# Adiponectin and Type 1 Diabetes Mellitus in Children

**PSN MENON**

*Consultant & Head, Department of Pediatrics, Jaber-Al-Ahmed Armed Forces Hospital, PO Box 5819, Salmiya, Kuwait.*
*psnmenon@yahoo.com*

There is an explosion of information related to adiponectin in the last decade. We know that adipose tissue secretes many adipocytokines of which adiponectin modulates a number of vital metabolic processes related to glucose homeostasis and fatty acid catabolism [1]. It is exclusively secreted from adipose tissue into the blood and is abundant in plasma at levels of 5-10 µg/mL. Girls have higher levels than boys. Levels of the hormone are inversely correlated with BMI and body fat percentage in adults. The association in infants and young children is less clear.

Genomic studies have helped us to understand the action of adiponectin better. Adiponectin self-associates into larger structures. Three adiponectin oligomers bind together to form a trimer; trimers self-associate to form hexamers, dodecamers or high molecular mass (HMW) isoforms consisting of at least 12 to 18 protomers. Thus adiponectin circulates in at least three different sub-forms. Each isoform of adiponectin exerts distinct biological properties in target tissues [2]. Recent studies indicate that HMW oligomer may be the most biologically active form concerning glucose homeostasis, whereas the central actions are attributed to the low molecular weight oligomers [3].

Adiponectin modulates a number of metabolic processes including those resulting in type 2 diabetes (T2DM), obesity, coronary artery disease and metabolic syndrome. Contrary to expectations, adiponectin is decreased in obesity. The association of low adiponectin levels with obesity and hyperinsulinemia has been confirmed in cross sectional studies in 5 and 10 year old children; however, the association with hyperin-sulinemia is not completely independent of obesity [4]. Probably adiponectin plays a less important role in whole body insulin sensitivity in children.

In adults with T2DM, circulating levels of HMW adiponectin are selectively decreased due to an impaired secretion of this oligomer from adipocytes [5]. Their levels increase after weight reduction and following bariatric surgery. Single-nucleotide polymorphisms in the adiponectin gene associated with low plasma adiponectin levels and T2DM have been identified.

The story is different in type 1 diabetes (T1DM). Adult T1DM patients, especially with diabetic nephropathy have elevated total levels of the adiponectin unlike T2DM. Adiponectin probably increases as a compensatory response in these patients with microvascular complications [4]. Renal failure may lead to the stimulation of adiponectin production as a physiological response to restrict endothelial damage. It may also decrease adiponectin clearance, and the kidney may develop secondary resistance to adiponectin. Still high total adiponectin levels were predictive of development of microalbuminuria in T1DM in some studies suggesting a causal association [1]. Studies on large cohorts of healthy subjects also have shown that adiponectin levels increase before the onset of nephropathy.

Recent studies have shown that the levels of adiponectin remain higher in persons with type 1 diabetes than in non-diabetics, even after controlling for renal function, obesity and HDL cholesterol. The absolute concentrations of total adiponectin and all subforms were higher in T1DM patients than healthy controls. This increase in concentration of total adiponectin was primarily caused by a major increase of the HMW sub-form. This association was not associated with gender or diabetic nephropathy status [2].

Compared to adults, studies in children are limited. A longitudinal study from Germany showed that children and adolescents with T1DM have BMI-dependent elevated serum adiponectin compared with healthy children [6]. There were similar observations in obese diabetic boys in an earlier study published in *Indian Pediatrics* [7]. In this issue of the journal, Habeeb, *et al.* provide another observation of adiponectin as a marker for complications in children with T1DM [8].

How these deleterious effects of adiponectin are induced is not well understood. *In vitro* experiments have suggested that adiponectin may increase NFkB

production. HMW oligomer may be protective with inhibition of NFkB, whereas the low and medium subforms are associated with nephropathy. Altered glycosylation of lysine leading to changed adiponectin function has been postulated as another mechanism.

Has adiponectin come of age as a routine test or as a predictor of obesity, T2DM, T1DM or even development of microangiopathy or comorbidities? Not yet. There are simpler and better clinical methods now. To some extent it may have role in adult T2DM. Its utility in T1DM, especially children, is far from clear.

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# Thalassemia: Cardiac Iron and Chelators

**AJAY GAUR**
*Department of Pediatrics, GR Medical College, Gwalior, 474 001, Madhya Pradesh, India.*
*drajaygaur@gmail.com*

Iron overload in thalassemia is a serious and potentially fatal condition as excess iron is toxic to tissues and organs, particularly the liver and the heart. The serum ferritin level is useful in assessing iron balance trends, but does not accurately predict quantitative iron stores. Measurement of the iron level by liver biopsy is the standard method for accurately determining the iron store. A ferritometer and specialized MRI software are emerging alternatives for liver biopsies. Although quantitative liver iron measurement accurately guides the use of iron chelators, it may not reflect cumulative changes in cardiac iron. Thalassemics may have cardiac iron overload even at the time of a safe liver iron measurement [1].

Cardiac damage caused by iron overload is the main cause of death in thalassemia. An increased risk of iron-induced cardiac disease is observed with liver iron concentration (LIC) values above 15mg of iron per gram of dry weight of liver, and in patients with serum ferritin values above 2500 microgram/liter. The rate of iron loading depends mainly on the rate of blood transfusions, which causes a net iron deposition in the body, of about 15-20 mg/day. In practice, the goal of chelation therapy is to achieve an iron balance by accessing two iron pools, namely intracellular labile iron pool (LIP) and iron from red cell catabolism [2].

After the introduction of deferoxamine in 1963, several efforts were made to synthesize orally active iron chelators. Following the screening of more than 700 chelators from various chemical classes, deferasirox emerged as a highly selective chelator for iron with high oral potency and tolerability. Deferasirox mobilizes iron stores by binding selectively to the ferric form of iron and enters most of the cells to reach the major intracellular sites of iron accumulation. For myocardial iron, deferasirox has the ability to enter myocardial cells and chelate iron from these cells. It was also observed from myocyte cultures that it rapidly gains entry in the myocytes and binds to labile intracellular iron, leading to decreased free radical production.

In recent years, clinical trials have been conducted to evaluate the effect of deferasirox on myocardial iron and