N. Banu et al /J. Pharm. Sci. & Res. Vol. 11(4), 2019, 1172-1174

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Adiponectin Level in Type 2 Diabetes and its Complication – A Review

Dr.N. Banu [1], K.S.Elango[2]

[1]*Assistant Professor, Bharathi Women's College (Autonomous), Chennai – 600 108*

[*2]*Research Scholar, Vel's University, Pallavaram, Chennai.*

Abstract

Finding insulin resistance and its complications through on novel biomarker is an essential in treating Type II diabetes. The insulin resistance is understood mostly by uncontrolled blood glucose level in Type II diabetes, and above the normal glucose level in prediabetes. Conditions like metabolic syndrome, fatty liver, arteriosclerosis, genetic and lifestyle factors (obesity) are also associated with insulin resistance. The lack of effective treatment in Type II diabetes is due to unavailability of early detection in insulin resistant. Diet, Exercise, Medicine are three factors necessary to control Type II diabetes. In our Indian population, Type II diabetes patients having central obesity, which is a fat deposition in the adipose tissue. Recent researches show adipose tissue plays an important role in finding IR and its induced complication. Adipose tissue produces and releases adipocyte proteins leptin, resistin, adiponectin and growth factors TNF alpha. In this adiponectin is a novel and important member of the adipocytokine family, it has an important role in the modulation of glucose and lipid metabolism in insulin-sensitive tissues. This article reviews the evidence of adiponectin level in insulin resistant and its complications in type 2 diabetes.

INTRODUCTION

In type 2 diabetes early diagnosis of insulin resistant will help in treat efficiently the type 2 disorder and its complication. Adipocytokine family have an important role in the modulation of glucose and lipid metabolism. Study the levels of adipocytokine family proteins and correlate the value with fasting glucose level and lipid level in diabetic and non-diabetic patient will give the view of prospective biomarker in type 2 insulin resistant and its complication. This review will include an overview of Insulin and its action, Phases of insulin and its complication, Insulin resistance, and prospective studies of adiponectin.

INSULIN AND ITS ACTION

Person with normal metabolism, after the food intake digestion starts in mouth by action of enzyme ptyalin, while partial digested carbohydrates reach stomach, ptyalin action stops due to the fall of pH to 3.0. In the stomach Hcl causes hydrolysis and the digested food move to Duodenum. The pancreatic amylase hydrolyses remaining residues and all these digested food reach small intestine. Where absorption takes place in three mechanisms (Passive diffusion, Facilitated diffusion, Active transport). Sodium Glucose transporter (SGLT 1,2) which is present on the intestinal cell absorbs glucose. The absorbed glucose enters the blood stream and pancreas releases insulin into the blood. Insulin and glucose circulate in the blood to cells in the body. Cells utilize the glucose to create ATP as energy source at aerobic condition in three stages (Glycolysis, Krebs cycle, Electron transport chain).

Insulin facilitates liver, muscle to absorb glucose from blood stream also stimulates store excess glucose in the form of Glycogen. In fasting condition, the level of the blood glucose further drops, at this stage the body releases Glucagon, this hormone stimulates the glycogenolysis (break down of stored glycogen in liver to glucose and released in to the blood stream).

Whereas in disturbed or abnormal metabolism (usually happens in Type II diabetes) produce more insulin than normal person insulin secretion, which means the body can't use insulin effective manner. The over work of beta cells, starts to fail in due course of time, this causes insufficient of insulin production leads more accumulation of blood sugar in the circulatory system[1].

PHASES OF INSULIN AND COMPLICATIONS

Insulin secretion and release happens in the physical body by Phase I, Phase II and Basal insulin release. To maintain whole day glucose level, mostly between meals and overnight fasting condition insulin secretion and release to blood system in lower amounts steadily, so that cells utilise Glucose as energy fuel. This process named **basal insulin release**.

While normal person starts to take food, after half-an-hour to 1 hr the glucose level raises, in response to this raise, the stored insulin released immediately. The early release of stored insulin after a meal was **First phase insulin release**. After first phase release, beta cell stops. If blood glucose level not drops to normal after 30 mts. of first phase then push out another smaller **second phase insulin release** response to bring back the sugar level normal[2,3].

In case of failing first phase insulin release, high level glucose circulation toxic to beta cells (Glucose toxicity) kill more beta-cells, making first and second phase insulin release even less able to control blood sugar concentrations. If first phase fails and second phase in sluggish action, the blood sugars start to rise to higher levels after a meal, take longer time to return to normal. This condition is called "impaired glucose tolerance." If the blood sugar rises over 200 mg/dl (11 mmol/L) after a meal, the condition is called Diabetes.

A study on beta cell death in diabetic patient's autopsy done by Mayo clinic found that patients diagnosed as diabetic had 63% less beta cell mass than normal people--which they attributed to beta cell death, not shrinking in the size of the individual cells[4,5].

INSULIN RESISTANCE

The first and second phase insulin release fails, then the person affected with insulin resistance. In this condition some receptors in the liver and the muscle cells stop responding properly to insulin. This indicates lots of insulin circulating in the body, the muscles and liver not respond until the insulin levels rise much higher.

In some of Type II diabetes, their beta-cells die when they attempt to reproduce in response to a need for more insulin, also another individual they may have a genetic defect which prevents their beta-cells from storing insulin though their beta-cells are still capable of secreting it.

Apart from these reasons recent research stress more on lipid deposition in liver and muscle causes IR. Consuming high fat foods (animal or plant) leads accumulation of lipids (not allow sugar enter in to tissues) causes mitochondrial dysfunction and cellular inflammation in muscles and liver also causes atherosclerosis and non-alcoholic fatty liver disease. Insufficient of doing Exercise have been increase the IR. Exercise stimulate the muscle tissue burn fat and allow the glucose, insulin enter the cell to utilise energy by the way reduce the glucose level[6,7].

This review discusses possibility of biomarkers alternatively to homeostasis model assessment (HOMA) also a single biomarker which can detect insulin resistant and complication(artherogenesis).

ADIPONECTIN:

Adiponectin is a hormonal protein produced from white adipose tissue (specifically in mature adipocytes) into blood stream, visceral fat adipose tissue is largely responsible for the secretion of adiponectin. It's a 30kDa protein with C terminal globular domain and collagen like N terminal domain. Plasma adiponectin levels correlate inversely with adiposity and fasting blood glucose levels, and that low adiponectin levels may precede declines in insulin sensitivity in humans. Furthermore, clinically used thiazolidinedione agents can induce adiponectin gene expression[8]. Adiponectin's regulation may relate to the connection between insulin sensitivity and the distribution (as opposed to the absolute amount) of body fat. It modulates metabolic processes like glucose regulation and fatty acid oxidation[8]. Adiponectin effects decreased gluconeogenesis and increases glucose uptake which ultimately leads balanced glucose homeostasis[9]. If this process stabilized, the insulin sensitivity increased due to the higher level of adiponectin. One of the prospective study by S Yamamoto et.al[10] shows that During the 3-year follow-up, a total of 214 patients were newly identified as having diabetes. Of these, 87% of patients were in a prediabetic condition at baseline (FPG $\geqslant$110 mg dl^{-1} (6.1 mmol l^{-1}) and/or HbA1c $\geqslant$6.0 (42 mmol mol^{-1})). Table 1 compares the baseline characteristics of study participants between those who developed diabetes and those who did not. Compared with participants who had been free of diabetes through the study period, patients who developed diabetes were older, had a higher mean of BMI, VFA, waist circumference, fasting plasma glucose, HbA1c, fasting insulin and HOMA-IR, but had a lower mean of serum adiponectin levels.

Table 1 Characteristics of study subjects at baseline

	Subjects without diabetes incidence	***Subjects with diabetes incidence***
Number	4377	214
Sex (% women)	10.3	7.9
Age (years)	52.2 (9.6)	55.9 (8.7)**
Family history of diabetes (%)	16.7	22.9*
Smoking (%)		
Never	35.2	32.2
Past	31.8	35.0
Current	32.9	32.7
Alcohol use (%)		
Nondrinker	28.5	26.6
Drinking <1 *go* per day	39.8	38.8
Drinking 1–1.9 *go* per day	22.1	22.9
Drinking 2 *go* per day	9.6	11.7
Physical activity, % 400 MET-min per week	49.2	51.4
Body mass index (kg m^{-2})	23.8 (2.9)	24.8 (3.4)**
Waist circumference (cm)	86.0(12.9)	88.4 (8.8)**
Visceral fat areas (cm^2)	115 (52)	137 (53)**
Fasting glucose (mg dl^{-1})	99.7 (7.9)	112.5 (7.9)**
Hemoglobin A1c (%, mmol mol^{-1})	5.7 (0.3), 39 (2.8)	6.0 (0.3)**, 42 (2.8)**
Fasting insulin (μU ml^{-1})	5.8 (3.5)	8.1 (6.1)**
HOMA-IR	1.46 (0.94)	2.26 (1.71)**
HOMA-β	57.6 (32.6)	59.3 (45.8)
Adiponectin (μg ml^{-1})	7.93 (4.09)	6.82 (3.57)**

Abbreviations: HOMA-β, homeostasis model assessment of β-cell function, HOMA-IR, homeostasis model assessment of insulin resistance; MET, metabolic equivalent.

Values are mean (s.d.), unless stated otherwise; *P<0.05 and **P<0.01.

[a]Physical activity during leisure time and on commuting to work.

Another case-control study in Pima Indians by Jonathan Krakoff et.al[11] examined the association between adiponectin a known predictor of diabetes in Pima Indians, and markers of inflammation and endothelial function in nondiabetic subjects to assess whether these markers predict later diabetes in a case-control study within a longitudinal health study in Pima Indians. The results show Adiponectin was negatively correlated with CRP ($r = -0.25$, $P < 0.05$), IL-6 ($r = -0.20$, $P < 0.05$), sPLA2 ($r = -0.22$, $P < 0.05$), (i.e.) adiponectin concentrations correlate with markers of inflammation and endothelial dysfunction. These correlations are modest but generally associated with subclinical inflammation and adiponectin associated with anti-inflammatory activity. Obesity and type 2 diabetes are interrelated, also type 2 diabetes prone to low grade inflammation. So low level adiponectin indirectly predicts onset of type 2 diabetes in obesity.

Genetic association of ADIPOQ Gene: Adiponectin is encoded by the *ADIPOQ* gene on chromosome 3q27[12]. A study conducted by Kandasamy Ramya et.al in 1100 normal glucose tolerant (NGT) and 1100 type 2 diabetic randomly selected from the south India population. The Fasting serum adiponectin levels were measured by radioimmunoassay and variants were screened by polymerase chain reaction-restriction fragment length polymorphism. Linkage disequilibrium was estimated from the estimates of haplotype frequencies. Results conclude that four Single nucleotide polymorphism, *−3971 A/G* (*rs822396*), *+ 276 G/T* (*rs1501299*), *− 4522 C/T* (*rs822393*) and *Y111H T/C* (*rs17366743*) were significantly associated with hypoadiponectinemia. The haplotypes GCCATGAAT and AGCGTGGGT conferred lower risk of T2DM in this south Indian population[13].

Relationship of adiponectin level in type 2 associated complication: One of the types 2 associated long term complication is Cerebro-vascular disease. Type-2 diabetic males with coronary heart disease when compared to healthy males showed significantly low levels of serum adiponectin and HDL-C and significantly high level of Fasting blood glucose. Serum adiponectin level shows a significant negative correlation with Fasting blood glucose, HbAlc and Triglyceride in type-2 diabetic men with coronary heart disease. Adiponectin showed a significant positive association with HDL-C in controls and patients of type-2 diabetes with Coronary heart disease[14]. Whereas In postmenopausal women diabetic patients with Ischemic heart disease (IHD) as compared with normal control subjects except for serum adiponectin and HDL cholesterol concentrations, which were significantly decreased in diabetic patients and diabetic patients with IHD group[15].

CONCLUSION:

The studies on south Indian population and Asian population shows the low-level adiponectin in type 2 diabetes and associated long term complication. So, we can consider adiponectin as a biomarker in early detection of type 2 diabetes associated insulin resistant and its complications like coronary heart disease**.**

REFERENCES

1. Brown P, Tompkins C, Juul S, Sonksen PH. 1978, Mechanism of action of insulin in diabetic patients: a dose-related effect on glucose production and utilisation, *BMJ* 1978 ; **i**: 1239–42.
2. Tefano Del Prato, Piero Marchetti, and Riccardo C. Bonadonna. 2002, Phasic Insulin Release and Metabolic Regulation in Type 2 Diabetes, *Diabetes 51:S109-S116*.
3. John E. Gerich. 2002, Is reduced first-phase insulin release the earliest detectable abnormality in individuals destined to develop type 2 diabetes? *Diabetes 51:S117-S121*.
4. Alexandra E. Butler, Juliette Janson, Susan Bonner-Weir, Robert Ritzel, Robert A. Rizza, and Peter C. Butler. 2003, Beta-Cell Deficit and Increased Beta-Cell Apoptosis in Humans with Type 2 Diabetes, *Diabetes 52:102-110.*
5. John E. Gerich. 2002, The Genetic Basis of Type 2 Diabetes Mellitus: Impaired Insulin Secretion versus Impaired Insulin Sensitivity, *Endocrine Reviews 19 (4): 491-503.*
6. Kusminski CM, Shetty S, Orci L, Unger RH, Scherer PE. 2009, Diabetes and apoptosis: lipotoxicity, *Apoptosis: Int J Program Cell Death, Dec;14(12):1484–95*.
7. Boden G. 2006, Fatty acid-induced inflammation and insulin resistance in skeletal muscle and liver, *Curr Diab Rep. Jun;6(3):177–81*.
8. Scherer PE. 2002, Adiponectin/ACRP30/AdipoQ. Symposium: Adipose tissue as a secretory organ, Program and abstracts of the 62nd Scientific Sessions of the American Diabetes Association, *Diabetes, Volume 51, Supplement 2*.
9. Díez JJ, Iglesias P. 2003, "The role of the novel adipocyte-derived hormone adiponectin in human disease", *Eur. J. Endocrinol*. **148** (3): 293–300.
10. S Yamamoto Y Matsushita T Nakagawa T Hayashi M Noda and T Mizoue. 2014, Circulating adiponectin levels and risk of type 2 diabetes in the Japanese, *Nutrition and Diabetes*, Aug; 4(8):e 130.
11. Krakoff J, Funahashi T, Stehouwer CD, Schalkwijk CG, Tanaka S, Matsuzawa Y, Kobes S, Tataranni PA, Hanson RL, Knowler WC, Lindsay RS. 2003, Inflammatory markers, adiponectin, and risk of type 2 diabetes in the pima Indian, *Diabetes Care.* Jun;26(6):1745-51.
12. Menzaghi C, Ercolino T, Di Paola R, Berg AH, Warram JH, Scherer PE, Trischitta V, Doria A. 2002, haplotype at the adiponectin locus is associated with obesity and other features of the insulin resistance syndrome, Diabetes. 2002;51(7):2306–2312.
13. Kandaswamy Ramya, Kuppuswamy Ashok Ayyappa, Saurabh Ghosh, Viswanathan Mohan, Venkatesan Radha. 2013. Genetic association of ADIPOQ Gene variants with type 2 diabetes, obesity and serum adiponectin levels in south indian population, Gene. 2013 Dec 15;532(2):253-62.
14. Durrani S, Shah J, Khan MA, Jan MR. 2015, Relationship of adiponectin level with lipid profile in type-2 diabetic men with coronary heart disease, J Ayub Med Coll Abbottabad. 2015 Jan-Mar;27(1):32-5.
15. Farhan Jaleel, Anila Jaleel, Jawed Aftab, M. Ataur Rahman. 2006, Relationship between adiponectin, glycemic control and blood lipids in diabetic type 2 postmenopausal women with and without complication of ischemic heart disease, Clinica Chimica Acta. Vol 370, 1–2, Pages 76-81.