Thiazolidinediones, Adiponectin and Insulin Resistance

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded one CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 May 2005.

Introduction

Individuals with the metabolic syndrome have increased mortality and morbidity from cardiovascular disease. Insulin resistance (IR) plays a central role in the pathogenesis of atherosclerosis in the metabolic syndrome. Hence targeting IR is an important therapeutic strategy in the management of the metabolic syndrome. Far from being an inert tissue for storage of excessive energy, the adipocytes are metabolically active endocrine cells which play a crucial role in governing energy homeostasis. Visceral adiposity is intimately related with IR and this may be mediated via adipokines secreted by the adipose tissues. One of these adipokines, adiponectin, has been shown by numerous studies to have a major role in the pathogenesis in IR. Thiazolidinediones (TZDs) are a new class of insulin-sensitising agents with diverse metabolic effects beyond glucose-lowering, including an effect on adiponectin. This article provides an overview on the relationship between TZDs, adiponectin and insulin resistance.

Adiponectin: a mediator of insulin resistance

Amongst the various adipokines secreted by the adipose tissue, adiponectin is by far the most extensively studied over recent years. There is an intimate relationship between adiponectin and IR. Circulating adiponectin levels have been shown to be negatively correlated with body mass index, plasma glucose, triglyceride, and insulin levels, and positively correlated with insulin sensitivity. Low levels of adiponectin have been consistently linked with states of insulin resistance including type 2 diabetes, hypertension, dyslipidaemia and women with polycystic ovary syndrome. Although substantial evidence accumulates to link low levels of adiponectin with insulin resistant states, it remains unclear whether it is the cause or the effect. From the adiponectin gene knockout mouse model, marked insulin resistance developed after feeding with high-fat and high-sucrose diet, whereas improvement of insulin resistance was observed after supplementation of adiponectin by adenovirus transfection. Another similar experiment further demonstrated significant inhibition of aortic plaque formation in apolipoprotein E-deficient mice (compared to controlled mice), two weeks after adenovirus-adiponectin injection. Consistent with these animal data, interventions that improve insulin action including weight loss, diet and exercise has been shown to elevate circulating adiponectin levels. Collectively, there is sufficient evidence to suggest that adiponectin is a mediator rather than just a para-pheno- menon of insulin resistance and atherosclerosis. Apart from glucose lowering and insulin sensitising functions, adiponectin also has anti-atherogenic, anti-inflammatory and anti-angiogenic effects. Preliminary data in animal models show that adiponectin also lowers plasma concentrations of free fatty acids, decreases hepatic fat content, with a potential therapeutic role in patients with fatty liver disease. Although the exact mechanisms whereby adiponectin improves insulin sensitivity have not been fully elucidated and further studies are necessary to explore the physiological role of this novel adipocyte-derived peptide, adiponectin may be a potential therapeutic target in the management of the metabolic syndrome and conditions characterised by insulin resistant states.

Thiazolidinediones: effect on circulating adiponectin

Thiazolidinediones represent a novel drug class that may directly decrease insulin resistance through their effects on peroxisome proliferators-activated receptor-γ (PPAR-γ). In adipose tissue, PPAR-γ has the highest expression levels compared with other tissues and from early studies using PPAR-γ knockout mouse models, adipose tissue may be the major site where TZDs improve insulin sensitivity. Results of several clinical studies indicate that TZDs increase circulating adiponectin levels via its PPAR-γ effects, which may (at least to some extent) explains their insulin sensitising action. In a small randomised double-blind study of non-obese type 2 diabetic patients, treatment with rosiglitazone (4mg daily) for 6 months led to a 2 fold increase in plasma adiponectin level compared to placebo. In another study of 136 Japanese patients with type 2 diabetes, treatment with pioglitazone (30 mg daily) for 3 months significantly increased plasma adiponectin.
concentrations, along with other index of atherogenic risk (such as c-reactive protein and pulse wave velocity), compared to placebo-control. Similarly, a recently published study investigating first-degree relatives of African Americans, treatment of rosiglitazone (4-8mg/day) for 3 months also showed increased adiponectin levels by two fold in patients with impaired glucose tolerance, and 2.5 fold in type 2 diabetic subjects, when compared with the first degree relatives having normal glucose tolerance. While beta-cell secretion of insulin remained unchanged, insulin sensitivity (measured by homeostasis model assessment) was reduced by 30%, in type 2 diabetes and impaired glucose tolerance group. Moreover, favourable effects have been observed in lipids and lipoproteins (increased HDL-cholesterol and decreased triglycerides), as well as a trend in reduction of blood pressure.

Interestingly, in a small clinical study, treatment with rosiglitazone for 16 weeks caused a 3-fold increase in plasma adiponectin concentration, which in turn, was strongly associated with a reduction in hepatic fat content and improvements in hepatic and peripheral insulin sensitivity. It is also plausible that TZDs exerts its favourable effects on lipid profiles through an increase in adiponectin level. Another commonly used insulin sensitizer, metformin, however, does not appear to possess this property at least in one study.

Conclusions

Increasing awareness has been focused on insulin resistance as a key element in a number of clinical disease states including type 2 diabetic patients. Thiazolidinediones have beneficial metabolic effects beyond glycaemic control. This could be achieved via a therapeutic increase in adiponectin levels which contributed to its effect in improving insulin sensitivity. Whether this can be translated into significant cardiovascular benefits should be subject for future research.

References


MCHK CME Programme Self-assessment Questions

Please read the article entitled “Thiazolidinediones, Adiponectin and Insulin Resistance” by Prof. Alice P S Kong and Dr. Norman Chan and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded 1 CME credit under the Programme for returning completed answer sheet via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 May 2005. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1A-E and 2A-E: Please answer T(True) or F(False).

1) The following statements regarding adiponectin
   A. Adiponectin is produced by the liver
   B. High levels of adiponectin is associated with an increase in insulin resistance
   C. Low adiponectin level is associated with increased incidence of myocardial infarction
D. Thiazolidinediones cause an increase in adiponectin levels
E. Adiponectin has anti-inflammatory actions

2) The following conditions are associated with low circulating adiponectin levels:
   A. Type 2 diabetes
   B. Polycystic ovarian syndrome
   C. Normal subjects with low body mass index
   D. Coronary heart disease
   E. Hypertension

**ANSWER SHEET FOR MAY 2005**

Please return the completed answer sheet to the Federation Secretariat on or before 31 May 2005 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

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1) A   B   C   D   E  
2) A   B   C   D   E

Name: _____________________________________________________ HKID No. ___ ___ - ___ ___ ___ ___ X X (x)
Signature: _____________________________  Contact Tel No.:_________________________

**Answers to April 2005 issue**

Domestic Violence in Pregnancy - The Scene in Hong Kong


**FMSHK 40th Anniversary Activities**

To celebrate the FMSHK’s 40th birthday, a series of special events and functions will be held year-round in 2005, a year which marks the history of FMSHK.

**Spring**

The FMSHK Art Exhibition
WE ARE PRIVILEGED AND HONOURED TO HAVE DR. PATRICK HO, SECRETARY FOR HOME AFFAIRS, AS THE PATRON OF OUR 40th ANNIVERSARY ART EXHIBITION.
Date: 20-22 May 2005  
Venue: Exhibition Gallery, Hong Kong Cultural Centre, TST, Hong Kong

**Autumn**

The FMSHK Golf Tournament  
Date: October 2005  
Venue: Fanling Golf Course, Hong Kong

**Winter**

The 40th Anniversary Gala Dinner  
Date: 28 November 2005  
Venue: Rm. 201, New Wing, The Hong Kong Convention and Exhibition Center, Hong Kong

The President Cup = Soccer Five  
Date: December 2005  
Venue: A suitable sports ground in Hong Kong

Enquiries: Ms. Kitty LEUNG (2821-3512 or kitty@fmshk.com.hk)

We wish you success in your 40th Anniversary.