METABOLIC SYNDROME and associated pathologies

- Obesity
- Insulin resistance
- Diabetes type 2
- Cardio Vascular disease
- PCOS
- Fatty Liver disease (NAFLD/NASH)

February 2015, prepared for: TECOmedical Group
Prepared by: Life-Force biomedical communications
Intact Proinsulin for Accurate and Early Detection of Pancreatic β-cell dysfunction and Type 2 Prediabetes.

Elevated fasting morning intact proinsulin is a highly specific indicator for advanced β-cell dysfunction and clinically relevant insulin resistance.

Elevated two-hour intact proinsulin during an oral glucose tolerance test (OGTT):
- Indicates progressive β-cell dysfunction and increased risk for progressive diabetes type 2 development and cardiovascular disease, prior to glucose deterioration.
- Enables earlier and more efficient prevention of diabetes and cardiovascular disease by lifestyle changes and medication (for example glitazone, GLP-1 and SGLT2).

Recommended testing involves:
- HOMA score (fasting glucose and insulin) in combination with intact proinsulin.
- OGTT with 0, 1, 2-hour glucose and 0, 2-hour intact proinsulin measurements:
  - 0-hour intact proinsulin >11 pmol/L indicates late stage β-cell dysfunction and insulin resistance.
  - 2-hour intact proinsulin >15 pmol/L indicates increased risk for progressive diabetes development and cardiovascular disease.

- The impact of lifestyle changes and treatment intervention to normalize intact proinsulin levels and β-cell function can be assessed by repeating above testing one month after initiation of the intervention therapy.

Clinical advice for this paper was provided by Prof. Andreas Pfützner, MD, PHD, Diabetes Center Mainz, Germany.

Authors:
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1. IFFE – Institute for Clinical Research and Development, Mainz/Germany
2. Concept: BEAK: (Beta-cell dysfunction, Visceral Adipose tissue & Insulin Resistance Patient pending
3. University of Applied Sciences, Rheinbach/Germany
4. Life Force Biomedical communication, Rheinbach/Germany

TECotechnical Bulletin

Intact Proinsulin

January 2013

METABOLIC SYNDROME

Metabolic Syndrome
and associated pathologies

Obesity
Diabetes type 2
Insulin resistance
PCOS
Cardiovascular risk

Fatty Liver disease
(NAFLD/NASH)
**METABOLIC SYNDROME**

description

- MSY is combination of risk factors:
  1. Insulin resistance and/or high blood sugar
  2. Abdominal obesity (belly fat)
  3. Elevated triglycerides/
     low HDL/high LDL cholesterol:
  4. Hypertension

- Increase risk for:
  1. Diabetes T2
  2. Cardiovascular disease
  3. Stroke
  4. Fatty liver disease
  5. PCOS in young women
# Metabolic Syndrome: Diagnostic Criteria

<table>
<thead>
<tr>
<th>WHO</th>
<th>EGIR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>World Health Organization</strong></td>
<td><strong>European Group for the Study of Insulin Resistance</strong></td>
</tr>
<tr>
<td>Presence of one of following:</td>
<td>Insulin resistance AND two or more of following:</td>
</tr>
<tr>
<td>DM / IGT / IFG / Insulin resistance</td>
<td>Central obesity (^{(4)})</td>
</tr>
<tr>
<td><strong>AND two of the following:</strong></td>
<td>Dyslipidemia (^{(5)})</td>
</tr>
<tr>
<td>BP ≥ 140/90</td>
<td>BP ≥ 140/90</td>
</tr>
<tr>
<td>Dyslipidemia (^{(1)})</td>
<td>FBG ≥ 6.1 mmol/L (110 mg/dL)</td>
</tr>
<tr>
<td>Central obesity (^{(2)})</td>
<td></td>
</tr>
<tr>
<td>Microalbuminuria (^{(3)})</td>
<td></td>
</tr>
</tbody>
</table>
METABOLIC SYNDROME
obesity, inflammation & atherosclerosis

▼ Increasing lipid tissue secretes hormones, **adipokines**.
▼ **Adipokines** (adiponectin, leptin, IL-6...) activate immune system locally & systemically, affect **insulin sensitivity** cells.
▼ **CRP**, Acute phase inflammatory protein is involved
▼ **Chronic inflammation** in walls of arteries caused by accumulation of macrophage white blood cells
▼ Leads to accumulation of fatty materials such as cholesterol and triglycerides and hardening of arteries:

➢ ✔ **Atherosclerosis** (arteriosclerosis)
METABOLIC SYNDROME

obesity, inflammation & atherosclerosis

Increasing amount of lipid tissue secretes hormones:

- Adipokines are proinflammatory, activate immune system locally and systemically

- CRP, acute phase inflammatory protein is involved

- Chronic inflammation in walls of arteries caused by accumulation of macrophage white blood cells

- Leads to accumulation of fatty materials such as cholesterol and triglycerides and hardening of arteries:

  - Atherosclerosis (arteriosclerosis)
METABOLIC SYNDROME

*adipokines*

- **Adipo(cyto)kines** are cytokines (cell-to-cell signalling proteins) secreted by adipose (fat)tissue
- **Adipokines** cause chronic inflammation
- Affect **insulin sensitivity** cells
- **Adiponectin, leptin** play major role in lipid metabolism

**Table 2, Recently described adipokines.**

<table>
<thead>
<tr>
<th>Adipokines</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>Free Fatty acids</td>
</tr>
<tr>
<td>Interleukine-6</td>
<td>PAI-I and tPA</td>
</tr>
<tr>
<td>Retinol Binding protein 4</td>
<td>Angiotensin II</td>
</tr>
<tr>
<td>Adipsin (<em>Complementation factor D</em>)</td>
<td>TNF-alpha</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Visfatin</td>
</tr>
<tr>
<td>Resistin</td>
<td>Vaspin</td>
</tr>
</tbody>
</table>
METABOLIC SYNDROME

**insulin resistance**

- Oxidative stress & inflammation cause **Insulin Resistance**
- Sugar levels in blood rise: **hyperglycemia**
- Pancreas β-cells produce more insulin: **hyperinsulinemia**
- Advanced stage: *increase Pro-insulin*, decrease insulin

**Pro-insulin**

⇒ blood sugar reducing effect is very low
⇒ **High adipogenic potency** > more lipid tissue

- More adipokines ..........more inflammation...more insulin resistance...
- Inflammation causes atherosclerosis

➢ **Vicious circle**
METABOLIC SYNDROME

vicious circle

Adiponectin

Intact Proinsulin

Hyperglycemia

hsCRP

Insulin Resistance

β-Cell Dysfunction

Insulin requirement ↑

Insulin ↑ Proinsulin ↑↑↑

Anti-insulinemic hormones ↑

Adiponectin ↓

Leptin ↑

Pre-Adipocyte

Lipid Cell

Stem Cell

Free Fatty Acids ↑

Angiotensin ↑

Atherosclerosis

Dyslipidemia ↑↑↑

Hypertension ↑↑↑

OBESITY
METABOLIC SYNDROME

development

- Food intake excess
- Genetic background
- Physical inactivity

Adipogenesis
Overweight
Obesity

A. Hyperinsulinemia
B. Hyperinsulinemia

Macrovascular complications
Hyperglycemia
Pancreatic beta cells stress & damage

Diabetes type 2

Life time
**Type 2 Diabetes mellitus (T2DM)**

- **Age-related** (onset 50-60 yrs), strong genetic components.
- Due to *increasing obesity* in children, T2DM occurs also at young age.
- T2DM is one possible outcome in metabolic syndrome.

  - Development of **β-cell dysfunction** is key.
  - **Early stage**: insulin secretion is normal or reduced.
  - **Advanced stage**: highly *elevated Proinsulin* levels.
**Type 2 Diabetes mellitus (T2DM) stages**

- **I**
  - Description: Insulin sensitive
  - Insulin: Normal
  - Proinsulin: Normal
  - Glucose: Normal

- **II**
  - Description: Insulin resistance without qualitative secretion disorder
  - Insulin: Elevated
  - Proinsulin: Normal
  - Glucose: Normal or elevated

- **IIIa**
  - Description: Insulin resistance with major β-cell secretion disorder
  - Insulin: Normal/Elevated
  - Proinsulin: Elevated
  - Glucose: Normal or Elevated

- **IIIb**
  - Description: Collapsed β-cell secretion
  - Insulin: Low
  - Proinsulin: Elevated to normal (in end stage)
  - Glucose: Elevated
Type 2 Diabetes mellitus (T2DM)

DIAGNOSIS
Type 2 Diabetes mellitus (T2DM)

Dx by blood glucose

- Fasting glucose blood levels > 126 mg/dL
- Oral Glucose Tolerance Test (OGTT) > 200 mg/dL

<table>
<thead>
<tr>
<th>Glucose levels</th>
<th>Normal</th>
<th>Impaired fasting glycaemia</th>
<th>Impaired glucose tolerance</th>
<th>Diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous Plasma</td>
<td>Fasting 2hrs</td>
<td>Fasting 2hrs</td>
<td>Fasting 2hrs</td>
<td>Fasting 2hrs</td>
</tr>
<tr>
<td>(mmol/L)</td>
<td>&lt;6.1 &lt;7.8</td>
<td>&gt; 6.1 &amp; &lt;7.0 &lt;7.8</td>
<td>&lt;7.0 &gt;7.8</td>
<td>&gt;7.0 &gt;11.1</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>&lt;110 &lt;140</td>
<td>&gt;110 &amp; &lt;126 &lt;140</td>
<td>&lt;126 &gt;140</td>
<td>&gt;126 &gt;200</td>
</tr>
</tbody>
</table>

Table 4: 1999 WHO Diabetes criteria - Interpretation of Oral Glucose Tolerance Test

2010 American Diabetes Association Standards of Medical Care in Diabetes added glycosylated hemoglobin (HbA1c) ≥ 48 mmol/mol as another criterion for the diagnosis of diabetes (not consensus!!!
Type 2 Diabetes mellitus (T2DM)
Dx by HOMA score

- **Homeostasis Model Assessment:**
  
  \[ Fasting \text{ insulin (µU/ml)} \times fasting \text{ glucose (mmol/l)} / 22.5. \]

- Assumption: in normal person, normal blood glucose is associated with normal insulin level.

- **IR** is assumed when elevated blood glucose is associated with normal insulin level, **HOMA score > 2**.

- Estimates β-cell dysfunction & insulin resistance (IR) in **non or early stage-diabetic** patients.

- **HOMA is NOT a good tool with**
  
  - high Proinsulin levels and late stage IR.
  - patients treated with **sulfonylurea drugs**
Type 2 Diabetes mellitus (T2DM)

Early diagnosis is key

TECO Technical Bulletin

Intact Proinsulin

Intact Proinsulin for Accurate and Early Detection of Pancreatic β-cell dysfunction and Type 2 Prediabetes.

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Recommended testing involves:

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- The impact of lifestyle changes and treatment intervention to normalize intact proinsulin levels and β-cell function can be assessed by repeating above testing one month after initiation of the intervention therapy.

Pfützer A et al Elevated Intact Proinsulin Concentrations During an Oral Glucose Challenge Indicate Progressive β-Cell Dysfunction and may be Predictive for Development of Type 2 Diabetes Diabetes Care 2014. Submitted paper.
Type 2 Diabetes mellitus (T2DM)

Early diagnosis is key

- β-cell dysfunction and IR remain undetected when blood sugar is still normal due to high Proinsulin.
- Prediabetic patients already suffer from cardiovascular damages which are irreversible.
- Cardiovascular damages are often cause of death later on in life (75%).
- Early diagnosis by Proinsulin and Proinsulin combined with OGTT can detect prediabetics.
1. 0-hour intact proinsulin >11 pmol/L indicates late stage β-cell dysfunction and insulin resistance.

2. 2-hour intact proinsulin > 15 pmol/L indicates increased risk for progressive diabetes development and cardiovascular disease.
Type 2 Diabetes mellitus (T2DM)

Proinsulin/OGTT predicts later T2D development

- After 5 years, all of the IGT patients had developed T2D.
- All individuals that had T2D had normal fasting but elevated 2 hour intact proinsulin values during the original OGTT, 5 years ago.
- In contrast, the individual insulin concentrations were not indicative for diabetes development.
- Elevated 2 hour Intact Proinsulin during OGTT indicated the onset of diabetes development prior to glucose deterioration and is predictive for later type 2 diabetes development.

**Elevated 2 hour intact proinsulin is useful as an additional diabetes risk assessment parameter, independent of blood sugar levels.**
Cardiovascular Disease

related to diabetes

- 75% of T2DM pts. die of cardiovascular disease.
- Cardiovascular damage is caused by IR and inflammation before diabetes is diagnosed.
- IR affects not only metabolic but also vascular receptors involved in vasoprotection.
- **Early detection** of prediabetics using **3 biomarkers** allows early intervention to prevent irreversible cardiovascular damages in diabetes pts.

  - **Adiponectin**, reverse indicator of fat tissue activity
  - **C-Reactive Protein**, inflammatory marker
  - **Proinsulin**, blood glucose independent marker for β-cell dysfunction & Insulin Resistance
Cardiovascular Disease

risk assessment and therapy monitoring

Non-diabetic men, n = 874, mean observation period = 26.7 years

Zethelius et al., Circulation. 105:2153-8, 2002
Metabolic Syndrome
diagnosis, risk assessment & therapy monitor

β-cell function
Insulin sensitivity
Cardiovascular risk

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact Proinsulin:</td>
<td>&lt;11 pmol/l = low risk</td>
<td>[GREEN]</td>
</tr>
<tr>
<td></td>
<td>≥11 pmol/l = high risk</td>
<td>[RED]</td>
</tr>
<tr>
<td>Adiponectin:</td>
<td>≥10 mg/l = low risk</td>
<td>[GREEN]</td>
</tr>
<tr>
<td></td>
<td>7–10 mg/l = grey zone</td>
<td>[YELLOW]</td>
</tr>
<tr>
<td></td>
<td>≤ 7 mg/l = high risk</td>
<td>[RED]</td>
</tr>
<tr>
<td>hsCRP:</td>
<td>0–1 mg/l = low risk</td>
<td>[GREEN]</td>
</tr>
<tr>
<td></td>
<td>≥1–3 mg/l = average risk</td>
<td>[YELLOW]</td>
</tr>
<tr>
<td></td>
<td>≥3–10 mg/l = high risk</td>
<td>[RED]</td>
</tr>
<tr>
<td></td>
<td>≥10 mg/l = unspecific</td>
<td>[RED]</td>
</tr>
</tbody>
</table>
Cardiovascular Disease

risk assessment and therapy monitoring

<table>
<thead>
<tr>
<th>Intervention</th>
<th>β-cell dysfunction</th>
<th>Visceral tissue activity</th>
<th>Chronic systemic inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>intact Proinsulin</td>
<td>Adiponectin</td>
<td>hsCRP</td>
</tr>
<tr>
<td>Diet &amp; Exercise</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Sulphonylurea/Glinides</td>
<td>↑ or ↓</td>
<td>↓ or ↑</td>
<td>↑ or ↓</td>
</tr>
<tr>
<td>Metformin</td>
<td>( )</td>
<td>( )</td>
<td>( )</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>DPPIV-Inhibitors</td>
<td>↓ or ( )</td>
<td>( )</td>
<td>( )</td>
</tr>
<tr>
<td>GLP-1 Analogs</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>SGLT-2 Inhibitors</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Insulin (early)</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Insulin (late)</td>
<td>↑ or ↓</td>
<td>↑ or ↓</td>
<td>( )</td>
</tr>
</tbody>
</table>
Fatty Liver Disease related to metabolic syndrome

- Increasing prevalence of obesity and metabolic syndrome leads to increase of nonalcoholic fatty liver disease (NAFLD).
- NAFLD can lead to NASH, liver cirrhosis and hepatocellular carcinoma
- Current Dx of liver injury have severe limitations:
  - AST/ALT levels frequently do not increase even when liver fibrosis is evident (up to 30 %)
  - Biopsy is invasive, expensive, gives sample errors
- Use of liver biomarkers to predict NAFLD progression into NASH in obese patients
  (e.g. apoptosis marker ccK18, M30 ELISA)

(Canbay et al.)
**Fatty Liver Disease related to metabolic syndrome**

<table>
<thead>
<tr>
<th>Liver damage biomarker</th>
<th>Indicative for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspases cleaved Keratin 18 (ccK18: M30 Elisa)</td>
<td>Hepatocyte apoptosis</td>
</tr>
<tr>
<td>Keratin 18 (cleaved and uncleaved: M65 Elisa)</td>
<td>Hepatocyte apoptosis and necrosis</td>
</tr>
<tr>
<td>Alpha Glutathione S-Transferase (α GST, serum)</td>
<td>Hepatocyte damage</td>
</tr>
<tr>
<td>Pi Glutathione S-Transferase (π GST, serum)</td>
<td>Bile duct damage</td>
</tr>
<tr>
<td>Collagen IV (serum)</td>
<td>Increased collagen deposition</td>
</tr>
</tbody>
</table>

**Figure 8. Liver damage biomarkers in diabetic patients**

For each diabetic patient, liver biomarker levels were expressed as a percentage of the upper limit of the normal range for the specific marker (upper limit for ccK18: 186 U/L; K18: 183 U/L; α GST: 12 μg/L).
Polycystic Ovary Syndr. related to obesity & IR

- Endocrine disorder in young women, characterized by increased levels of androgenic hormones.
- Often associated with obesity and IR.
- PCOS pts have increased risk for developing NASH.
- Canbay: investigate PCOS pts for NASH and female NASH pts for PCOS.
PRODUCT
INFORMATION
PROINSULIN
Biochemical & clinical

Intact Proinsulin

• Produced in and secreted by pancreatic β-cells.
• Normally further processed to insulin and C-peptide.
Insulin production in the β-cell

Proinsulin ---→ Insulin + C-Peptide

Ribosome

Vesicles

β-Cell membrane

Plasma

Pfützner et al., Diabetes Technol. Ther. 6:405-412, 2004
Qualitative β-Cell Secretion Disorder in T2 Diabetes

Proinsulin ---\rightarrow Insulin + C-Peptide

Pathologically increased insulin secretion

Ribosome

Plasma

Pfützer et al., Diabetes Technol. Ther. 6:405-412, 2004
Biochemical & clinical

Intact Proinsulin

- Normally, intact proinsulin is rapidly degraded >> low concentrations in the plasma of healthy subjects.
- Increase in insulin demand, caused by insulin resistance in later stages of type 2 diabetes, can result in increased secretion of proinsulin into the blood.
- Considered as an independent cardiovascular risk factor.
- High levels can also be due to insulinoma (very rare benign pancreatic tumor).
Biochemical & clinical

INTACT VS. TOTAL PROINSULIN

• Intact proinsulin is the molecule just secreted by β-cells, this makes it an excellent and dynamic biomarker to measure β-cell dysfunction.
• Secreted Intact Proinsulin is rapidly degraded: $T_{1/2} = 15’$.
• Total Proinsulin = Intact + Cleavage products (des32,33).
• Cleavage products are stable: $T_{1/2} = $ several hours, can be up to 30-50% of Total Proinsulin.
• Total Proinsulin is not suitable as marker to measure β-cell dysfunction
Proinsulin fragments

Intact Proinsulin

Des31,32-Proinsulin

Des64,65-Proinsulin

C-Peptide

Insulin

**Intact Proinsulin** diagnostic use

- Fasting morning proinsulin can be used as **highly specific indicator of insulin resistance**.
- Staging of insulin resistance /β-cell dysfunction, without or with Glucose Tolerance Test.
  - Early detection of prediabetics using Proinsulin may allow early intervention to prevent irreversible cardiovascular damages in diabetes pts.
- High levels (> 11 pmol/L) can indicate:
  - **Insulin resistance and secretion disorder.**
  - **High cardiovascular risk.**
  - **Insulinoma** *(benign insulin producing tumor of pancreas).*
Intact Proinsulin & Coronary Risk

Non-diabetic men, $n = 874$, mean observation period = 26.7 years

Zethelius et al., *Circulation.* 105:2153-8, 2002
# Intact Human Proinsulin assay

<table>
<thead>
<tr>
<th>Cat. No.:</th>
<th>TE1012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tests:</td>
<td>96</td>
</tr>
<tr>
<td>Method:</td>
<td>ELISA mono/mono</td>
</tr>
<tr>
<td>Range:</td>
<td>~ 3 - 100 pmol/L</td>
</tr>
<tr>
<td>Sensitivity:</td>
<td>0.3 pmol/L</td>
</tr>
<tr>
<td>Incubation time:</td>
<td>2.5 hours</td>
</tr>
<tr>
<td>Sample volume:</td>
<td>50 µl</td>
</tr>
<tr>
<td>Sample type:</td>
<td>Serum, EDTA / Heparin plasma, cell culture</td>
</tr>
</tbody>
</table>
Intact Proinsulin reference values

- Fasting values: ≤ 11 pmol/l
- Mean value: 3.99 ± 1.58 SD, Median 3.61.
- Non-diabetic patients versus HOMA positive samples (score > 2).
Intact Proinsulin assay interpretation

< 11 pmol/l
- No severe β-cell dysfunction
- Insulin resistance not excluded, perform HOMA
- lower cardiovascular risk.

≥ 11 pmol/l
- β-cell dysfunction with clinically relevant insulin resistance
- high cardiovascular risk.
- Exclude insulinoma.

▼ Intact Proinsulin indicates improvement in cardiovascular risk profile.
PRODUCT INFORMATION

ADIPONECTIN
Biochemical & clinical

Adiponectin

- Mainly synthesized by mature (white) adipose tissue.
- Present as monomer and as multimers; detection of either low and/or high MW form seems irrelevant.
- **Functions as insulin sensitizer** by
  - decreasing excessive glucose levels without increasing insulin concentrations.
  - by stimulating the burning of fat in muscle and liver.
  - potent anti-inflammatory, atheroprotective and antidiabetic effects.
Biochemical & clinical

Adiponectin

- Plasma levels are very sensitive to changes in metabolic state of lipid tissue and changes in insulin resistance.

- Low levels are associated with insulin resistance, metabolic syndrome and increased risk of diabetes Type II.

- Adiponectin is most likely the link between obesity, coronary artery disease (CAD), type II diabetes and insulin resistance.
Diagnostic use
Adiponectin

- **Cardiovascular risk marker.**
- **Biomarker for:**
  - Hormonal activity of the visceral lipid tissue (driving insulin resistance and chronic systemic inflammation)
  - Cardiovascular disease, especially CAD
  - Metabolic condition.
  - Insulin resistance.
  - Therapy efficacy: increase is indicator for improved metabolic and inflammatory condition.
- *Possible role in rheumatoid arthritis. Plasma and synovial fluid levels were high in RA.*

Schöndorf et al., Clin. Lab. 55:489-494, 2005
## Total human Adiponectin assay

<table>
<thead>
<tr>
<th>Cat. No.:</th>
<th>TE1013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tests:</td>
<td>96</td>
</tr>
<tr>
<td>Method:</td>
<td>ELISA</td>
</tr>
<tr>
<td>Range:</td>
<td>1 - 100 ng/ml native Adiponectin</td>
</tr>
<tr>
<td>Sensitivity:</td>
<td>&lt; 0.6 ng/ml</td>
</tr>
<tr>
<td>Incubation time:</td>
<td>2 hours</td>
</tr>
<tr>
<td>Sample volume:</td>
<td>100 µl (diluted)</td>
</tr>
</tbody>
</table>
| Sample type:      | Serum, heparin plasma (dilution 1:200 to 1:500)  
                     breast milk, urine, saliva, CSF (dilution 1:2 to 1:10),  
                     Cell culture (dilution 1:5 to 1:200) |
Adiponectin reference values

- Values are **age and sex dependent**.
- For detailed age values, see D.I.

<table>
<thead>
<tr>
<th>Gender</th>
<th>n</th>
<th>Mean (μg/ml)</th>
<th>Median (μg/ml)</th>
<th>SD</th>
<th>5th Percentile (μg/ml)</th>
<th>95th Percentile (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>101</td>
<td>10,2</td>
<td>9,1</td>
<td>4,6</td>
<td>4,0</td>
<td>19,4</td>
</tr>
<tr>
<td>Men</td>
<td>125</td>
<td>6,8</td>
<td>6,1</td>
<td>4,1</td>
<td>2,0</td>
<td>13,9</td>
</tr>
<tr>
<td>All</td>
<td>226</td>
<td>8,3</td>
<td>7,5</td>
<td>4,6</td>
<td>2,4</td>
<td>19,3</td>
</tr>
<tr>
<td>Girls</td>
<td>131</td>
<td>8,71</td>
<td>8,18</td>
<td>4,32</td>
<td>3,05</td>
<td>15,6</td>
</tr>
<tr>
<td>Boys</td>
<td>134</td>
<td>8,97</td>
<td>8,12</td>
<td>5,13</td>
<td>3,36</td>
<td>18,6</td>
</tr>
<tr>
<td>All</td>
<td>265</td>
<td>8,84</td>
<td>8,18</td>
<td>4,74</td>
<td>3,33</td>
<td>16,5</td>
</tr>
</tbody>
</table>
Cutoff Wert Adiponektin für das cardiovaskuläre Risiko beim metabolischen Syndrom

Evaluierung der klinischen Aussage mittels Adiponektin, intakt Proinsulin und CRP.

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PRODUCT INFORMATION

LEPTIN
**Function**

**Leptin** *(from Greek λεπτός leptos, "thin")*

- hormone made by fat cells, regulates amount of fat stored in the body.
- adjusts both the sensation of hunger and energy expenditures.
- when the amount of fat stored reaches a certain level, leptin is secreted and activates leptin receptors in the hypothalamus.
- hunger is then inhibited (satiety) and energy expenditure increased
- The effect of leptin is opposite to that of ghrelin, the "hunger hormone".
Biochemical & clinical

**Leptin** *(from Greek λεπτός leptos, "thin")*

- circulating leptin is directly proportional to the total amount of fat in the body
- Absence of leptin (or its receptor) in mice leads to uncontrolled appetite and obesity.
- Fasting/diets lower leptin levels.
- Key role in lipid metabolism
- Key role in regulation body weight
- Suppressing food intake, increasing energy expenditure
  - Obesity
  - Fertility
  - Angiogenesis
  - Bone formation
Diagnostic use

Leptin

- Metabolic syndrome
- Obesity
- Cachexia and metabolic disorders
- Nutritional disorders
Human Leptin assay

<table>
<thead>
<tr>
<th>Cat. No.</th>
<th>TE1015</th>
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</thead>
<tbody>
<tr>
<td>Tests:</td>
<td>96</td>
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<tr>
<td>Method:</td>
<td>ELISA</td>
</tr>
<tr>
<td>Range:</td>
<td>1 - 100 ng/ml, recombinant Leptin WHO NIBSC 97/594</td>
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<tr>
<td>Sensitivity:</td>
<td>0.2 ng/ml</td>
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<tr>
<td>Incubation time:</td>
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<tr>
<td>Sample volume:</td>
<td>20 µl</td>
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<tr>
<td>Sample type:</td>
<td>Serum, heparin plasma, urine, CSF, cell culture EDTA and Citrat-Plasma will show 20 % lower results</td>
</tr>
</tbody>
</table>
**Leptin reference values**

- Depends on body fat mass with low levels in lean and high levels in obese subjects.

- Gender difference with higher levels in females at a given percentage body fat.

- Influenced by pubertal development (Tanner stages).

  Serum leptin levels are referred to BMI and stratified according to gender and pubertal development.
Leptin reference values

- See examples and D.I. for details:
Leptin Therapy behaviour

- A decrease in Leptin over time is an indicator of stabilization of the metabolic condition with lower body weight.

- Weight reduction, especially fat, lowers leptin levels.

- The brain needs to become accustomed to low leptin levels, otherwise the body is forced to eat more (jojo effect).
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