

Early Risk Assessment of Type 2 Diabetes Mellitus
Through the use of the Biomarker Adiponectin



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I. BACKGROUND

The prevalence of type 2 diabetes mellitus (T2DM) has reached epidemic levels, affecting ~7% of the U.S. population, and current epidemiological trends indicate that the prevalence will continue to increase dramatically (1).

The global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014 (2). About 422 million people worldwide have diabetes (3). Furthermore, the prevalence of diabetes is growing most rapidly in low and middle-income countries (2).

Millions more people are also at risk. 1 in 3 adults have prediabetes, and 9 out of 10 those with prediabetes don't know they have it (4).

Early risk assessment is vital for a number of reasons. Diabetes is one of the leading causes of death in the world – in 2012 it was the direct cause of 1.5 million deaths (2). 50% of people with diabetes die of CVD (5). Additionally, diabetes is the leading cause of newly diagnosed adult blindness for people between the ages of 20 and 74 (6).

Several long-term prospective clinical trials have shown that interventions can delay or possibly prevent the onset of T2DM in high risk individuals (7, 8), highlighting the importance of identifying individuals at risk to begin interventions as early as possible and focus resources on those with the highest risk.

Furthermore, when diagnosed, many patients already have organ damage or advance subclinical atherosclerosis. An early diagnosis could allow the implementation of lifestyle changes and treatment options aimed at delaying the progression of the disease and to avoid cardiovascular complications (9).

Economically, diabetes and its complications bring about substantial economic loss to people with diabetes and their families, and to health systems and national economies through direct medical costs and loss of work and wages. While the major cost drivers are hospital and outpatient care, a contributing factor is the rise in cost for analogue insulins which are increasingly prescribed despite little evidence that they provide significant advantages over cheaper human insulins (10).

2. TRADITIONAL METHODS FOR DIABETES RISK ASSESSMENT

Non-biochemical methods for assessing a patient's risk of developing T2DM traditionally take into account gender; age; family history of T2DM; BMI waist size; and high blood pressure to give a risk score. Other factors which health services may take into account include ethnicity (UK NHS); history of gestational diabetes (GDM) (American Diabetes Association (ADA)); physical activity (ADA and Finnish Diabetes Association (FDA)); blood glucose history (FDA) and diet (FDA).

It is widely recognised that people who are overweight are at higher risk of developing T2DM. However, assessing those who are overweight can be challenging. Studies have shown that measuring waist circumference alone measures total abdominal fat reliably, but its association with visceral fat depends on visceral fat/ subcutaneous fat ratios that vary by gender and ethnicity (17). Body mass index (BMI) (weight kg / height m²) is another common method of determining which patients are classed as overweight or obese, however it has limitations in measuring athletes and varies in reliability based on age, sex, and race.

Furthermore, it has been found that risk prediction for T2DM and cardiovascular disease (CVD) remains suboptimal even after the introduction of global risk assessment by various scores. This has prompted the search for additional biomarkers (11).

The most commonly used biochemical method of assessing risk of T2DM is measuring fasting plasma glucose (FPG); however, the specificity of this test is poor (12, 13). Although many individuals are identified as having impaired fasting glucose (IFG), their absolute risk of conversion to diabetes is only 5–10% per year (14). The oral glucose tolerance test (OGTT) is more accurate for risk assessment. However, it is rarely used in practice because it is unpleasant for the patient and requires 2 hours to perform. Another challenge is that by the time glucose regulation is abnormal, the underlying disease has been progressing for many years, and complications have already occurred in a significant number of individuals (15). Thus, the rationale of using one variable to assess risk is questionable, when the risk of harm actually varies based on a range of variables and would be better assessed using a multivariable individualized risk score (16).

Given the limitations of the OGTT, FPG, and indexes that the clinician must calculate, it is clear that an improved method for assessing T2DM risk, with a convenient format for routine clinical use, would enable physicians to accurately evaluate more individuals (18).

3. WHAT IS ADIPONECTIN AND APPLICATION TO DIABETES

A. CLINICAL SIGNIFICANCE

A number of recent, key publications have advocated the testing of adiponectin in clinical settings. It has applications in assessing risk in a number of several diabetes-related conditions including prediabetes, T2DM and GDM.

I. PREDIABETES RISK

BMJ (2016): Adiponectin levels predict prediabetes risk: the Pathobiology of Prediabetes in A Biracial Cohort (19)

- » The Pathobiology of Prediabetes in A Biracial Cohort study followed non-diabetic offspring (333 participants) of parents with T2DM for the occurrence of prediabetes, defined as impaired fasting glucose and/or impaired glucose tolerance. The contribution of adiponectin to risk of progression to prediabetes was evaluated.
- » Conclusion: Among healthy white and black adults with parental history of T2DM, adiponectin level is a powerful risk marker of incident prediabetes. Thus, the well-known association of adiponectin with diabetes risk is evident at a much earlier stage in pathogenesis, during transition from normoglycemia to prediabetes.

Journal of Diabetes Investigation (2015): Association between the level of circulating adiponectin and prediabetes: A meta-analysis (20)

- » A systematic literature search was conducted of PubMed, EMBASE, and other databases for case-control studies and cohort studies measuring adiponectin levels in serum or plasma from prediabetes patients and healthy controls. The pooled weighted mean difference (WMD) and 95% confidence interval (CI) were used to estimate the association between adiponectin levels and prediabetes. Three cohort studies and 15 case-control studies with a total of 41,841 participants were included in the meta-analysis. The results showed that circulating adiponectin levels in prediabetes patients were significantly lower than that of healthy controls.
- » Conclusion: The present meta-analysis supports adiponectin levels in prediabetes patients being lower than that of healthy controls, indicating that the level of circulating adiponectin decreases before the onset of diabetes.

II. TYPE 2 DIABETES MELLITUS RISK

JAMA (2009): Adiponectin Levels and the Risk of Type 2 Diabetes – a Systematic Review and Meta-Analysis (21)

- » A meta-analysis involving 13 prospective studies with a total of over 14,598 participants and 2,623 cases of T2DM

- » Conclusion: Higher adiponectin levels are associated with a lower risk of T2DM across diverse populations.

Fig. 2 Below: each graph is consistent with a declining risk of T2DM with increasing adiponectin

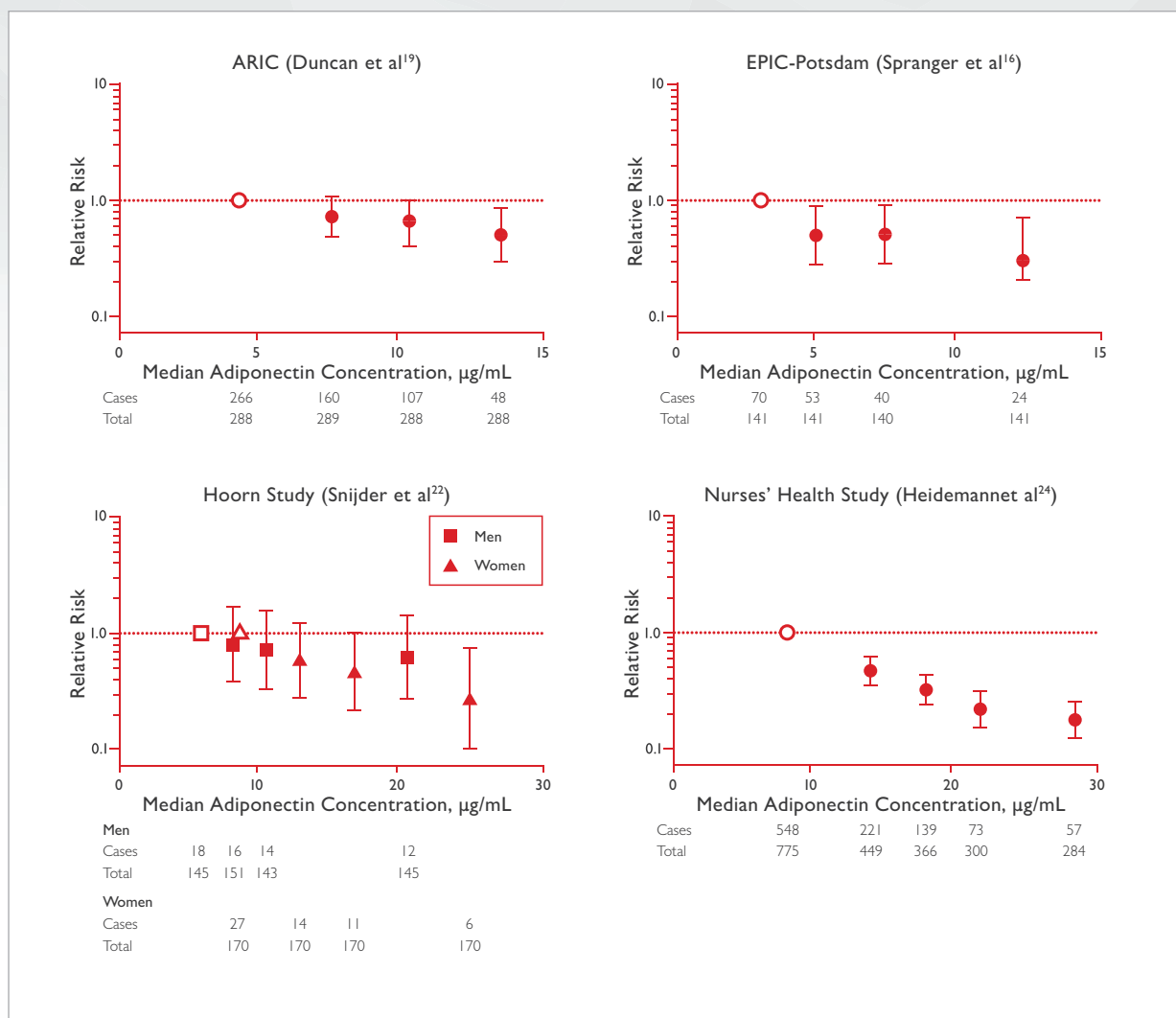


Fig. 2: Risk of T2DM According to Categories of Total Adiponectin Levels for Studies That Provided Results for Quartiles or Quintiles of Adiponectin Levels²¹

Preventative Cardiology (2015): Adiponectin, T2DM and Cardiovascular Risk (22)

- » A prospective study following 5349 randomly selected men and women from the community, without T2DM or CV disease. Plasma adiponectin was measured at study entry. Median follow-up time was 8.5 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).
- » Conclusions: increasing plasma adiponectin is associated with decreased risk of T2DM and subsequently reduced risk of CV events.

III. GESTATIONAL DIABETES RISK

Diabetes Care (2013): Low Pre-pregnancy Adiponectin Concentrations Are Associated With a Marked Increase in Risk for Development of Gestational Diabetes Mellitus (23)

- » A study of 4098 women – all had children within 6 years of initial blood sample, and none of whom were pre-diabetic or diabetic.

- » Conclusion: Lower adiponectin concentration measured on average 6 years before pregnancy were associated with a 5-fold increased risk of developing GDM.

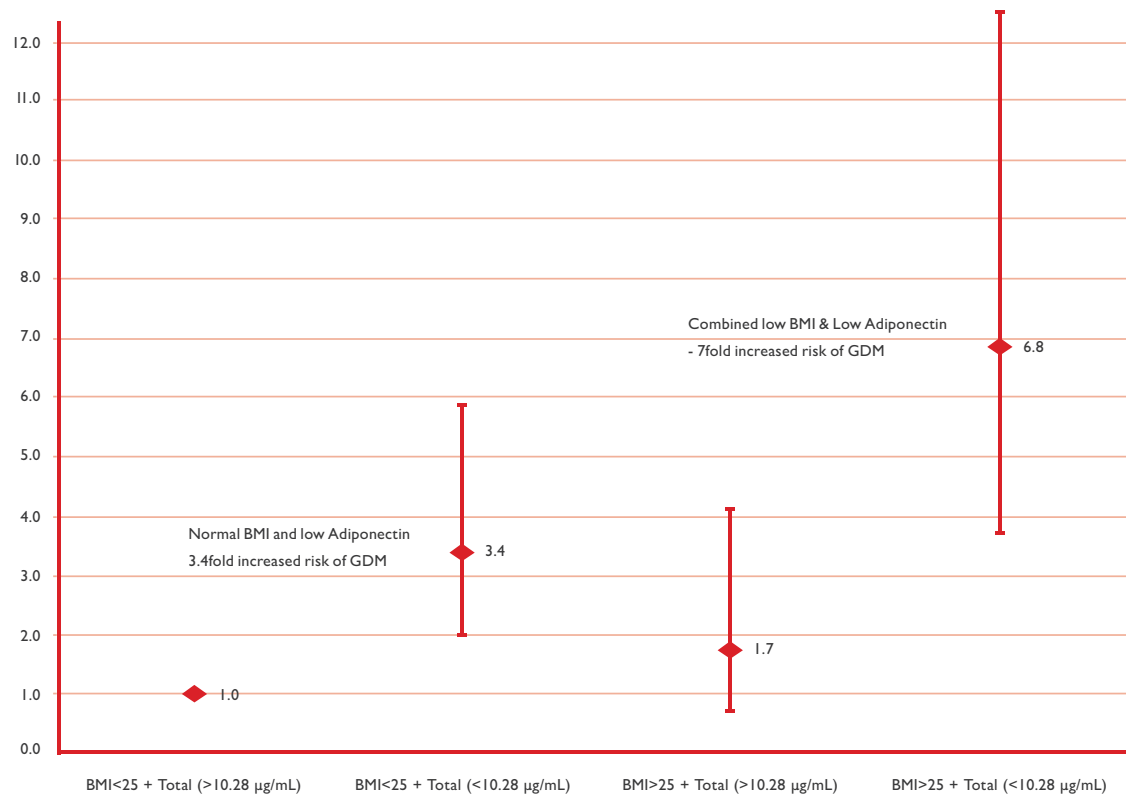


Fig. 3: A multivariate competing risk Cox-regression proportional hazards model estimating risk of incident type 2 diabetes mellitus during 8.5 years of follow up.

Diabetologia (2016): Accuracy of circulating adiponectin for predicting gestational diabetes: a systematic review and meta-analysis (24)

- » A meta-analysis involving 13 studies that met the eligibility criteria, 11 of which (2,865 women; 794 diagnosed with GDM) had extractable data.
- » Conclusion: Pre-pregnancy and early pregnancy measurement of circulating adiponectin may improve the detection of women at high risk of developing GDM. Prospective evaluation of the combination of adiponectin and maternal characteristics for early identification of those who do and do not require OGTT is warranted.

B. IMPLICATIONS FOR CLINICIANS

Adiponectin measurement is not yet a routinely run test in the majority of laboratories worldwide, and it is therefore not available for many clinicians to request. Yet the clinical implications of this becoming widely available could be extremely valuable, as it can help to assess:

- » Among healthy white and black adults with parental history of T2DM, adiponectin level is a powerful risk marker of incident prediabetes (19).
- » Adiponectin levels in prediabetes patients is lower than that of healthy controls, indicating that the level of circulating adiponectin decreases before the onset of diabetes (20).
- » Higher adiponectin levels are associated with a lower risk of T2DM across diverse populations (21).
- » Increasing plasma adiponectin is associated with decreased risk of T2DM and subsequently reduced risk of CV events (22).

- » Lower adiponectin concentration measured on average 6 years before pregnancy were associated with a 5-fold increased risk of developing GDM (23).
- » Pre-pregnancy and early pregnancy measurement of circulating adiponectin may improve the detection of women at high risk of developing GDM (24).

When risk via adiponectin measurement is identified, lifestyle modification to reduce visceral fat should become a primary measure for the prevention of the development of cardiovascular diseases as well as its risks including T2DM in metabolic syndrome with visceral fat accumulation (metabolic syndrome in the narrow sense) through the improvement of adiponectin production (25).

4. METHODS OF MEASURING ADIPONECTIN

Historically, the only method of adiponectin measurement available was through an ELISA assay. However, making the switch to an automated method has many benefits for the laboratory, including:

Efficiencies

The use of ELISAs for clinical testing within a laboratory is notably time and personnel consuming, with heavy resources used on manual interaction. Moving from ELISA technique to an automated biochemistry method for detection of the same analyte increases time and personnel efficiency considerably – time and management efficiencies equal cost effectiveness. The significance of ensuring quality in testing practices, and as such confidence in clinical results, is also a key consideration for running automated biochemistry tests over manual ELISA testing techniques. The risk of error, contamination and therefore compromising clinical results (which is higher when running ELISA methods) will be greatly reduced through the alternative biochemistry automation.

Expansion

By transitioning analytes historically only available on ELISA to automated biochemistry methods, laboratories are able to expand their test offerings to patients and clinicians. Adiponectin being available in an automated biochemistry format allows laboratories to expand their testing and test menu with ease; and enables the inclusion of adiponectin into routine testing panels. Automated biochemistry analytes increase testing range, with little adjustment within the laboratory, allowing for detailed patient testing profiles, without the manual restrictions placed by running ELISA techniques.

Randox is presently the only diagnostic manufacturer who has a globally available automated biochemistry test for adiponectin measurement.

5. RANDOX AUTOMATED ADIPONECTIN ASSAY

Randox adiponectin is a Latex-Enhanced Immunoturbidimetric assay. Assay principal:

- » The sample is reacted with a buffer and anti-Adiponectin coated latex.
- » The formation of the antibody-antigen complex during the reaction results in an increase in turbidity - this is measured as the amount of light absorbed at 570 nm.
- » A sample with higher adiponectin levels will contain more adiponectin and so more antibodyantigen complexes will be formed and the increase in turbidimetry.
- » By constructing a standard curve from the absorbance of the standards, the adiponectin concentration of the sample can be determined.

Further benefits of the Randox assay include:

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

- » 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

The Randox automated immunoturbidimetric adiponectin test offers an improved method for assessing T2DM risk, with a convenient format for routine clinical use, to enable physicians to accurately evaluate at-risk individuals.

6. CONCLUSIONS

Diabetes is on the rise. No longer a disease of predominantly rich nations, the prevalence of diabetes is steadily increasing everywhere, most markedly in the world's middle-income countries (10).

Early risk assessment is vital not only because of the health implications of diabetes and its complications, but also because economically, diabetes and its complications bring about substantial economic loss to people with diabetes and their families, and to health systems and national economies through direct medical costs and loss of work and wages (10).

Given the limitations of traditional T2DM risk assessment, it is clear that an improved method for assessing risk, with a convenient format for routine clinical use, would enable physicians to accurately evaluate more individuals.

Adiponectin measurement is not yet a routinely run test in the majority of laboratories worldwide, and it is therefore not available for many clinicians to request. Yet the clinical implications of this becoming widely available could be extremely beneficial, as it can help to assess prediabetes, T2DM risk and GDM risk.

The Randox automated immunoturbidimetric adiponectin test offers an improved method for assessing T2DM risk, with a convenient format for routine clinical use, to enable physicians to accurately evaluate at-risk individuals. Randox is presently the only diagnostic manufacturer who has a globally available automated biochemistry test for adiponectin measurement to assess T2DM risk.

References

1. Blonde L. State of diabetes care in the United States. *Am J Manag Care* 2007;13 (Suppl. 2):S36–S40
2. WHO Media Centre (2016). Diabetes Fact Sheet. [online] Available at: <http://www.who.int/mediacentre/factsheets/fs312/en/> [Accessed 8 May 2017].
3. WHO Media Centre (2016). 10 Facts About Diabetes. [online] Available at: <http://www.who.int/features/factfiles/diabetes/en/> [Accessed 8 May 2017].
4. Centres for Disease Control and Prevention (2016). About Prediabetes and Type 2 Diabetes. [online] Available at: <https://www.cdc.gov/diabetes/prevention/prediabetes-type2/> [Accessed 8 May 2017].
5. WHO Media Centre (2010). Diabetes – The Problem. [online] Available at: http://who.int/nmh/publications/fact_sheet_diabetes_en.pdf [Accessed 8 May 2017].
6. NIDDK (2016) Title. Diabetes in America, 3rd Edition: National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.
7. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346: 393–403
8. Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, Shaw J, Zinman B, Holman RR. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006;368:1096–1105
9. Salinero-Fort, M. A., de Burgos-Lunar, C., Prieto, J. M., Rallo, C. L., Abánades-Herranz, J. C., Gómez-Campelo, P., Cuesta, F. L., De Cabo, E. E., Iglesias, F. G., Alegre, T. G., Puntero, B. F., Sánchez, L. M., López, D. V., Del Río, V. C., García, P. J. F., Rodríguez, C. S., López, S. L., Barandío, P. P. and the SPREDIA-2 Group. Validating prediction scales of type 2 diabetes mellitus in Spain: the SPREDIA-2 population-based prospective cohort study protocol. *BJM* (2015). Vol. 5, No. 7.
10. World Health Organisation (2016). Global Report on Diabetes. [online] Available at: http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf [Accessed 11 May 2017].
11. Herder, C., Karakas, M. and Koenig, W. Biomarkers for the prediction of type 2 diabetes and cardiovascular risk. *Clin. Pharmacol. Ther.* vol. 90, no. 1, p. 52–66 (2011).
12. Genuth S, Alberti KG, Bennett P, Buse J, DeFronzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lernmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern M, Tuomilehto J, Zimmet P. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003;26: 3160–3167
13. Nichols GA, Hillier TA, Brown JB. Progression from newly acquired impaired fasting glucose to type 2 diabetes. *Diabetes Care* 2007;30:228–233
14. Gerstein HC, Santaguida P, Raina P, Morrison KM, Balion C, Hunt D, Yazdi H, Booker L. Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: a systematic overview and meta-analysis of prospective studies. *Diabetes Res Clin Pract* 2007;78: 305–312
15. Wong TY, Liew G, Tapp RJ, Schmidt MI, Wang JJ, Mitchell P, Klein R, Klein BE, Zimmet P, Shaw J. Relation between fasting glucose and retinopathy for diagnosis of diabetes: three population-based cross-sectional studies. *Lancet* 2008;371:736–743
16. Mohamed Q, Evans A. Retinopathy, plasma glucose, and the diagnosis of diabetes. *Lancet* 2008;371:700–702
17. Grundy, S. M., Neeland, I. J., Turer, A. and Vega, G. L. Waist circumference as measure of abdominal fat compartments. *Journal of Obesity*, vol. 2013, 9 pages (2013).
18. Kolberg, J. A., Jørgensen, T., Gerwien, R. W., Hamren, S., McKenna, M. P., Moler, E. Rowe, M. W., Urdea, M. S., XU, X. M., Hansen, T., Pedersen, O. and Borch-Johnsen, K. Development of a Type 2 Diabetes Risk Model From a Panel of Serum Biomarkers From the Inter99 Cohort. *Diabetes Care*. Vol. 32, pp. 1207–1212 (2009).
19. Jiang, Y., Owei, I., Wan, J., Ebenibo, S. and Dagogo-Jack, S. Adiponectin levels predict prediabetes risk: the Pathobiology of Prediabetes in A Biracial Cohort (POP-ABC) study. *BMJ Open Diabetes Research and Care*, vol. 4 (2016).
20. Lai, H., Lin, N., Xing, Z., Weng, H., and Zhang, H. Association between the level of circulating adiponectin and prediabetes: A meta-analysis. *Journal of Diabetes Investigation*, vol. 6, no. 4, p. 416–429 (2015).
21. Li, S., Shin, H. J., Ding, E. L. and van Dam, R. M. Adiponectin Levels and Risk of Type 2 Diabetes – a Systematic Review and Meta-Analysis. *JAMA*, vol. 302, no. 2, p. 179–188 (2009).
22. Lindberg, S., Skov Jensen, J., Bjerre, Pedersen, S. H., Frystyk, J., Flyvbjerg, A., Galatius, S., Jeppensen, J. and Mogelvang, R. Adiponectin, type 2 diabetes and cardiovascular risk. *Preventative Cardiology*, vol. 22, no. 3, p. 276–283 (2013).
23. Hedderson, M. M., Darbinian, J., Havel, P. J., Quesenberry, C. P., Sridhar, S., Ehrlich, S. and Ferrara, A. Low Prepregnancy Adiponectin Concentrations are Associated with a Marked Increase in Risk for Development of Gestational Diabetes Mellitus. *Diabetes Care*, vol. 36, no. 12, p. 3930–3937 (2013).
24. Iliodromiti, S., Sassarini, J., Kelsey, T. W., Lindsay, R. S., Sattar, N. and Nelson, S. M. Accuracy of circulating adiponectin for predicting gestational diabetes: a systematic review and meta-analysis. *Diabetologia*, vol. 59, p. 692–699 (2016).
25. Matsuzawa, Y. Obesity and metabolic syndrome: the contribution of visceral fat and adiponectin. *Diabetes Management*, vol. 4, no. 4, p. 391–401.

Head Quarters

Randox Laboratories Ltd, 55 Diamond Road, Crumlin, County Antrim, BT29 4QY, United Kingdom

☎ +44 (0) 28 9442 2413

✉ reagents@randox.com

🌐 randox.com/adiponectin