THE ROLE OF ADIPONECTIN IN OBESITY AND ITS CLINICAL UTILITY IN OBESITY - ASSOCIATED HEALTH RISKS
The Role of Adiponectin in Obesity and its Clinical Utility in Obesity - Associated Health Risks

1. BACKGROUND

Obesity, a major global health epidemic that burdens on healthcare systems, has increased at an alarming rate with 39% of adults (18+) classed as overweight and 13% were classed as obese in 2016. Moreover, in the same year, 340 million children aged between 5 and 16 were identified as overweight or obese and 41 million children under 5 years of age were also classed as overweight or obese. Worldwide, obesity prevalence rates have almost tripled between 1975 and 2016.

The main reason obesity is a massive health problem is because of the secondary diseases that develop due to obesity. Obesity has contributed to 23% of ischaemic heart disease cases, 7-41% of specific cancer cases and 44% of diabetes cases. Obesity is now no longer confined to developed countries. As the industrialisation of developing countries continues to emerge, high calorie diets and subsequently obesity increases.

Obesity reduces the number of disease-free years. It was uncovered that those who were mildly obese lost 3-4 more disease-free years and those who were severely obese lost 7-8 more disease-free years than non-obese individuals. Consequently, at least 2.8 million deaths per year are attributed to obesity.

Obesity is a major risk factor for type 2 diabetes mellitus (T2DM), insulin resistance (IR), cardiovascular disease (CVD) and various types of malignancies. These secondary health-related problems cost the economy “$2 trillion annually and roughly 2.8% of the global gross domestic product (GDP)”.

Moreover, childhood obesity costs the economy $14.1 billion annually. Whilst there are numerous parties involved to aid in the prevention of obesity, urgent actions are required to prevent obesity and the subsequent secondary health-related problems.

2. BIOLOGICAL SIGNIFICANCE

Adiponectin (adipocyte complement-related protein of 30 kDa (Acrp30)) is an adipokine (protein hormone) produced and secreted by the adipose tissue, an energy reservoir and a secretory endocrine organ of proteins, hormones and cytokines that contribute to the functionality of tissues and cells around the body. Adiponectin acts as a messenger in the communication of adipose tissue and metabolic organs. In doing so, adiponectin suppresses the production of glucose in the liver through inhibiting the genes involved in glucose production and enhances fatty acid oxidation in skeletal muscle. Consequently, adiponectin is a strong protector against several pathological events in various cells through inhibiting inflammation, suppressing cell death and enhancing cell survival.

Adiponectin has been identified as having pleiotropic functions widely associated with anti-atherogenic, anti-diabetic, cardioprotective and anti-inflammatory effects. Adiponectin levels inversely correlate with insulin levels, body mass index (BMI), triglyceride levels, IR, glucose, and most importantly, visceral fat accumulation. These conditions as well as haemodynamics, waist circumference, HDL cholesterol concentrations and glycaemia are considered in the definition of metabolic syndrome (MetS). Physiological functions of adiponectin have also been observed in inflammation and cardiovascular disease (CVD), especially in atherosclerosis.

![Fig. 1: Proposed Salutary Effects Adiponectin](image)

Protection from
- Insulin Resistance
- Type 2 Diabetes
- Coronary-Artery Disease
3. VISCERAL OBESITY

Obesity is defined as “excessive fat accumulation that may impair health resulting from social behaviour and environmental and genetic factors”.

Obesity causes adverse alterations in the adipose tissue promoting metabolic dysregulation. Such alterations include: accrual of inflammatory macrophages which in turn activate the inflammatory pathways, reduction of lipid turnover, and the deposition of fat in ectopic locations. Consequently, these alterations are the precursors in the development of IR and metabolic dysfunction.

Excess visceral adipose tissue (VAT) is known as visceral obesity. It is the excess VAT as opposed to subcutaneous fat (fat that sits beneath the skin) that is associated with MetS, CVD and several malignancies including colorectal, prostate and breast cancers.

The biggest challenge that exists in diagnosing visceral obesity is that commonly utilised methods including BMI and waist circumference both have clinical limitations.

Waist circumference: Studies have found that waist circumference measures abdominal fat reliably, however, its association with visceral fat depends on the visceral fat / subcutaneous fat ratios that vary by gender and ethnicity. Fig. 2 details the variation in visceral fat content in men with the same waist circumference.

4. TYPE 2 DIABETES MELLITUS (T2DM)

It has been identified that as obesity cases continue to rise, so have the incidence and prevalence rates of T2DM. T2DM is a chronic condition characterised by IR (body does not respond to the insulin produced) or defective beta cells (the beta cells are unable to produce enough insulin). IR is more commonly observed in T2DM as increased levels of adipose tissue leads to obesity due to excess visceral fat.

The three traditional biomarkers utilised in the diagnosis and monitoring of diabetes have limitations. The oral glucose tolerance test (OGTT) has been recognised to produce false - positive results. The fasting plasma glucose (FPG) test requires the patient to fast. During prolonged fasting, glucagon, produced in the pancreas, signals the liver to release glucose into the bloodstream, resulting in FPG levels remaining high. Whilst HbA1c testing is also utilised in the risk assessment of diabetes, any condition that reduces the survival rate of erythrocytes such as haemolytic anaemia will falsely lower the HbA1c test results regardless of the assay method utilised.
These findings highlight the inadequacies of traditional diabetes tests and the necessity for a superior biomarker, such as adiponectin, in the risk assessment of T2DM.

1. JAMA (2009): Adiponectin levels and risk of type 2 diabetes: A systematic review and meta-analysis

Objective: A meta-analysis examined 13 prospective studies with a total of 14,598 participants and 2,623 cases of T2DM to review the association of plasma adiponectin levels and the risk of T2DM.

Findings:

Conclusion: Higher adiponectin levels are associated with a lower risk of T2DM across diverse populations and is currently the strongest and most consistent biomarker of T2DM risk assessment.
2. BMJ Open Diabetes Research & Care (2016): Adiponectin levels predict prediabetes risk: the pathobiology of prediabetes in a biracial cohort (POP - ABC) study

Objective: A US study prospectively evaluated 333 subjects from the Pathobiology of Prediabetes in A Biracial Cohort study which followed non-diabetic offspring of parents with T2DM to assess the occurrence of pre-diabetes over the course of 5.5 years.

Findings:

Fig. 4: Plasma adiponectin levels by race/ethnicity (A) and gender (B) among study subjects who developed prediabetes/diabetes (P) in comparison to the incident free subjects (NP).

Conclusion: Baseline adiponectin levels were inversely related to the risk of pre-diabetes among the healthy African Americans and European Americans with a parental history of T2DM enrolled on the POP - ABC study. Despite gender and ethnic differences, this predictive relationship was evident.

5. METABOLIC SYNDROME

The most commonly observed component of metabolic syndrome (MetS) is abdominal obesity. MetS encompasses several conditions including: hypercholesterolemia, triglyceridemia, glycaemia, hypertension, abdominal obesity and dyslipidaemia. The prevalence of MetS is 31% and is associated with a 1.5-fold increased risk of all-cause mortality, a 2-fold increased risk of coronary heart disease (CHD) and cerebrovascular accident (CVA), and a 5-fold increased risk of T2DM.

Adiponectin has been identified as a glucose regulator and lipid homeostasis through its insulin sensitising properties which are associated with MetS.
Findings:

Conclusion: Decreasing adiponectin levels begins at an early stage before the onset of hypertension, diabetes, MetS or dyslipidaemia. Moreover, in those with metabolic / physiological abnormalities, adiponectin is an important biomarker for the risk of atherosclerosis both independently and as a reflection of the accumulation of AVF.
Objective: A cross-sectional analysis was undertaken to include 1,217 control participants to analyse the contribution of low adiponectin and high free fatty acids (FFAs) with IR in non-diabetic subjects.

Findings:

Conclusion: Subjects with high AVF or low adiponectin had a 3-fold increased risk of IR. The combination of low adiponectin with high AVF doubled this probability.
6. CARDIAC CONCERNS

It has been recognised that mRNA expression of the adiponectin gene and the section of high molecular weight (HMW) oligomeric adiponectin are impaired in adipose tissue of obese patients. Fig. 10 illustrates the pleiotropic role of adiponectin in the cardiovascular system. Epidemiological studies undertaken in different ethnic groups established that low adiponectin levels, especially in HMW oligomer, is an independent risk factor for CVD.
I. Diabetes Research and Clinical Practice (2014): Relative contribution of obesity and serum adiponectin to the development of hypertension

Objective: A South Korean study prospectively evaluated 1,553 participants (584 men and 969 women) without hypertension, aged between 40 and 70 years to investigate the association between adiponectin levels and new-onset hypertension. This cohort study retrieved baseline results between 2005 and 2008 and followed up between 2008 and 2011.

Findings:

Table 1a: Odds ratios (ORs) for new-onset hypertension in men and women according to baseline body mass index and serum adiponectin level

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-obese/high adiponectin</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Non-obese/low adiponectin</td>
<td>1.48 (0.75 - 2.93)</td>
<td>0.73 (0.40 - 1.34)</td>
</tr>
<tr>
<td>Obese/high adiponectin</td>
<td>1.04 (0.32 - 3.41)</td>
<td>1.58 (0.75 - 3.32)</td>
</tr>
<tr>
<td>Obese/low adiponectin</td>
<td>2.80 (1.35 - 5.81)</td>
<td>1.77 (0.96 - 3.25)</td>
</tr>
</tbody>
</table>

Table 1b: Odds ratios (ORs) for new-onset hypertension in women according to baseline serum adiponectin and menopausal status

<table>
<thead>
<tr>
<th></th>
<th>Pre-menopausal women (n = 350)</th>
<th>Post-menopausal women (n = 350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonobese/high adiponectin</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Nonobese/low adiponectin</td>
<td>0.43 (0.09 - 2.05)</td>
<td>0.81 (0.40 - 1.64)</td>
</tr>
<tr>
<td>Obese/high adiponectin</td>
<td>5.25 (0.86 - 32.04)</td>
<td>1.32 (0.56 - 3.11)</td>
</tr>
<tr>
<td>Obese/low adiponectin</td>
<td>0.99 (0.22 - 4.58)</td>
<td>2.41 (1.16 - 5.04)</td>
</tr>
</tbody>
</table>

a Adjusted for age, baseline systolic blood pressure, baseline diastolic pressure, LDL cholesterol, HDL cholesterol, fasting blood glucose, smoking, and regular exercise.

b The obese group was defined as a body mass index ≥ 25 kg/m².

c The high adiponectin group was defined as the highest tertile of adiponectin in the study population (≥13.62μg/ml in men and ≥13.62μg/ml in women)

Conclusion: Low adiponectin levels were associated with an increased risk of new-onset hypertension in obese men and post-menopausal women.
Objective: A Danish study prospectively investigated 5,349 randomly selected men and women from the community without T2DM or CVD to determine the relationship between adiponectin, T2DM and CVD. Adiponectin levels were assessed on study entry and the median follow-up time was 8.5 years.

Findings:

**Table 2: A competing risk Cox-regression proportional hazards model predicting risk of incident major cardiovascular adverse events following the development of incident T2DM**

<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>0.34 (0.16 - 0.72)</td>
<td>0.005</td>
</tr>
<tr>
<td>Age at diagnosis of T2DM (per 1-year increase)</td>
<td>1.10 (1.03 - 1.17)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Nonsignificant result (p > 0.1) were obtained for the variables gender, smoking, plasma proBNP, hsCRP, HbA1c, blood glucose, eGFR, total cholesterol, HDL, LDL, triglycerides, hypertension, systolic and diastolic blood pressure, alcohol consumption, physical activity and BMI.

Conclusion: Increasing adiponectin levels in plasma is associated with a decreased risk of T2DM and subsequently, a reduced risk of CVD.

**7. CANCER**

Excess body fat is not only associated with T2DM and CVD, but also with various types of malignancies. Many cancer cell lines express adiponectin receptors, and adiponectin in vitro limits cell proliferation and induces apoptosis. Fig. 13 illustrates the association between obesity, low levels of adiponectin and cancer progression.

Evidence exists supporting adiponectin as a novel risk marker in the diagnosis and prognosis of cancer.

Objective: A meta-analysis reviewing 31 eligible studies containing 15,879 subjects, following a systematic search on Embase, PubMed, the Chinese National Knowledge Infrastructure and the USU Web of Science databases to determine the involvement of adiponectin in breast cancer (BC).

Conclusion: The meta-analysis indicates an intriguing association between low levels of adiponectin and an increased risk of BC. Furthermore, adiponectin has the potential to serve as a biomarker of BC risk and aid in the identification of those at a high risk of developing BC.


Objective: A review of current literature to determine the potential role of adiponectin and the underlying mechanism of adiponectin in the development and progression of prostate cancer (PC).

Findings: Oxidative stress has been identified as a key event in the initiation, development and progression of PC. Adiponectin increased cellular anti-oxidative defence mechanisms and inhibited oxidative stress through increasing the NADPH oxidase NOX2 and NOX4 expressions in human 22Rv1 and DU - 145 PC cell lines.

Conclusions: Numerous studies analysed in this review support adiponectin as a protective and safe factor to prevent the progression of PC.
8. METHODOLOGY

Previously, the only method available for adiponectin testing was the ELISA methodology. Today, automated methods are available, offering numerous benefits for the laboratory.

EFFICIENCIES

In a laboratory, employing the ELISA method for clinical testing is notably time and personnel consuming, with heavy resources utilised on manual interaction. Moving from this method to an automated method is considerably more time efficient. The significance of ensuring quality in testing practices and confidence in patient results is a key consideration for running automated biochemistry tests over manual ELISA techniques. The risk of errors and contamination of samples, thereby compromising patient results is greatly reduced using automated methods as opposed to manual methods.

EXPANSION

Automated biochemistry methods enable laboratories to expand their test menu with ease, allowing the inclusion of adiponectin into routine testing panels due to reduced manual work. Automated biochemistry assays increase testing ranges, enabling detailed patient testing profiles without the manual restrictions placed by running ELISA techniques.

Randox is currently one of the only diagnostic manufacturers who offer an automated biochemistry test for adiponectin measurement worldwide.

9. RANDOX AUTOMATED ADIPONECTIN ASSAY

The Randox adiponectin assay utilises the latex enhanced immunoturbidimetric (L.E.I) method delivering high performance and producing results in as little as 10 minutes. The Randox adiponectin assay offers the following key benefits:

• A niche product from Randox meaning that Randox are one of the only manufacturers to offer the adiponectin test in an automated clinical chemistry format.

• Extensive measuring range of 0.32 - 23.8μg/ml for the comfortable detection of clinically important results outside of the healthy range, 2 - 22μg/ml.

• Excellent correlation coefficient of r=0.989 when compared to commercially available methods.

• Liquid ready - to - use format for convenience and ease - of - use.

• CE marked for diagnostic use.

• Stable to expiry date when stored at +2 to +8°C.

• Dedicated adiponectin controls and a 6 - point calibrator available offering a complete testing package.

• Applications available detailing instrument - specific settings for the convenient use of the Randox adiponectin assay on a wide range of clinical chemistry analysers.

The Randox automated L.E.I adiponectin test offers an improved method for assessing obesity and obesity - associated health risks combined with a convenient format for routine clinical use, enabling physicians to accurately evaluate at risk patients.
10. CONCLUSION

Obesity, a major global health epidemic which burdens healthcare systems, has reached an alarming extent with 39% of adults (18+) classed as overweight and 13% classed as obese in 2016. Moreover, in the same year, 340 million children aged between 5 and 16 were overweight or obese and 41 million children under 5 years of age were also classed as overweight or obese. Worldwide, obesity prevalence rates have almost tripled between 1975 and 2016.\(^1\)\(^2\)

The main reason why obesity is a massive health problem is due to the secondary diseases that develop due to obesity. Obesity has contributed to 23% of ischaemic heart disease cases, 7 - 41% of specific cancer cases and 44% of diabetes cases. This can partly be attributed to obesity - induced IR.\(^3\)

Obesity is a major risk factor for T2DM, IR, CVD and various types of malignancies. These secondary health - related problems cost the economy “$2 trillion annually and roughly 2.8% of the global gross domestic product (GDP)”\(^4\). Moreover, childhood obesity costs the economy $14.1 billion annually.\(^5\)\(^6\)\(^1\)

These statistics highlight the necessity for an improved method for assessing those at risk, combined with a convenient format for routine clinical use, will enable physicians to accurately assess and evaluate more patients to aid in the prevention of secondary obesity - associated health risks.

The Randox automated L.E.I adiponectin test offers an improved method, combined with a convenient format for routine clinical use, for the early assessment of at risk patients. Randox is currently one of the only diagnostic manufacturers who offer an automated biochemistry test for adiponectin measurement worldwide.

REFERENCES


29. Role of adiponectin and free fatty acids on the association between abdominal visceral fat and insulin resistance. Medina - Urrutia, Aida, et al. Mexico City: Cardiovascular Diabetology, 2021.5.


