ADIPONECTIN
CLINICAL DIAGNOSTIC BIOMARKER FOR METABOLIC RISK ASSESSMENT
ADIPONECTIN

Metabolic Syndrome | Type 2 Diabetes
Cancers | Cardiovascular Disease
ADIPONECTIN IN ASSESSING TYPE 2 DIABETES RISK

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METABOLIC AND INSULIN CONCERNS

CARDIAC CONCERNS

CANCER

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RELATED PRODUCTS

RANNOX - A GLOBAL DIAGNOSTIC SOLUTIONS PROVIDER

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A niche product from Randox meaning that we are one of the only manufacturers to provide the adiponectin test in an automated biochemistry format.

CE marked for diagnostic use.

Automated assay which removes the inconvenience and time consumption associated with traditional ELISA based testing.

Applications available for a wide range of automated biochemistry analysers - to ensure ease of programming and confidence in results.

Liquid ready-to-use reagents for convenience and ease-of-use.

Latex Enhanced Immunoturbidimetric method delivering high performance.

Extensive measuring range for measurement of clinically important results.

Complementary controls and calibrators available offering a complete testing package.

“higher adiponectin levels are associated with a lower risk of T2DM across diverse populations”3
Adiponectin is a protein hormone and is secreted by adipocytes, with anti-inflammatory and insulin-sensitising properties. It plays an important role in a number of metabolic processes such as glucose regulation and fatty acid oxidation.

Adiponectin levels are inversely correlated with abdominal visceral fat (AVF) levels, which have proven to be a strong predictor of several pathologies including metabolic syndrome, type 2 diabetes mellitus (T2DM), cancers and cardiovascular disease (CVD).

It is widely recognised that people who are overweight are at higher risk of developing T2DM.

» Measuring waist circumference alone has limitations: studies have shown that waist circumference measures total abdominal fat reliably, but its association with visceral fat depends on visceral fat/subcutaneous fat ratios that vary by gender and ethnicity.¹

» Body mass index (BMI) (weight kg / height m²) is another common method of determining which patients are classed as overweight or obese, however using BMI as a measuring tool has limitations in measuring athletes and varies in reliability based on age, sex, and race.

As such adiponectin levels are a much more reliable indicator of at-risk patients. It is not influenced by these factors.
ADIPONECTIN IN ASSESSING T2DM RISK

Traditional methods of T2DM risk assessment

Traditional biomarker tests used to assess T2DM risk include FPG (Fasting Plasma Glucose), OGTT (Oral Glucose Tolerance Test), and HbA1c. However these are not risk assessment biomarkers. At diagnosis, beta cell damage in the pancreas has already occurred, and insulin insensitivity is already underway.

As described before, measuring waist circumference and BMI are not reliable enough for assessing at-risk patients. As such, adiponectin levels are a much more reliable indicator of at-risk patients.

A number of key publications have advocated the testing of adiponectin in clinical settings

1. JAMA (2009): Adiponectin Levels and the Risk of Type 2 Diabetes – a Systematic Review and Meta-Analysis³
   - A meta-analysis involving 13 prospective studies with a total of over 14,598 participants and 2,623 cases of type 2 diabetes
   - Conclusion: higher adiponectin levels are associated with a lower risk of T2DM across diverse populations

Open data markers indicate reference values for each plot; error bars, 95% confidence intervals. ARIC indicates Atherosclerosis Risk in Communities; EPIC, European Prospective Investigation Into Cancer and Nutrition.

Fig 2: Risk of T2DM According to Categories of Total Adiponectin Levels for Studies That Provided Results for Quartiles or Quintiles of Adiponectin Levels³

Each graph is consistent with a declining risk of T2DM with increasing adiponectin concentrations.
2. Preventative Cardiology (2015): Adiponectin, Type 2 Diabetes and Cardiovascular Riska

» A prospective study following 5349 randomly selected men and women from the community, without T2DM or CV disease.

» Findings: After adjustment for all baseline variables, adiponectin remained independently associated with reduced risk of T2DM; each doubling in plasma adiponectin was associated with a HR of 0.55 (95% CI 0.41–0.74; p<0.001).

Increasing adiponectin remained a significant and strong predictor of T2DM. Importantly, adiponectin was the only variable associated with reduced risk of T2DM. Increasing adiponectin at baseline (adjusted for confounding risk factors) was still associated with reduced risk of CV events (HR 0.34, 95% CI 0.16–0.72; p¼0.005) for each doubling in plasma adiponectin.

» Conclusion: Adiponectin measured long before diagnosis of T2DM is not only associated with reduced development of T2DM but also of subsequent CVD.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin (per doubling)</td>
<td>0.55 (0.41-0.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (per kg/m²)</td>
<td>1.13 (1.09 - 1.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood-glucose (per mmol/L)</td>
<td>1.16 (1.08 - 1.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c per (%)</td>
<td>1.23 (1.00-1.50)</td>
<td>0.052</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>1.67 (1.36 - 2.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma proBNP (per doubling)</td>
<td>1.12 (0.99 - 1.28)</td>
<td>0.070</td>
</tr>
<tr>
<td>Male sex (yes/no)</td>
<td>1.27 (0.88 - 2.00)</td>
<td>0.299</td>
</tr>
<tr>
<td>High-sensitivity CRP (per doubling)</td>
<td>1.16 (0.99 - 1.35)</td>
<td>0.077</td>
</tr>
<tr>
<td>eGFR (per 10 ml/min)</td>
<td>1.03 (0.92 - 1.17)</td>
<td>0.388</td>
</tr>
<tr>
<td>Current smoking (yes/no)</td>
<td>0.86 (0.57 - 1.29)</td>
<td>0.463</td>
</tr>
<tr>
<td>Total Cholesterol (per 1 mmol/L)</td>
<td>0.99 (0.61 - 1.59)</td>
<td>0.805</td>
</tr>
<tr>
<td>High density Lipoprotein (per 1 mmol/L)</td>
<td>0.98 (0.49 - 1.97)</td>
<td>0.956</td>
</tr>
<tr>
<td>Low density Lipoprotein (per 1 mmol/L)</td>
<td>0.94 (0.39 - 1.49)</td>
<td>0.777</td>
</tr>
<tr>
<td>Triglyceride (per 1 mmol/L)</td>
<td>1.09 (0.88 - 1.35)</td>
<td>0.441</td>
</tr>
<tr>
<td>Systolic blood-pressure (per 10 mmHg)</td>
<td>1.01 (0.91 - 1.14)</td>
<td>0.812</td>
</tr>
<tr>
<td>Diastolic blood-pressure (per 10 mmHg)</td>
<td>1.07 (0.89 - 1.28)</td>
<td>0.495</td>
</tr>
<tr>
<td>Alcohol consumption (per 50 gW)</td>
<td>0.96 (0.88 - 1.04)</td>
<td>0.320</td>
</tr>
<tr>
<td>Physical activity (yes/no)</td>
<td>0.94 (0.63 - 1.46)</td>
<td>0.856</td>
</tr>
</tbody>
</table>

Fig. 3: A multivariate competing risk Cox-regression proportional hazards model estimating risk of incident type 2 diabetes mellitus during 8.5 years of follow up.

The global burden of type 2 diabetes...

– The global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014 (WHO, 2017)
– About 422 million people worldwide have diabetes (WHO, 2017)
– The prevalence of diabetes is growing most rapidly in low and middle-income countries (WHO, 2017)

…And millions more are at risk!
– 1 in 3 adults have prediabetes, and 9 out of 10 those with prediabetes don’t know they have it (CDC, 2017)

Why is early risk assessment vital?

– Diabetes is one of the leading causes of death in the world – in 2012 it was the direct cause of 1.5 million deaths (WHO, 2017)
– 50% of people with diabetes die of CVD (WHO, 2017)
– Diabetes is the leading cause of newly diagnosed adult blindness for people between the ages of 20 and 74 (NIDDK, 2017)
THE ROLE OF ADIPONECTIN IN OTHER METABOLIC AND INSULIN CONCERNS


   » A cross-sectional analysis was performed including 1217 control participants. The association of high AVF with insulin resistance was assessed, stratifying according to gender, and to normal or low adiponectin and normal or high free fatty acids serum levels.

   » Subjects with high AVF or low adiponectin had a three-fold increased risk of insulin resistance. The combination of low adiponectin with high AVF doubled this probability.

2. Diabetes Care (2013): Low Prepregnancy Adiponectin Concentrations Are Associated With a Marked Increase in Risk for Development of Gestational Diabetes Mellitus

   » To examine whether circulating total and high-molecular weight (HMW) adiponectin concentrations, measured before pregnancy, are associated with subsequent risk of gestational diabetes mellitus (GDM). A study of 4098 women – all had children within 6 years of initial blood sample, and none of whom were pre-diabetic or diabetic.

   » Findings: The combined effects of having total adiponectin levels below the median (<10.29 mg/mL) and being overweight or obese (BMI ≥25.0 kg/m2) were associated with a sevenfold increased risk of GDM compared with normal-weight women with adiponectin levels above the median (OR 6.7 [95% CI 3.6–12.5]). (See Fig. 4 above.)

   » Conclusion: Prepregnancy low adiponectin concentrations, a marker of decreased insulin sensitivity and altered adipocyte endocrine function, is associated with reduced glucose tolerance during pregnancy and may identify women at high risk for GDM to target for early intervention. Lower adiponectin concentrations measured, on average, 6 years before pregnancy were associated with a 5.0-fold increased risk of developing GDM. Similar associations were found between total and HMW adiponectin and GDM even when the measurement occurred ≥6 years before pregnancy, confirming the robustness of the association. Of note, these relationships were independent of known risk factors for GDM, including BMI, age, and race/ethnicity, as well as markers of insulin resistance (specifically, glucose and insulin) that have been associated with adiponectin concentrations and the development of reduced glucose tolerance in both pregnant and nonpregnant populations.
THE ROLE OF ADIPONECTIN IN CARDIAC CONCERNS


Adiponectin levels were measured in frozen plasma samples (−80°C) in a total of 3,188 male and female participants in cycle 6 of the Framingham Offspring Study, using a novel fully automated assay. CHD cases at baseline were excluded, and participants were followed for a mean of 7.5 years (mean age was 57 years in both men and women, and mean BMI 28.5 kg/m² in men and 27.3 kg/m² in women).

Conclusion: Data in the Framingham Offspring Study indicate that low adiponectin is a significant independent CHD risk factor in men. For middle age individuals, low plasma adiponectin is a considerable risk for CHD. Any intervention for raising adiponectin levels >7.0μg/ml could be helpful for preventing CHD.


1553 adults were analysed (584 men and 969 women) without hypertension, aged 40-70 years, who had participated in a cohort study in both time periods from 2005 to 2008 for baseline and 2008 to 2011 for follow-up. Participants were divided into sex-specific tertiles according to serum adiponectin levels. The highest tertile of serum adiponectin was defined as 'high adiponectin'. Participants were then stratified into four groups: the non-obese with high adiponectin; the non-obese with low adiponectin; the obese with high adiponectin; and the obese with low adiponectin.

Conclusion: Baseline low adiponectin levels were an independent predictor of hypertension in men. In addition, the study provides evidence of the relative contribution of low adiponectin levels and obesity to the development of new-onset hypertension. These results suggest that high serum adiponectin levels might play a protective role against the development of hypertension in obese men and obese postmenopausal women. Further studies should be performed to assess the specific endocrinologic abnormalities leading to increased blood pressure in obese individuals and to investigate the role of menopause in the pathogenesis of hypoadiponectinemia-related hypertension.

3. Preventative Cardiology (2015): Adiponectin, Type 2 Diabetes and Cardiovascular Risk

5349 randomly selected men and women from the community were prospectively followed, without T2DM or CV disease. Plasma adiponectin was measured at study entry. Median follow-up time was 8.5 years (IQR 8.0–9.1 years). During follow up, 136 participants developed T2DM. Following their diagnosis, 36 of the 136 participants experienced a CV event (myocardial infarction, ischaemic stroke, or CV death).

Conclusion: Increasing plasma adiponectin is associated with decreased risk of T2DM and subsequently reduced risk of CV events. As such, increasing adiponectin is associated with reduced CV events after development of T2DM is of high importance since the opposite has previously been described in the general population. Thus it appears, that in the subgroup developing T2DM, adiponectin associates favourably with CV outcome, whereas in the general population increasing adiponectin associates unfavourably. It seems that adiponectin has beneficial abilities, especially related to insulin sensitizing; however, at the same time may be a marker of metabolic status and underlying CVD.
THE ROLE OF ADIPONECTIN IN CANCERS


   Adiponectin, an adipocyte secreted endogenous insulin sensitizer, appears to play an important role not only in glucose and lipid metabolism but also in the development and progression of several obesity-related malignancies. In this review, we present recent findings on the association of adiponectin with several malignancies including breast cancer, endometrial cancer, colon cancer, gastric cancer, prostate cancer and leukaemia.

   Conclusions: Accumulating evidence indicates that adiponectin measurements may serve as a useful screening tool for predicting cancer for, and/or for early detection of obesity related cancers. Adiponectin per se or adiponectin analogues may prove to be effective anticancer agents and may have important therapeutic implications.


   In the Physicians’ Health Study, the association of prediagnostic plasma concentrations of adiponectin and leptin with risk of developing incident prostate cancer was prospectively examined (654 cases diagnosed 1982–2000 and 644 age-matched controls) and, among cases, risk of dying from prostate cancer by 2007.

   Conclusions: Higher prediagnostic adiponectin (but not leptin) concentrations predispose men to a lower risk of developing high-grade prostate cancer and a lower risk of subsequently dying from the cancer, suggesting a mechanistic link between obesity and poor prostate cancer outcome.

![Endocrine and autocrine/paracrine effects of adiponectin](image)

Fig. 5. Endocrine and autocrine/paracrine effects of adiponectin. The figure indicates that adiponectin in circulation (blood vessel, center) is derived primarily from adipose tissue (top). Circulating adiponectin can travel to numerous tissues and mediate endocrine effects. In addition, several tissues can also produce adiponectin (solid gray arrow) which can then act locally (twisted gray arrow) to mediate functional autocrine or paracrine effect.
REFERENCES


DIABETES BIOCHEMISTRY PANEL

Randox is committed to supporting the advancement of diabetes related chemistry testing and offers a comprehensive range of high quality reagents. From diabetes diagnosis to the monitoring of associated complications, Randox diabetes reagents cover the full clinical spectrum of laboratory testing requirements. Diabetes represents one of the biggest challenges for healthcare today as the number of people both at risk of developing, as well as living with this disease continues to increase across the world.

Risk Assessment
Adiponectin

Diagnosis and Monitoring
Glucose | HbA1c | Fructosamine

Complications Monitoring
Cystatin C | Enzymatic Creatinine | JAFFE Creatinine | D-3-Hydroxybutyrate (Ranbut)
Microalbumin | Albumin | Non-Esterified Fatty Acids (NEFA) | β2 Microglobulin

HIGH QUALITY RANGE OF ROUTINE AND NOVEL REAGENTS FOR DIABETES DIAGNOSIS & MONITORING
CARDIAC & LIPIDS BIOCHEMISTRY PANEL

The need for a more extensive lipid profiling is on the increase, to truly identify the risk of cardiovascular diseases, both in primary and secondary risk categories; and as such provide the necessary tools to prevent and reduce the risks. Randox offer a comprehensive cardiology product profile which includes high performance chemistry reagents for the detection of conventional risk factors, as well as emerging biomarkers associated with further risk.

Risk Assessment

Adiponectin | Apolipoprotein A-I | Apolipoprotein A-II | Apolipoprotein B
Apolipoprotein C-II | Apolipoprotein C-III | Apolipoprotein E | Total Cholesterol
HDL Cholesterol | LDL Cholesterol | HDL2/3 Cholesterol | sLDL Cholesterol
Triglycerides | Lipoprotein (a) | sPLA2-IIA | Homocysteine | hsCRP

Diagnosis of MI

Heart-type Fatty Acid Binding Protein (H-FABP) | CK-MB | Myoglobin

Therapy Monitoring

Digoxin | TxBCardio™
Randox has been supplying laboratories worldwide with revolutionary diagnostic solutions for over 30 years. Our experience and expertise allow us to create a leading product portfolio of high quality diagnostic tools which offer reliable and rapid diagnosis. We believe that by providing laboratories with the right tools, we can improve health care worldwide.

RX SERIES OF CLINICAL ANALYSERS

The RX series combines robust hardware and intuitive software with the world leading RX series test menu, including routine chemistries, specific proteins, lipids, therapeutic drugs, drugs of abuse, antioxidants and diabetes testing. Renowned for quality and reliability, the RX series boasts one of the most extensive dedicated clinical chemistry test menus on the market guaranteeing real cost savings through consolidation of routine and specialised tests onto a single platform. This extensive dedicated test menu of high quality reagents guarantees excellence in patient care reducing costly test re-runs or misdiagnosis and offers unrivalled precision and accuracy for results you can trust.

ACUSERA

Randox is a world leading manufacturer of multi-analyte, true third party controls. Thousands of laboratories rely on us to accurately assess test system performance and ultimately empower them with the confidence required to release patient test results. With more than 390 analytes available across the Acusera range we can uniquely reduce the number of individual controls required while simultaneously reducing costs, time and storage space. A choice of formats are available, including liquid or lyophilised, ensuring flexibility and suitability for laboratories of all sizes and budgets. Some of our principle products include Clinical Chemistry, Immunoassay, Urine, Immunology/Proteins, Cardiac Markers and Therapeutic Drugs among others. As a primary manufacturer, Randox are also able to offer the unique service of custom made controls.

RIQAS

Boasting over 45,000 participants and more than 360 parameters across 32 comprehensive & flexible EQA programmes, RIQAS is the largest international EQA scheme. Designed to cover all areas of clinical testing, each of our multi-analyte programmes benefit from a wide range of concentrations, frequent reporting, rapid feedback and informative yet user-friendly reports.

BIOCHIP ARRAY TECHNOLOGY

Biochip Array Technology (BAT) is an innovative assay technology for multi-analyte screening of biological samples in a rapid, accurate and easy to use format. BAT offers highly specific tests, coupled to highly sensitive chemiluminescent detection, providing quantitative results in easy to interpret reports. Randox BAT assays offer diagnostic, prognostic and predictive solutions across a variety of disease areas including sexually transmitted infection, cardiovascular disease (CVD), familial hypercholesterolemia (FH), colorectal cancer and respiratory infection,
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