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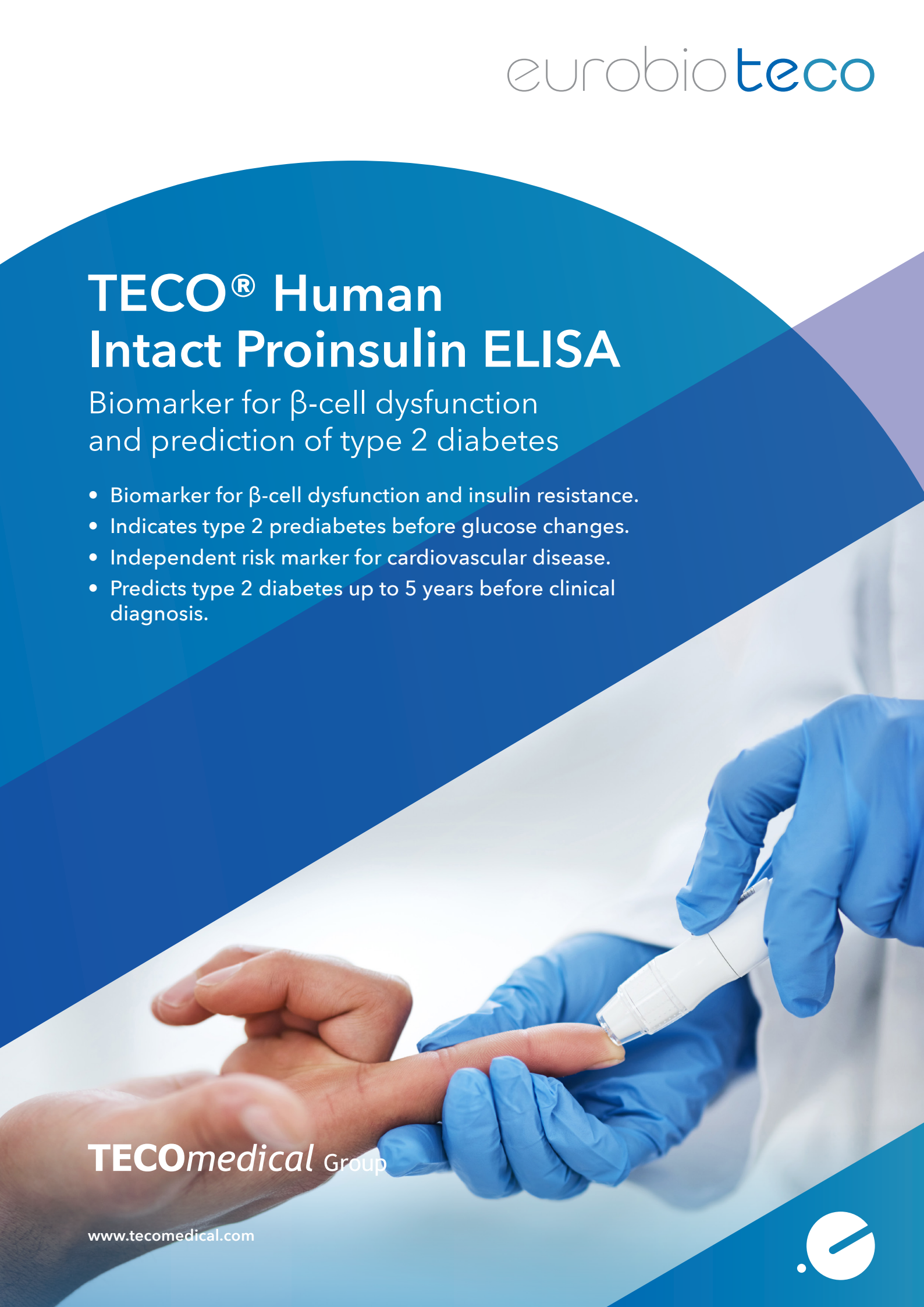
TECO® Human Intact Proinsulin ELISA

Biomarker for β-cell dysfunction and prediction of type 2 diabetes

- Biomarker for β-cell dysfunction and insulin resistance.
- Indicates type 2 prediabetes before glucose changes.
- Independent risk marker for cardiovascular disease.
- Predicts type 2 diabetes up to 5 years before clinical diagnosis.



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TECO® HUMAN INTACT PROINSULIN ELISA

Proinsulin is synthesized in pancreatic β-cells and cleaved into insulin and C-peptide. Insulin resistance (IR) or hyperglycemia causes increased secretion and finally a secretion disorder. Intact proinsulin levels in plasma then increase while insulin levels may decrease. Intact proinsulin lowers glucose. Elevated fasting intact proinsulin is a specific biomarker for β-cell dysfunction and insulin resistance as well as an independent risk factor for cardiovascular disease. The elevated 2-hour intact proinsulin level during oral glucose tolerance test predicts type 2 diabetes manifestation up to 5 years in advance.

Clinical use

Increased fasting intact proinsulin as a highly specific biomarker for pancreatic β-cell dysfunction.

Increased intact proinsulin is observed in three clinical situations:

A. The most important clinical situation is progressive β-cell dysfunction and type 2 diabetes (T2D) development. Increased intact proinsulin can occur at any stage of diabetes development. It specifically indicates the underlying cause of T2D, β-cell dysfunction and associated insulin resistance.
B. Shortly prior to manifestation of type 1 diabetes, exhausted β-cells secrete insulin and intact proinsulin.
C. In proinsulinoma, a very rare and benign tumor of the pancreatic β-cells.

Increased intact proinsulin during OGTT to diagnose prediabetes.

Up to 30 % of insulin resistant and (pre)diabetic patients remain undiagnosed due to normal blood glucose and HbA1c levels. Early detection of insulin resistance is very important, as many T2D patients already show cardiovascular damages during the first clinical diagnosis of their disease and these damages are, in part, not reversible. Still, 75 % of T2D patients die of cardiovascular events, whereas this is only true for 35 % of patients with type 1 diabetes.

Stage	Description	Insulin	Intact Proinsulin	Glucose
I	Insulin sensitive but lack of acute insulin response	Normal	Normal	Normal
II	Insulin resistance without qualitative secretion disorder	Elevated	Normal	Normal or elevated
IIIa	Insulin resistance with major ß-cell secretion disorder	Elevated to normal, at the end reduced	Elevated	Elevated, but normal in 30% of patients
IIIb	Collapsed ß-cell secretion	Low	Elevated to normal to low at the end	Elevated

Table 1:
Stages in the development of β-cell dysfunction (based on fasting determinations). In stage IIIa, when glucose levels remain normal, insulin resistance and cardiovascular damage remain undiagnosed.

In case of genetic predisposition, insulin resistance can result in pancreatic β-cell secretion disorder; intact proinsulin levels will increase while insulin levels may decrease. Because of the blood sugar reducing effect of proinsulin, glucose and HbA1c levels can remain normal for months or years even during OGTT, despite a severe and progressive dysfunction of pancreatic β-cells (stage IIIa, table 1 and figure 1).

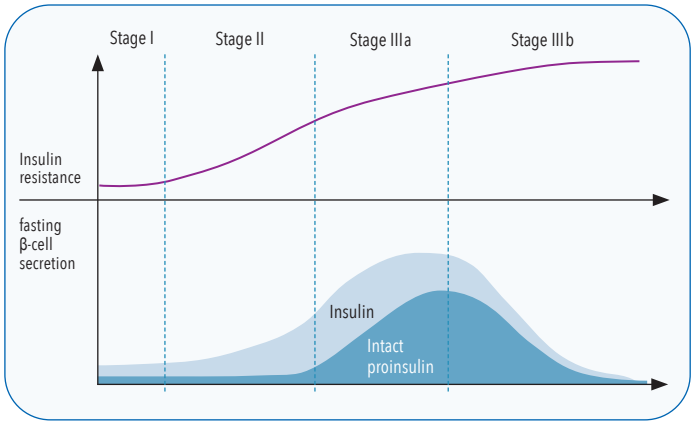

Figure 1:
Staging of β-cell dysfunction on the basis of insulin resistance and com- position of secretion product (fasting insulin and intact proinsulin) independently from the glucose value (Adapted from [2]).

Elevated intact proinsulin measured at time point 2 hours during OGTT indicates type 2 prediabetes even before glucose changes are detectable. Elevated intact Proinsulin can predict T2D development up to 5 years before clinical diagnosis. In addition, it can lead to irreversible cardiovascular damage irrespective of glucose control. [1-4]

CASE STUDIES

Intact proinsulin measured during oral glucose tolerance testing predicts type 2 diabetes development up to 5 years to clinical manifestation. [3-4]

20 normal individuals (10 male, 10 female, age 29-83) were subjected to OGTT. Glucose, HbA1c, insulin and intact proinsulin levels were measured at time points 0,1 hour and 2 hours after oral administration of 75 grams of glucose. Intact proinsulin was measured using TECO® Human Intact Proinsulin ELISA. Cut-off value for Intact Proinsulin is 7 pmol/L.

Four patients showed remarkable results: their glucose, insulin and HbA1c levels were normal at time point 0 and 2 hours, however intact proinsulin was also normal at time point 0 but increased (> 7 pmol/L) at time point 2 hours. These patient cases are described below in further detail, they all developed clinically manifest T2D 3-5 years later on. All others (16) showed normal values for all markers and did not develop T2D.

Case 1

Male, 83 years old, (BMI: 29.5 kg/m2) with controlled hypertension and a family history of T2D (mother). During OGTT in 2011, HbA1c was normal (5.7 %). OGTT results were as follows:

	Glucose	Intact Proinsulin
Normal value	80-120 mg/dL	< 7 pmol/L
0 h	104	1.56
2 h	67	11.94

End 2014, T2D was clinically confirmed in this patient, in 2015 is was under control with Metformin medication.

Case 2

Female, 83 years old, (BMI: 28.5 kg/m2) with controlled dyslipidemia and hypertension, no family history of T2D. Both parents had died 25 years ago from myocardial infarction. During OGTT in 2011, HbA1c was normal (5.5 %). OGTT results were as follows:

	Glucose	Intact Proinsulin
Normal value	80-120 mg/dL	< 7 pmol/L
0 h	86	2.36
2 h	126	10.21

Patient was subsequently followed with intervals of 6 months. Early 2015 fasting intact proinsulin suddenly increased to 12.3 pmol/L. T2D manifested during another OGTT (glucose values 0: 123 mg/dL and 2 h: 196 mg/dL). T2D was successfully treated with medication.

Case 3

Female, 46 years old, (BMI: 34.2 kg/m2) with manifest obesity. Family history of dyslipidemia and hyperuricemia and T2D in both living parents. During OGTT in 2011, HbA1c was normal (5.6 %). OGTT results were as follows:

	Glucose	Intact Proinsulin
Normal value	80-120 mg/dL	< 7 pmol/L
0 h	94	1.88
2 h	72	12.45

Patient was subsequently followed regularly. Although patient was able to reduce weight by 15 kg, clinically manifest T2D was diagnosed end of 2013 during another OGTT (glucose values 0: 105 mg/dL and 2 h: 211 mg/dL).

Case 4

Male, 29 years old, (BMI: 38.3 kg/m2) with morbid obesity. Father had died at age 48 from myocardial infarction, no record of disease with the mother. During OGTT in 2011, HbA1c was normal (5.6 %). OGTT results were as follows:

	Glucose	Intact Proinsulin
Normal value	80-120 mg/dL	< 7 pmol/L
0 h	86	3.55
2 h	92	11.94

Patient was subsequently followed regularly. Attempts to reduce weight were unsuccessful. Clinically manifest T2D was diagnosed end of 2014 during another OGTT (glucose values 0: 117 mg/dL and 2 h: 243 mg/dL). After con- sultation, patient agreed to bariatric surgery and a gastric band. Weight loss was over 30 kg in 6 months (BMI: 26.2 kg/m^2).

CONCLUSIONS

In all 4 cases, later development of T2D was already predicted up to 5 years earlier with increased intact proinsulin 2-hour levels during OGTT. All other 16 patients were also closely followed over 6 more years, no T2D was diagnosed. Figure 2 shows the OGTT results for both patient groups in 2011.

Intact proinsulin indicates type 2 prediabetes before glucose changes are detectable. It can predict type 2 diabetes development up to 5 years before clinical diagnosis. Glucose, insulin and HbA1c cannot detect prediabetes and predict later T2D development.

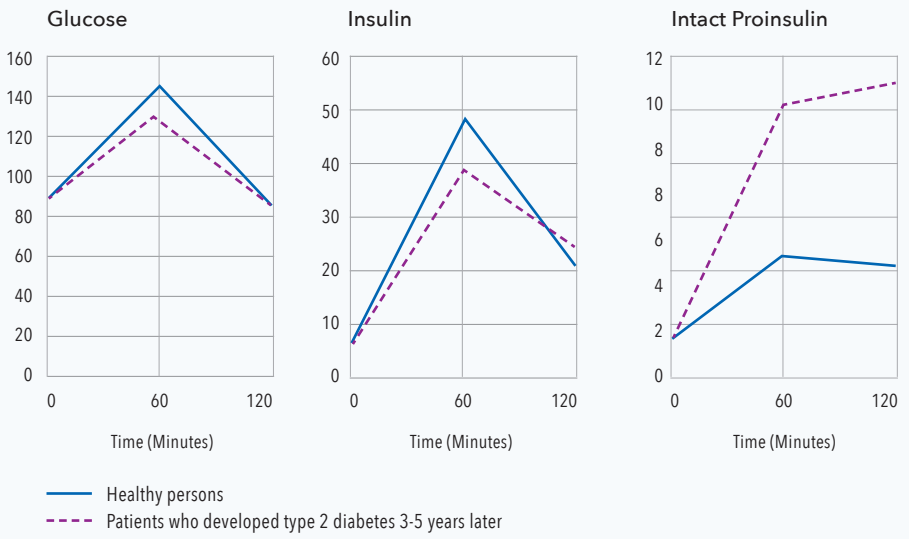

Figure 2:
Glucose, insulin and intact proinsulin profiles in OGTT for patients who developed T2D within 5 years from this test. Results are compared to healthy persons who did not develop T2D.

> *Only intact proinsulin predicts later T2D development. [4]*
> *(glucose in mg/dL; insulin in µU/mL); intact proinsulin in pmol/L.*

Early detection of increased risk for macrovascular complications and cardiovascular events.

Insulin resistance and prediabetes are closely correlated with macrovascular complications and increased mortality rate. Chronic systemic inflammation associated with insulin resistance and β-cell dysfunction can result in atherosclerosis, myocardial infarction and heart failure. Fasting intact proinsulin indicates the increased risk of patients for macrovascular complications, allowing early intervention and decrease of mortality risk.

TECO® HUMAN INTACT PROINSULIN ELISA

Intact versus total proinsulin - standardization and reference ranges

The TECO® Human Intact Proinsulin ELISA measures intact active proinsulin only. In contrast, total proinsulin tests also measure inactive and stable breakdown products. Therefore, only intact pro- insulin is a direct measure of pancreatic β-cell function.

Important for clinical use: only intact proinsulin can be standardized against the WHO standard 09/296 (International WHO-Standard for Intact Proinsulin)

CUT-OFF VALUES FOR INTACT PROINSULIN

Fasting values:

- values ≤ 7 pmol/L (WHO 09/296) are considered normal.
- values > 7 pmol/L (WHO 09/296) suggest progressive β-cell dysfunction, insulin resistance and possibly type 2 (pre)diabetes. It is also a high-risk indicator for cardiovascular disease.

Oral Glucose Tolerance Testing:

- values ≤ 7 pmol/L (WHO 09/296) are considered normal and suggest normal β-cell function and no risk for type 2 diabetes and cardiovascular disease.
- values > 7 pmol/L (WHO 09/296) indicate progressive β-cell dysfunction and insulin resistance and are highly predictive of development of type 2 diabetes within 5 years.

Intact Proinsulin ELISA - Cat. No.: TE1012 - UDI-DI : 7640146270016

CE IVD

Sample type	Serum, EDTA / heparin plasma
Sample preparation	Blood sampling – fasting. Because of better sample stability EDTA plasma and heparin plasma are the preferred sample types. The sample collection can take place in HbA1C tubes. These samples are stable at room temperature and should be centrifuged within 48 hours.

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