VOLUME-7, ISSUE-1, JANUARY-2018 • PRINT ISSN No 2277 - 8160

Original Research Paper

Biochemistry

A CORRELATION BETWEEN SERUM ADIPONECTIN LEVEL AND TYPE 2 DIABETES: A META- ANALYSIS OF 5403 SUBJECTS

Akanksha Dubey — Assistant Professor and PhD Student, Department of Biochemistry People's College of Medical Sciences and Research Centre Bhopal MP

Dr P. J. Hisalkar* — Professor and PhD Guide, Department of Biochemistry Government Medical College and Hospital Dungarpur, Rajasthan *Corresponding Author

KEYWORDS :

Introduction

The increasing prevalence of Type 2 Diabetes has become a major public health challenge throughout the world, with 366 million prevalent diabetic cases in 2011 and a projected 552 million cases expected by the year 2030[1]. Both lifestyle factors, including diet and physical activity, and genetic factors contribute to the accelerating diabetes epidemic [2]. The designation of the adipose tissue as a pivotal active endocrine organ has indeed drawn much scientific interest in the last few years. The adipose tissue is now viewed as the largest endocrine organ in the body [3] It secretes numerous bioactive proteins, collectively known adipocytes, into the circulation. [4] The most abundant of these adipo-cytokines is the adiponectin which is secreted by white adipose tissue and accounts for 0.01% of total plasma proteins. [5,6]

Adiponectin (also referred to as GBP 28, apM1, AdipoQ and Acrp30) is a protein which in humans is encoded by the *ADIPOQ* gene[7] It is involved in regulating glucose levels as well as fatty acid breakdown. Adiponectin shares homology with collagen and complement 1q family.[8] It consists of 244 amino acids, which form four different domains[9].

Adiponectin modulates a number of metabolic processes via the activation of 5^0-adenosine monophosphate-activated protein kinase (AMPK) and perox- isome proliferator activated receptor-a (PPAR-a)[10]

In addition, it plays an important role in the suppression of the metabolic derangements that cause insulin resistance and type 2 diabetes mellitus (type 2 DM)[9]

Interestingly, although adiponectin is secreted by mature adipocytes , its plasma level shows a negative correlation with body fat mass. It has been found that adiponectin plasma level in obese individuals was lower than in non-obese ones.[11] Adiponectin has been also shown to be negatively correlated with obesity-related diseases such as Type 2 Diabetes. Furthermore, low adiponectin levels predicts the incidence of Type 2 Diabetes[12] Over 30 million have now been diagnosed with diabetes in India. The CPR (Crude prevalence rate) in the urban areas of India is thought to be 9 per cent. In rural areas, the prevalence is approximately 3 per cent of the total population. The estimate of the actual number of diabetics in India is around 40 million. (Diabetes UK Report). Adiponectin is the exclusive adipokine of which the plasma concentration is reduced when the adipose tissue volume is increased[13] Hypoadiponectinemia has been detected in Type 2 Diabetes[14] In the current study, a meta-analysis of 07 individual studies and 01 Meta analysis with a total of 5403 subjects was conducted to determine whether there was a relationship between serum adiponectin value and Type 2 Diabetes.

Materials and Methods

Search Strategy: Articles were identified through a comprehensive systematic electronic search of PubMed , Google scholar and other databases up to year 2017 using the following MeSH terms: 'impaired glucose tolerance, 'Type 2 Diabetes, and 'adiponectin.' Also, reference lists of relevant articles were screened for eligibility. Our meta-analysis was carried out according to the Meta-analysis of Observational Studies in Epidemiology guidelines[15] The research studies from year 2008 to 2017 were selected. The selected studies had to be in accordance with the following major criteria.

a) The serum adiponectin level and Type 2 Diabetes must be evaluated.
b) The Type 2 Diabetes diagnosis criteria were derived from the American Diabetes Association fasting plasma criteria (2005).

Criteria for Diabetes Diagnosis: 4 options
FPG ≥126 mg/dL (7.0 mmol/L)* Fasting is defined as no caloric intake for ≥8 hours
2-hr PG ≥200 mg/dL (11.1 mmol/L) during OGTT (75-g)* Using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water
A1C ≥6.5% (48 mmol/mol)* *Performed in a lab using NGSP-certified method and standardized to DCCT assay*
Random PG ≥200 mg/dL (11.1 mmol/L) In individuals with symptoms of hyperglycemia or hyperglycemic crisis

c) The individual studies should be case-control or cohort studies published in the official journals or peer-reviewed postgraduate dissertations.
d) Data of total adiponectin mean and standard deviation (SD), or sufficient data to estimate adiponectin mean and SD should be provided.
e) No medications known to influence circulating adiponectin were used.

We excluded literature reviews, letters to the editor, cross-sectional studies, randomized controlled trials, studies of animals or cell lines, studies of genetic variation in adiponectin related genes and studies of gestational diabetes. We also excluded studies on populations with diseases other than Type 2 Diabetes.

Data extraction: The data were abstracted according to a standard protocol. Studies that did not follow the Inclusion criteria, those considered double publications, or those that provided inadequate data were excluded. If the same data appeared in different studies, the data were used only once. The following information was extracted from each eligible study:

a) First author's name, year of publication, region of studies,
b) Type of study design, sample size,
c) Methods of adiponectin measurement, the type of blood sample,
d) Adiponectin levels of cases and controls (mean and SD),
e) The number of males and females, the age of cases and controls (mean and SD).

Statistical Analysis: The mean, SD or standard error (SE) on plasma or serum adiponectin levels were extracted in all included studies.

The meta-analysis was based on sufficient information directly providing the mean and SD. Weighted mean differences (WMDs) along with the corresponding 95% confidence intervals (CIs) in adiponectin levels of all suitable cases and controls were estimated.[16] Many subgroups were analyzed according to geographic region, sample size, age, blood sample, method, quality score and sex[17] Furthermore, cumulative meta-analysis was carried out to evaluate the evolution of the combined estimates over time according to the ascending date of publication.[18]

Study Characteristics: The meta-analysis of 08 studies involved 5403 participants out of which 2702 were cases of type II diabetes and 2701 were healthy controls. The studies were published between 2008 and 2014, including case–control studies. Geographically, all the studies were carried out in Asia. Adiponectin levels were measured by enzyme-linked Immunosorbent assay in maximum studies, whereas Immunoturbidimetric assay was also used in few studies. Studies used serum specimens to measure the adiponectin level. Furthermore, 05 studies elucidated that no participant took medications that could affect the adiponectin level, whereas 03 studies did not mention the medication records.

Results:

By searching above databases 06 case control studies with 920 cases and 4688 controls were included in meta-analysis. Very few studies were published in India and maximum articles were published in Asia. The serum adiponectin level was included. Most of the articles were hospital based case control studies.

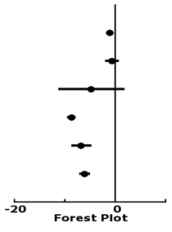
Study	Region	Type of Sample	Method	Sample Size		Sex		Age		Adiponectin	
				Control	cases	M	F	Control	cases	Control	cases
S Yamamoto et al	Asia	Serum	Immunoturbidimetric	4377	214	437	16	52.2±9.9	55.9±8.7	7.93±4.09	6.82±3.57
Shereen Aleidi et al	Asia	Serum	ELISA	19	61	31	12	43.05 ± 9.19	56.15 ± 12.02	5.71 ± 2.35	5.05 ± 2.61
V. C. Renju et al	Asia	Serum	ELISA	20	60	-	-	41.4±5.4	46.4±6.2	11.6±14.51	6.86±4.99
Yoshinari Obata et al	Asia	Serum	Immunoturbidimetric	200	504	-	-	67.4 – 9.3	56.6 – 9.9	12.0±5.02	3.3±2.97
V. Urbanavičius et al	Asia	Serum	RIA	24	33	-	-	47.87 ± 9.06	55.82 ± 8.45	14.37±4.08	7.63±2.57
Mojtaba Izadi et al	Asia	Serum	ELISA	48	48	-	-	45 ± 9.2	44 ± 9	11.34±3.26	5.3 ± 1.23

Pooled analysis:

In whole population a significant association was found between serum Adiponectin and Type II DM.

Study	WMD	95% CL	
		LOW	HIGH
S Yamamoto et al	-1.110	-1.603	0.617
Shereen Aleidi et al	-0.660	-1.903	0.583
V. C. Renju et al	-4.750	-11.233	1.733
Yoshinari Obata et al	-8.700	-9.442	-7.958
V. Urbanavičius et al	-6.740	-8.700	-4.780
Mojtaba Izadi et al	-6.040	-7.026	-4.780
S Yamamoto et al	-1.130	-1.150	-1.510

WMD	95% CL	
	LOW	HIGH
-1.110	-1.603	0.617
-0.660	-1.903	0.583
-4.750	-11.233	1.733
-8.700	-9.442	-7.958
-6.740	-8.700	-4.780
-6.040	-7.026	-4.780
-1.130	-1.150	-1.510



- Subgroup meta-analysis for adiponectin levels in diabetes patients and healthy controls by geographic region. Results are expressed as weighted mean difference (WMD) and 95% confidence intervals (95% CI). Significant decrease of adiponectin levels was observed between diabetes patients and healthy controls in the included studies carried out in Asia

Discussion

This meta-analysis of relevant studies suggests that patients with type 2 diabetes have lower value of serum adiponectin when compared with healthy controls. A meta-analysis published in Journal of the American Medical Association in 2009 with a total of 14,598 participants and 2,623 incident cases showed that lower adiponectin levels were associated with a higher incidence of insulin resistance and Type 2 Diabetes in humans. Furthermore, a most recent and up-to-date cohort study in 2014 carried out by Yamamoto Sin Japan suggested that higher levels of circulating adiponectin are associated with a lower risk of Type 2 Diabetes and that adiponectin could confer a benefit in both persons with and without pre-diabetes[19] The same results were shown in other studies[20-22] Thus, the relationship between adiponectin values and insulin resistance or inflammation is unclear as a result of other confounding diseases[23]The insulin-sensitizing effect of adiponectin was summarized by three independent routes[24] First, in vitro studies have suggested that both isoforms of adiponectin receptor (AdipoR1 and AdipoR2) can increase adenosine monophosphate-activated protein kinase phosphorylation and peroxisome proliferator-activated receptor-a activity by adiponectin binding, thus increasing fatty acid oxidation and glucose uptake[25]The mechanism is related to phosphorylation of acetyl coenzyme A carboxylase, fatty-acid oxidation, glucose uptake and lactate production in myocytes, and reducing gluconeogenesis in the liver[26] Second, in skeletal muscle, adiponectin activates the expression of involved molecules in fatty-acid transport, such as uncoupling protein is required. During energy dissipation and CD36, acyl-coenzyme A oxidase involved in combustion of fatty acid [27] These changes result in decreased triglyceride content in skeletal muscle.Third, adiponectin activates fatty-acid combustion and energy consumption through peroxisome proliferators-activated receptor-a activation[28] which leads to decreased triglyceride content in the liver and skeletal muscle, and thus increased insulin sensitivity. An animal study carried out by Maeda et al[29] showed that adiponectin/ACRP30-knockout mice delayed clearance of free fatty acid in plasma, lower levels of fatty-acid transport protein 1 messenger ribonucleic acid in muscle, higher levels of tumour necrosis factor-alpha messenger ribonucleic acid in adipose tissue and high plasma tumour necrosis factor-alpha concentrations, resulting in severe diet-induced insulin resistance. Iwabu et al [30] found that decreased levels of adiponectin and AdipoR1 in obesity could have causal roles in mitochondrial dysfunction and insulin resistance seen in Muscle-R1KO mice. In the present study, the meta-analysis showed that there was large heterogeneity among studies. To the best of our knowledge, this is the most comprehensive meta-analysis to estimate the association between adiponectin levels and Type 2 Diabetes. Adequate numbers of cases and controls were included from all available publications concerned with circulating adiponectin levels and diabetes, which greatly increased the statistical power of the analysis and provided enough evidence for us to make a correct conclusion. Furthermore, no publication bias was detected in the present meta-analysis, which showed that the pooled results of our study should be reliable. To summarize, these results confirm the strengths of our meta-analysis the possible limitations of the present study should also be considered. First, 07 case–control studies and 01 meta-analysis, but no randomized controlled trial included in the meta-analysis, might substantially weaken the quality of this study. Second, our results were concluded without adjusting the confounding factors, such as smoking status, alcoholic consumption, environmental factors and other diet lifestyle factors. Third, this meta-analysis included small sample size studies and the backgrounds of patients varied, which would result in low statistical power and inconsistent results among studies. Finally, insufficient data were available. The influence of visceral

adiposity could not be evaluated, as waist circumference or waist-to-hip ratio was not available in the majority of studies.

Despite these limitations, the present findings could provide useful information on the diseases, and might help impose a stricter follow up and possibly an early treatment initiation, thus preventing the progression to diabetes. Furthermore, our findings might motivate more randomized controlled trials to be carried out to obtain better understanding of causal relationships between the level of adiponectin and diabetes.

Conclusion

In conclusion, higher levels of serum adiponectin were associated with decreased risk of type 2 diabetes. This conclusion contributes to the formulation of more effective individual Type 2 Diabetes therapy strategies.

In consideration of the aforementioned limitations, 3more large-scale studies as per Indian scenario are necessary to validate the significance of our findings.

References:

1. Li G, Zhang P, Wang J et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: A 20-year follow-up study. Lancet. 2008; 371: 1783–9.
2. Lindstrom J, Ilanne-Parikka P, Peltonen M et al. Sustained reduction in the incidence of Type 2 Diabetes by lifestyle intervention: Follow-up of the Finnish Diabetes Prevention Study. Lancet. 2006; 368: 1673–9.
3. Oh, D.K., Ciaraldi, T., Henry, R.R., 2007. Adiponectin in health and disease. Diabetes Obes. Metab. 9, 282–289.
4. Chandran, M., Phillips, S.A., Ciaraldi, T., Henry, R.R., 2003. Adiponectin: more than just another fat cell hormone? Diabetes Care 26, 2442–2450.
5. Gil-Campos, M., Canete, R.R., Gil, A., 2004. Adiponectin, the missing link in insulin resistance and obesity. Clin. Nutr. 23, 963–974.
6. Heiker, J.T., Kosel, D., Beck-Sickinger, A.G., 2010. Molecular mechanisms of signal transduction via adiponectin and adiponectin receptors. Biol. Chem. 391, 1005–1018.
7. Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, Matsubara K (April 1996). "cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPose Most abundant Gene transcript 1)". Biochemical and Biophysical Research Communications. 221 (2):286–289.
8. Simpson, F., Whitehead, J.P., 2010. Adiponectin–it's all about the modifications. Int. J. Biochem. Cell Biol. 42, 785–788.
9. Sheng, T., Yang, K., 2008. Adiponectin and its association with insulin resistance and type 2 diabetes. J. Genet. Genomics. 35, 321–326.
10. Fagerberg, B., Kellis, D.,Bergstrom, G., Behre, C.J., 2011. Adipo- nectin in relation to insulin sensitivity and insulin secretion in the development of type 2 diabetes: a prospective study in 64-year-old women. J. Int. Med. 269, 636–643.
11. Arita, Y., Kihara, S., Ouchi, N., Takahashi, M., Maeda, K., Miyagawa, J., Matsuzawa, Y., 2012. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem. Biophys. Res. Commun. 425, 560–564.
12. Han, S.H., Sakuma, I., Shin, E.K., Koh, K.K., 2009. Antiatheroscle- rotic and anti-insulin resistance effects of adiponectin: basic and clinical studies. Prog. Cardiovasc. Dis. 52, 126–140.
13. Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF (1995) A novel serum protein similar to C1q, produced exclusively in adipocytes. J Biol Chem 270:26746–26749.
14. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, et al. (2001) Hypoadiponectinemia in obesity and Type 2 Diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 86:1930– 1935.
15. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008–2012.
16. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557–560.
17. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539–1558.
18. Song F, Khan KS, Dinnes J, et al. Asymmetric funnel plots and publication bias in meta-analyses of diagnostic accuracy. Int J Epidemiol 2002; 31: 88–95.
19. Yamamoto S, Matsushita Y, Nakagawa T, et al. Circulating adiponectin levels and risk of type 2 diabetes in the Japanese. Nutr Diabetes 2014; 4: e130.
20. Knobler H, Benderly M, Boyko V, et al. Adiponectin and the development of diabetes in patients with coronary artery disease and impaired fasting glucose. Eur J Endocrinol 2006; 154: 87–92.
21. 38. Jalovaara K, Santaniemi M, Timonen M, et al. Low serum adiponectin level as a predictor of impaired glucose regulation and type 2 diabetes mellitus in a middle-aged Finnish population. Metabolism 2008; 57: 1130–1134.
22. 39. Bonneau GA, Pedrozo WR, Berg G. Adiponectin and waist circumference as predictors of insulin-resistance in women. Diabetes Metab Syndr 2014; 8: 3–7.
23. Mente A, Meyre D, Lanktree MB,et al. Causal relationship between adiponectin and metabolic traits: a Mendelian randomization study in a multiethnic population. PLoS One 2013; 8: e66808.
24. Yadav A, Kataria MA, Saini V, et al. Role of leptin and adiponectin in insulin resistance.Clin Chim Acta 2013; 417: 80–84.
25. Yamauchi T, Kamon J, Ito Y, et al. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature 2003; 423: 762–769.
26. Yamauchi T, Kamon J, Minokoshi Y, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med 2002; 8: 1288–1295.
27. Xu A, Yin S, Wong L, et al. Adiponectin ameliorates dyslipidemia induced by the human immunodeficiency virus protease inhibitor ritonavir in mice. Endocrinology 2004; 145: 487–494.
28. Zhu M, Miura J, Lu LX, et al. Circulating adiponectin levels increase in rats on caloric restriction: the potential for insulin sensitization. Exp Gerontol 2004; 39: 1049–1059.
29. Maeda N, Shimomura I, Kishida K, et al. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. Nat Med 2002; 8: 731–737.
30. Iwabu M, Yamauchi T, Okada-Iwabu M, et al. Adiponectin and AdipoR1 regulate PGC-1alpha and mitochondria by Ca (2+) and AMPK/SIRT1.Nature 2010; 464: 1313–1319)