reagents of different lots. Do not use expired reagents.

The microplate contains snap-off strips. Unused wells must be stored at 2 - 8°C in the sealed foil pouch and used in the frame provided.

Caution: This kit contains material of human and/or animal origin. Source human serum for the Control Sera and Standards provided in this kit were tested by FDA recommended methods and found non-reactive for Hepatitis-B surface antigen (HBsAg). Hepatitis C virus (HCV). and Human Immunodeficiency Virus 1 and 2 (HIV) antibody. No known test methods can offer total assurance of the absence of infectious agents; therefore all components and patient's specimens should be treated as potentially infectious.

Stop solution contains 0.2 M Sulfuric Acid (H_2SO_4)

R36/38 Irritating to eyes and skin
S26 In case of contact with eyes. rinse immediately with plenty of water and seek medical advice
S28.1 After contact with skin. wash immediately with plenty of water
S36/37 Wear suitable protective clothing and gloves.

Pipetting of samples and reagents must be done as quickly as possible and in the same sequence for each step. Use separate pipette tips for each sample. control and reagent to avoid cross contamination. Use reservoirs only for single reagents. This especially applies to the substrate reservoirs. Using a reservoir for dispensing a substrate solution that had previously been used for the conjugate solution may turn solution colored. Do not pour reagents back into vials as reagent contamination may occur. Mix the contents of the

microplate wells thoroughly to ensure good test results. Do not reuse microwells. Do not let wells dry during assay; add reagents immediately after completing the rinsing steps.

2-Methyl-4-Isothiazolin-3-one
contained in following components: **AK. EK. PP**
< 0.01% 2-Methyl-4-isothiazolin-3-one Solution

R34	Irritating to eyes and skin
R43	Sensibilisation through skin contact possible
S26	In case of contact with eyes. rinse immediately with plenty of water and seek medical advice
S36/37	Wear suitable protective clothing and gloves
S45	In case of accident or if you feel unwell seek medical advice

5-chloro-2-methyl 2H isothiazol-3-one and 2-methyl-2H-Isothiazol-3-one
contained in following components: **AK. EK. WP.PP**
< 0.01% (w/w) 5-chloro-2-methyl 2H isothiazol-3-one and 2-methyl-2H-Isothiazol-3-one
Solution

R36/38	Irritating to eyes and skin
R43	Sensibilisation through skin contact possible
S26	In case of contact with eyes. rinse immediately with plenty of water and seek medical advice S28.1 S28.1 After contact with skin. wash immediately with plenty of water

TMB-Substrate (S) contains 3.3´.5.5´ Tetramethylbenzidine.

R20/21/R22	Harmful by inhalation. in contact with skin and if swallowed
R36/37/38	Irritating to eyes. respiratory system and skin
S26	In case of contact with eyes. rinse immediately with plenty of water and seek medical advice
S28.1	After contact with skin. wash immediately with plenty of water
S36/37	Wear suitable protective clothing and gloves

General first aid procedures:
Skin contact: Wash affected area thoroughly with water. Discard contaminated cloths and shoes.
Eye contact: In case of contact with eyes. rinse immediately with plenty of water at least 15 minutes. In order to assure an effectual rinsing spread the eyelids.
Ingestion: If swallowed. wash out mouth thoroughly with water. Immediately see a physician.
Do not eat. drink or smoke in these areas.
Never pipette the materials with the mouth.
Spilled material must be wiped off immediately and should become disinfected. Clean contaminated areas and equipment with a suitable detergent.

ASSAY PROCEDURE

NOTES: All determinations (Standards. Control Sera and samples) should be assayed in duplicate. For optimal results. accurate pipetting and adherence to the protocol are recommended.
When performing the assay. the Standards. Control Sera and the samples should be pipette as fast as possible (e.g.. <15 minutes). To avoid distortions due to differences in incubation times. the **Antibody Conjugate AK** and **Enzyme –Conjugate EK** as well as the following **Substrate Solution S** should be added to the plate in the same order and in the same time interval as the samples. **Stop Solution SL** should be added to the plate in the same order as the Substrate Solution.

1) Please pipette on before in **all needed wells 50 µL biotinylated antibody (AK)**.
2) Pipette in positions A1/2 **50µL** each **Standard A (0 mU/ml)**.
   pipette in positions B1/2 **50µL** each **Standard B (1.5 mU /ml)**.
   pipette in positions C1/2 **50µL** each **Standard C (6.25 mU /ml)**.
   pipette in positions D1/2 **50µL** each **Standard D (12.5 mU /ml)**.
   pipette in positions E1/2 **50µL** each **Standard E (25 mU /ml)**.
   pipette in positions F1/2 **50µL** each **Standard F (40 mU /ml)**.
   To control the correct accomplishment **50 µLeach** of the 1:100 (or in respective dilution rate of the sample) in Sample Buffer **PP** diluted **Control Sera KS1 and KS2** can be pipetted in positions G1/2 and H1/2
   Pipette **50 µL each** of the **diluted sample** (generally 1:100 diluted in Sample Buffer **PP**) in the rest of the wells. according to requirements. Please mix the dilutions immediately after sample addition and use within 60 minutes.
3) Cover the wells with the sealing tape and incubate the plate for **2 hours** at **room temperature** (shake at ≥350 rpm).

4) After incubation aspirate the contents of the wells and wash the wells 5 times with **250 µL Washing Buffer WP**.
5) Following the last washing step. pipette **100 µL** of the **Enzyme Conjugate EK** in each well.
6) Cover the wells with the sealing tape and incubate **0.5 hours** at **room temperature** (shake at ≥350 rpm).
7) After incubation wash the wells 5 times with **Washing Buffer WP** as described in step 5)
8) Pipette **100 µLof the TMB-Substrate solution S** in each well.
9) Incubate the plate for **30 Minutes in the dark at** room **temperature**.
10) After incubation pipette **100 µL Stop Solution SL** in each well.
11) Measure the absorbance **within 30 minutes at 450 nm (Reference filter ≥590 nm. e.g. 620 nm)**.

CALCULATION OF RESULTS

For the evaluation of the assay it is required that the absorbance values of the blank should be below 0.20. and the absorbance of standard F should be greater than 1.00.
Samples. which yield higher absorbance values than **Standard F**. are beyond the standard curve. for reliable determinations such samples should be retested at a higher dilution.

Establishing the Standard Curve

The standards provided contain the following concentration of ALS

Standard	**A**	**B**	**C**	**D**	**E**	**F**
mU/mL	0	1.5	6.25	12.5	25	40

1) Calculate the **mean absorbance** (MA) value for the blank from the duplicated determination (well A1/A2).
2) Subtract the mean absorbance (MA) of the blank from the mean absorbances of all other values.
3) Plot the standard concentrations on the x-axis versus the mean value of the absorbance of the standards on the y-axis on semi-log paper (lin-log).
4) Recommendation: Calculation of the standard curve should be done by using a computer program. because the curve is in general (without respective transformation) not ideally described by linear regression. **Non-linear regression**. a higher-grade polynomial or four parametric logistic (4-PL) lin-log curve fit are suitable for the evaluation. A good fit is provided with cubic spline. 4 Parameter Logisitcs or Logit-Log.
5) The ALS concentration in mU/mL of the samples can be calculated by multiplication with the respective dilution factor.

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SUMMARY –ALS ELISA

Reconstitution/ Dilution of Reagents		
Standards A-F	Reconstitution in **Sample Buffer PP** (red)	**1000 µLeach**
Control Serum KS1/KS2	Reconstitution in **Sample Buffer PP** (red)	**250 µL each**
Washing Buffer WP	dilute in **A. dest.** (e.g. add the complete contents of the flask 50 mL into a graduated flask and fill with A.dest. to 1000 mL)	**1:20**
Sample Dilution + Control Sera KS1 &KS2: 1:100 in Sample Buffer PP (red colored; e.g. 10 µL in 1 ml **PP**). **mix directly and use within max. 60 min.** Use **50 µL per determination** (pipetting control= red coloration)		
Before assay procedure bring all **reagents** to **room temperature**		

Assay Procedure for Double Determination

Pipette	**Reagents**	**Well Positions**
50 µL	Biotinylated Antibody **(AK)**	Pipette **in <u>all</u> required number of wells**
50 µL	Standard **A** (**0 mU /mL**)	A1 and A2
50 µL	Standard **B** (**1.5 mU /mL**)	B1 and B2
50 µL	Standard **C** (**6.25 mU/mL**)	C1 and C2
50 µL	Standard **D** (**12.5 mU/mL**)	D1 and D2
50 µL	Standard **E** (**25 mU/mL**)	E1 and E2
50 µL	Standard **F** (**40 mU/mL**)	F1 and F2
50 µL	Control Serum **KS1**	G1 and G2
50 µL	Control Serum **KS2**	H1 and H2
50 µL	**Sample**	Pipette sample in the rest of the wells according to requirements
Cover the wells with the sealing tape		

Incubation: 2 h at RT. **≥ 350 rpm**

5x 250 µL	Aspirate the contents of the wells and wash **5x** with **250 µL** each **WP**/**well**	each well
100 µL	**Enzyme Conjugate EK**	each well

Incubation: 0.5 h at RT. ≥350 rpm

5x 250 µL	Aspirate the contents of the wells and wash **5x** with **250 µl** each **WP**/**well**	each well
100 µL	Substrate Solution **S**	each well

Incubation: 30 min in **the dark** at RT

100 µL	Stop Solution **SL**	each well
Measure the absorbance within 30 min at **450 nm** (≥590 nm Reference)		

International Test description

CAL A-F	A -F	Rec in 1000 µL PP	
Control	KS1 / KS2	Rec in 250 µL PP	
WASHBUF 20x	WP		1:20 DILU A. dest.

Control	1:100 DILU PP
SPE	1:100 DILU PP
°C 20-25 °C	

50 µL	AK	A1 - End
50 µL	CAL A (0 mU/mL)	A1/2
50 µL	CAL B (1.5 mU/mL)	B1/2
50 µL	CAL C (6.25 mU/mL)	C1/2
50 µL	CAL D (12.5 mU/mL)	D1/2
50 µL	CAL E (25 mU/mL)	E1/2
50 µL	CAL F (40 mU/mL)	F1/2
50 µL	CONTROL KS1 1:100 DILU PP ↔	G1/2
50 µL	CONTROL KS2 1:100 DILU PP ↔	H1/2
50 µL	SPE 1:100 DILU PP	
TAPE		

2 h °C 20-2 ↔ ≥ 350 rpm

5x 250 µL	5x WASHBUF WP
100 µL	CONJ EK
TAPE	

0.5h °C 20-2 ↔ ≥ 350 rpm

5x 250 µL	5x WASHBUF WP
100 µL	SUBST TMB S

0.5 h °C 20-25

100 µL	H_2SO_4 SL
MEASURE	

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