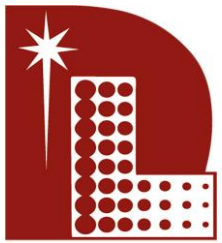
What If All is Well Except Insulin:

A macroinsulin case report

Dr. Cevdet ZÜNGÜN

DUZEN LABORATORIES GROUP, TURKEY



Patient and Results

75 years old male patient (May 2019)

Analytes		Results	[RI]
Glucose (mg/dL), fasting		91.00	[80 - 115]
Glucose (mg/dL), postprandial		141.00	[70 - 120]
A1c (%)		5.50	[4.00 – 5.60]
Insulin (uIU/mL)	**Fasting**	**128.90***	[2.60 – 25.00]
	PP	252.60	[14.00 – 160.00]

*** Fasting Insulin result in 2017 : 18.2 uIU/mL (Roche, ECLIA)**

Fasting C-peptide measurement was added as reflective test. C-peptide result was 4.39 ng/mL (RI: 1.10 – 4.40)

Extremely high insulin results **inconsistent with**

1. **Normal fasting C-peptide and glucose levels**
2. **Previous insulin result** in 2017

Patient History

- No diagnosis or family history of DM
- No diabetic symptoms
- Lipid profile results are normal
- Hypertension under control
- Wide waist (117 cm) and hip circumference (119 cm) and BMI > 30 kg/m2
- Mediterranean diet
- Limited exercise because of **knee prosthesis** for two years.

Further Investigation and Analysis

Physician's comment: insulin levels were high for insulin resistance and suspected a **mixed tumor** *in which insulin and glucagon production could be seen to gether.*

and ordered;

Tests represented in the table below and lower-upper dynamic abdominal MRI.

Analytes		**Results**	**[RI]**
Glucose (mg/dL), Fasting		97.00	[80 – 115]
Insulin (uIU/mL), Fasting		**110.80**	**[2.60 – 25.00]**
C-Peptide (ng/mL)	Fasting	3.41	[1.10 – 4.40]
	PP	6.89	
Islet Ab (titer)		Negative	
GAD Ab (IU/mL)		6.72	[<10.00]
Insulin Ab (%)		**62.5**	**[<8.20]**

Causes of Hyperinsulinemia

Interference ???

Hyperinsulinemic hypoglycemia

Mutation in genes;

Congenital
ABCC8, KCNJ11, GLUD1

Acquired
MEN1(insulinoma)

EIAS (Exogenous Insulin Autoimmune Syndrome)

Immune response to **exogenous insulin**

Insulin Autoimmune Syndrome

Hyperinsulinemia
Insulin Ab (+)
No exogenous insulin
Hypoglycemia
Neuroglycopenic symptoms

HLA alleles associated
HLA DRB1*0406, DQA1*0301, DQB1*0302
HLA DRB1*0403, DRB1*0406, DRB1*0407, DR9
DRB1*1104

Asulfhydril Group containing drugs;
Methimazole, glutathione, captopril, corticosteroids, INT-a, a- lipoic acid, imipenem, penicillin G

Our Case

Hyperinsulinemia
Insulin Ab (+)
No exogenous insulin
Normoglycemia
No neuroglycopenic symptoms

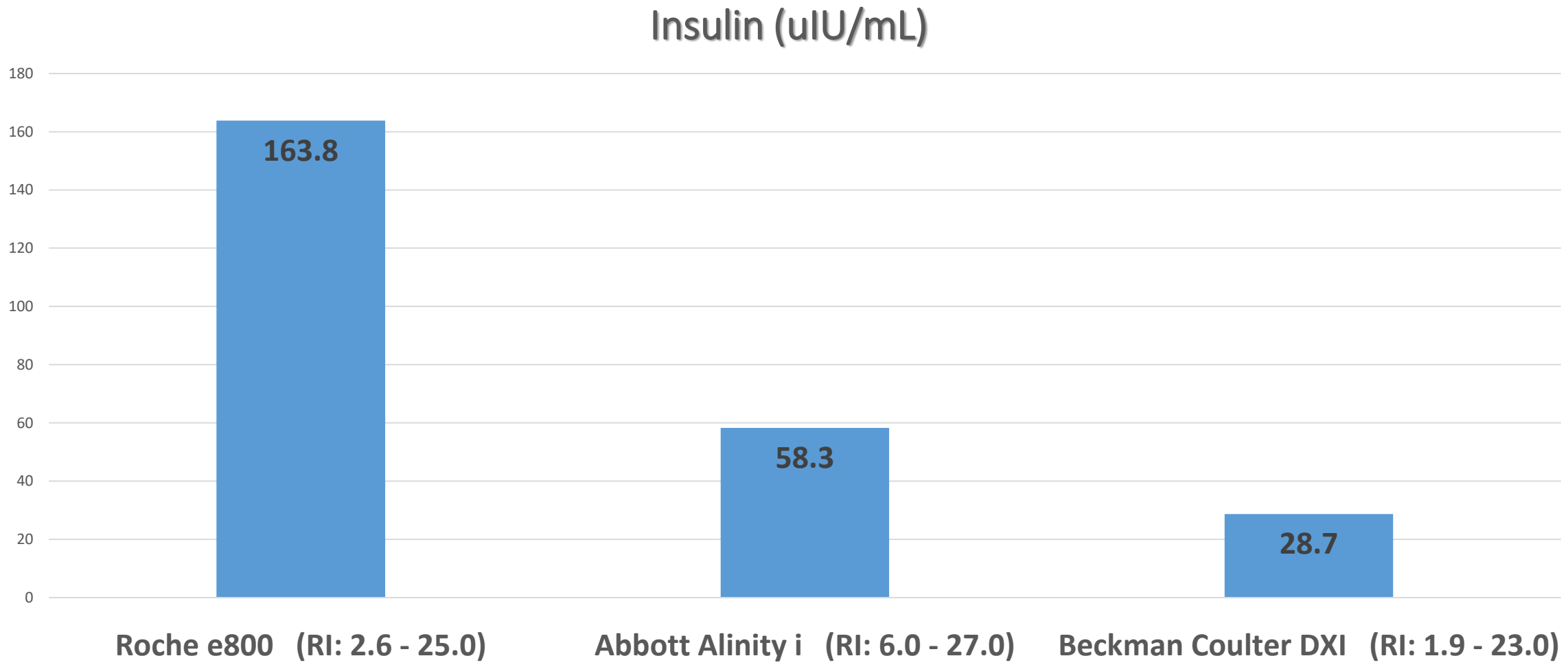
Precipitation by using Polyethylene Glycol (PEG)

	Insulin (uIU/mL)	
	Native Sample	**PEG-treated Sample**
Control Serum 1	129.80	133.60
Control Serum 2	49.20	48.40
Our Patient*	**110.80**	**19.20**

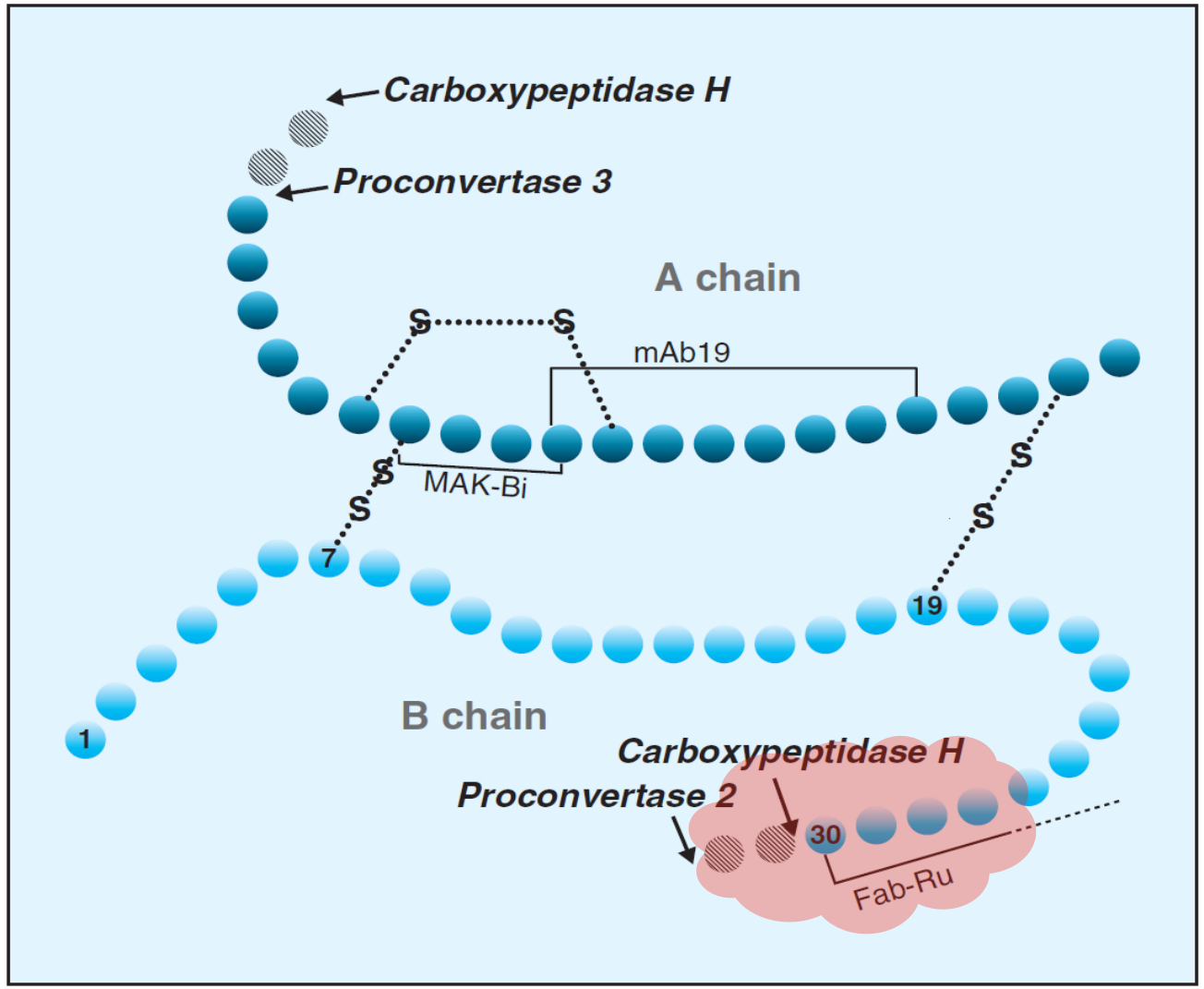
*:Insulin result in PEG-treated sample of the patient has been found to be **decreased 80% of the first insulin measurement**

(Current insulin CVa (%): 2.32)

Insulin Results on Different Immunoassay Systems



Insulin and Mapping of Anti-Insulin Antibodies Used in IMA's



Roche Anti-Insulin Abs;

MAK-Bi: Recognizes the A7-A10 portion of the A-chain

Fab-Ru: Recognizes the C-terminal part of the B-chain

Bi-Insulin IRMA Bio-Rad and
Insulin IRMA CIS bio assays use

mAB19: Recognizes A10-A17 portion of the A-chain

Roche anti-insulin Abs may be recognizing an anti-insulin/insulin complex made up by antibodies targeting the B-chain

High fasting serum insulin level due to autoantibody interference in insulin immunoassay discloses autoimmune insulin syndrome: a case report

Ann Biol Clin 2016; 74 (4): 490-4

Result Summary and Comments

- Why **«macroinsulin*» ?**
- C-peptide levels within reference interval, indicate normal circulating insulin levels.
- Insulin antibodies which potentially forms complex with insulin are tought to be the misleading insulin results in this case. T
- These complexes are probably ineffective since patient doesn't have any symptoms.

**: Diagnosis of insüline autoimmune syndrome using polyethylene glycol precipitation and gel filtration chromatography with ex vivo insülin change. Clinical Endocrinology (2017) 86, 347-353.*

Limitation of the Study

- **Not to be able to reveal the insulin-insulin ab complexes**

as the exact cause of the interference by enhanced analytical techniques

such as **gel-filtration chromatography**

which could be able to seperate insulin-insulin ab complexes and free insulin.

Conclusion

In cases of high insulin levels where the C-peptide level is normal, for Roche ECLIA**, the pre-treatment of the serum sample with PEG** or **reanalyse the test with another immunoassay** system may be considered.