CORRELATION OF OBESITY AND THE NOVEL ADIPOCYTOKINES, LEPTIN AND ADIPONECTIN WITH INSULIN RESISTANCE IN TYPE 2 DIABETES MELLITUS

Piyali Das[1], Subir Kumar Bandyopadhyay[2], Subhradev Biswas[3] Gorachand Bhattacharya[4], Madhumita Manna[5]

1 Associate Professor, Department of Physiology, Calcutta National Medical College (CNMC), Kolkata, Kolkata-700014

2 Professor and Head, Department of General Medicine, Calcutta National Medical College (CNMC), Kolkata- 700014

3 Assistant Professor, Department of ENT, IPGMER, Kolkata-700019

4 Professor and Ex Head, Department of Biochemistry, Calcutta National Medical College (CNMC), Kolkata- 700014

5 Associate Professor, Department of Zoology, Bethun College, Kolkata- 70006

ABSTRACT

Back ground*: Type 2 Diabetes mellitus is state of uncompensated insulin resistance. But what actually predisposes to it, is still a controversy. Obesity is often marked as a precondition for such insulin resistance. But the degree of association and mode of pathogenesis are grossly debated.*

Methods: *Here we explored the correlation of physical parameters for obesity like BMI (Body Mass Index), abdominal circumference, waist- hip ratio and the adipocytokines like leptin and adiponectin with the degree of insulin resistance (HOMA-IR score) in 167 patients of type 2 Diabetes mellitus.*

Result: *We found significant positive correlation between BMI, abdominal circumference, waist-hip ratio and insulin resistance. Leptin showed significant positive correlation with all the said physical parameters. But, adiponectin showed a negative correlation with abdominal circumference, waist- hip ratio and fasting insulin. Leptin- adiponectin ratio showed a significant positive correlation with insulin resistance.*

Conclusion: *Leptin shoots up with increased adiposity where as adiponectin gets reduced in central obesity which may contribute to insulin resistance. Though neither of leptin and adiponectin showed any significant correlation with insulin resistance individually, a significant positive correlation was found between leptin and adiponectin ratio and HOMA –IR score. Therefore, the ratio can be an authentic predictor of insulin resistance as it takes into account the interplay of both of the adipocytokines for its causation.*

Key words: *cervical cancer, screening, bottleneck.*

(Bangladesh J Physiol Pharmacol 2014;30(1):29-32.)

INTRODUCTION

It has been seen that insulin resistance is often an ancillary metabolic derangement in type II Diabetes mellitus characterized by postprandial hyperglycemia and compensatory hyperinsullinemia. Overt Diabetes results when beta cells of pancreas no longer can afford excess insulin secretion in compensation of insulin resistance.[1] But exact underlying mechanism that may lead to such insulin resistance is still controversial. Where as obesity, sedentary life style, over intake of high caloric diet in genetically predisposed individuals are some possible contributory factors for insulin resistance by some school of thoughts [1-2] there are another group of studies who failed to establish any direct association between insulin resistance and obesity.[3,4] Traditionally, fat tissue was considered to be solely an energy storage depot having only a passive function in the body. However, recent studies have shown that fat tissue exerts important endocrine functions liberating a number of hormonal substances called adipocytokines. Adiponectin and leptin are the most abundant adipocytokines produced by adipocytes, and the best-studied molecules in this class so far. Their role has been studied in relation to deranged energy homeostasis, leukocyte migration, polycystic ovary etc.[5] But adequate evidence is still lacking regarding the influence of above molecules in the pathogenesis of insulin resistance. Moreover, data pertaining to Indian population in this regard is quite insufficient. With this background, in this present study attempt was made to verify whether there is any association among obesity, leptin, adiponectin and

Address of Correspondence: Dr. Piyali Das, Assistant Professor, Department of Physiology, CNMC, Lake Gardens Govt. Housing, Flat No: I-7, 48/4 Sultan Alam Road, Kolkata- 700033. Emai: dr.piyali@yahoo.com

insulin resistance in type 2 diabetes mellitus. Thereby we tried to explore the potential of adiponectin and leptin as a marker of obesity and its probable association with the pathogenesis of insulin resistance.

MATERIALS AND METHODS

This was a hospital based cross-sectional study

Inclusion criteria: 167 patients of recent onset (<5 years of disease duration) type-2 diabetes mellitus of 30- 60 years of ages and of both sexes, attending the General Medicine and Diabetic OPD of Calcutta National Medical College and Hospital , were included in the study . Informed consent was duly taken from each subject under study, and the entire procedure was done as per the Institutional ethical permission.

Exclusion criteria: subjects with any other chronic illness like tuberculosis, malignancy, hepatitis due to any cause, hormonal derangements other than diabetes like Cushing's syndrome, hypothyroidism etc, pregnancy, alcoholism, and any acute or chronic illness related or unrelated to diabetes were excluded from the study. Patient on insulin therapy or on oral hypoglycemics other than short acting 2nd generation sulfonylureas were also excluded .

Study Design: All the selected subjects were assessed for physical parameters (e.g. height, weight, BMI, abdominal circumference, waist/hip ratio). Then after 12 hours of fasting, blood samples were collected from them for blood glucose, serum insulin, leptin, adiponectin. From the findings degree of insulin resistance was calculated by HOMA- IR method (Homeostatic Model Assessment). HOMA-IR scores were derived by multiplying fasting blood glucose (in millimoles/liter) and fasting serum insulin (in microunits/ milliliter) divided by 22.5. Blood glucose was measured by Glucose Oxidase method by using Eco Gluco Kit from Crest Biosystems, Santacruz, India. Serum insulin was measured by using human ELISA kit from MAPS, Monobind Inc, Lake Forest, USA. Levels of leptin and adiponectin were estimated by ELISA method by using human ELISA kit from Ray Biotech, USA. All the chemical parameters (leptin, adiponectin and HOMA-IR score) were compared between obese and non- obese subgroups (BMI 25 and above = obese group and BMI up to 24.99= non-obese group). (3)

Statistical analysis: Data was analyzed in Microsoft Excel and SPSS software. Value of individual parameter was expressed as mean and one standard deviation. Association among the parameters was tested by calculating co-efficient of correlation (r) and significance of difference of the means within the groups was tested by unpaired Student's t- test. Every where $p < 0.05$ was considered to be significant.

RESULTS

Total 167 type 2 diabetics (<5 years disease duration) were studied. Values of different parameters found in them are summarized in table 1 below.

Parameters under study	values
Age (years)	47.47 ± 9
Male: Female	27: 33
Total body weight (Kg)	64.16±12.44
BMI (Weight in Kg/Height in Meter^2)	27.34±5.24
Abdominal circumference (cm)	93.53±12.35
Waist/Hip ratio	0.93±0.059
Fasting Blood Glucose (mg/dL)	168.97 ± 77.21
Fasting Insulin (IU/L)	5.86 ± 4.91
HOMA -IR Score	2.14 ± 1.96
Leptin (ng/mL)	15.6 ± 15.09
Adiponectin (µg/mL)	7.39 ± 7.24

Leptin showed significant positive correlations with BMI, abdominal circumference, waist- hip ratio while adiponectin showed negative correlation with abdominal circumference, waist- hip ratio (r is significant at that particular df, $p<0.05$ in each case). Correlations between leptin, adiponectin and HOMA- IR score were not significant, though leptin showed a significant positive correlation and adiponectin a negative correlation with fasting insulin. Leptin –adiponectin ratio showed a significant positive correlation with HOMA-IR score ($r= 0.753$, $p<0.05$). Obese and non obese groups showed significant difference in leptin level, HOMA-IR score and leptin- adiponectin ratio ($p<0.05$).

Physical parameters showed significant positive correlations with HOMA- IR score ($p< 0.05$ in each occasion). Among the physical parameters strength of association was found highest between abdominal circumference and HOMA-IR score.

DISCUSSION

According to the World Health Organization's 2005 global estimates, about 1.6 billion adults are overweight and 400 millions are obese. Globally, obesity is a major contributor to the burden of disabilities and several chronic diseases including hypertension, type 2 diabetes and heart diseases.[6]

Present study reveals a significant positive correlation among the physical parameters of obesity and degree of insulin resistance (HOMA-IR score). Further the strength of association was found to be highest between abdominal circumference and insulin

resistance. This suggests a probable role of obesity mainly the central or visceral type in the pathogenesis of insulin resistance. Finding is corroborative with some previous studies who also found direct correlation between central obesity, insulin resistance and cardiovascular risk factors.[7,8] Regarding the adverse effects of obesity in particular the visceral obesity on glucose metabolism many probable mechanisms have been suggested which include, excessive lipid "supply" by a mechanism currently referred to as "lipotoxicity." When FFA (Free Fatty Acids) are elevated for a prolonged period, they have a direct effect on insulin action in skeletal muscle tissue and liver, reducing the normal responses to insulin to promote glucose uptake and to suppress hepatic glucose output, respectively. In both of these tissues, FFA increase cellular levels of acyl-CoA derivatives, which leads to an increase in the activity of cellular signaling molecules termed serine kinases that oppose the normal tyrosine phosphorylation cascade of the insulin receptor. The increased intracellular lipid accumulation that occurs in obese subjects as "ectopic fat", that is, triglyceride stored in the target organs themselves rather than in a benign adipose depot is an important source of intracellular acyl-CoA molecules that can affect normal insulin signal transduction. Other proteins secreted by adipose tissue, including the important inflammatory mediators like interleukin- 6 (IL-6) and tumor necrosis factor- (TNF), may have adverse effects on energy metabolism and insulin sensitivity in liver and muscle and play key roles in the development of insulin resistance in obesity.

In the past decade, it has become better appreciated that the relationship between obesity and the insulin resistance is mediated by the release of several hormones from adipose tissue, collectively called adipocytokines.

Human adiponectin contains 244 amino acid residues and consists of a 20-residue signal sequence, accounting for 0.01% of total proteins in plasma.[9] Reduction in adiponectin gene expression in adipose tissue is associated with obesity and insulin resistance in some animal models. In humans many clinical studies reported that plasma adiponectin concentrations decreased with increasing adiposity. Our study showed almost similar correlatios, but here we only got inverse relation between central obesity and adiponectin concentration significantly which is also supported by some previous study.[10] Probable explanation of such correlation may be that, it is not the visceral fat but the subcutaneous adipocytes that contributes to the level of adiponectin. Central obesity on the other hand is mainly due to the visceral adiposity or the ectopic fat which rather inhibits adiponectin production. This is ensured further by the finding of Statnick et al who found a lower adiponectin m -RNA level in omental than subcutaneous adipose tissue in an in vitro study with type 2 diabetics.[11] Although adiponectin seems to be implicated in the development of insulin resistance, explicit mechanisms linking adiponectin to incident type 2 diabetes remained speculative. Genetic polymorphisms might be involved in the regulation of adiponectin plasma concentration, especially when we take into account the existing linkage in the region of the adiponectin gene with type 2 diabetes.[9]

Leptin is a multiple-function adipocytokine involved in the regulation of food intake, energy storage and saccharide and lipid metabolism. Impaired regulation of food intake in consequence of leptin resistance is presented in connection with the aetiopathogenesis of obesity and insulin resistance, but its role in the development of these diseases is still not clear.[12] Our study revealed a positive correlation between leptin and adiposity. This has been supported by various previous studies.[13] Being the product of the ob gene secreted from adipose tissue leptin signals the amount of energy stores to the brain and is implicated in the regulation of food intake and energy balance. Hyperleptinemia in obesity may be due to leptin resistance which may arise from impaired leptin transport across the blood-brain barrier (BBB), defects in leptin receptor signaling, and blockades in downstream neuronal circuitries.[14] Being supported by all these, our study emphasizes the potential of leptin to be used as a marker for obesity.

Leptin and aiponectin showed a direct and inverse correlation with insulin resistance respectively, though not statistically significant. This may be due to multifactorial causation of insulin resistance in type-2 diabetics. Strikingly we found a significant positive correlation between leptin- adiponectin ratio and insulin resistance. This is also supported by some of the previous studies which also reported that the leptin/adiponectin ratio is a more effective parameter of insulin resistance than adiponectin or leptin alone.[15] Insulin resistance thus seems to be resultant of interplay between these two adipocytokines which should be therefore taken into account combinedly.

CONCLUSION

Our study concludes that obesity mainly central type may be an essential precondition for development of insulin resistance. Leptin has a potential to be used as an obesity marker as it is directly correlated with all physical parameters of obesity. Adiponectin on the contrary has an inverse correlation with central obesity as well as fasting insulin indicating its protective role in insulin resistance. Leptin - adiponectin ratio is a better predictor of insulin resistance than leptin or adiponectin alone.

REFERENCES

1. Ceriello A, Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the United States. JAMA 2001; 286: 1195–5.

2. Meyre D, Froguel P. ENPP1, the first example of common genetic link between childhood and adult obesity and type 2 diabetes. Med Sci (Paris) 2006; 22(3): 308-12.

3. K. Park. Obesity. In: Park's textbook of preventive and social medicine, 20th Edition. Premnagar. Banarasidas Bhanot 2005: 316-3.

4. Meigs JB, Larson MG, Fox CS, Keaney JF, Vasan RS, Benjamin EJ. Association of Oxidative Stress, Insulin Resistance, and Diabetes Risk Phenotypes. Diabetes Care 2007; 30: 2529–6.

5. Lang K, Ratke J. Leptin and Adiponectin: new players in the field of tumor cell and leukocyte migration. Cell Communication and Signaling 2009; 7: 27.

6. Doumatey AP, Lashley KS, Huang H. Relationships Among Obesity, Inflammation, and Insulin Resistance in African Americans and West Africans. Obesity 2010; 18(3): 598–5.

7. Klaus JR, Hurwitz BE, Llabre MM. Central obesity and insulin resistance in the cardiometabolic syndrome: pathways to preclinical cardiovascular structure and function. J Cardiometab Synd 2009; 4(2): 63-8.

8. McKeigue PM, Shah B, Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. Lancet 1991; 337(8738): 382-6.

9. Soodini GR, Hamdy O. Adiponectin and Leptin in Relation to Insulin Sensitivity. Metabolic Syndrome and Related Disorders 2004; 2(2): 114-9.

10. Yadav A, Jyoti P, Jain SK. Correlation of Adiponectin and Leptin with insulin resistance: A pilot study in Healthy North Indian Population. Ind J Clin Biochem 2011; 26(2): 193-3.

11. Statnick MA, Beavers LS, Conner LJ, Corominola H, Johnson D, Hammond CD. Decreased expression of apM1 in omental and subcutaneous adipose tissue of humans with type 2 diabetes. Int J Exp Diabetes Res 2001; 1: 81-8.

12. Lichnovská R, Gwozdziewiczová S, Chlup R. Serum leptin in the development of insulin resistance and other disorders in the metabolic syndrome. Biomed. Papers 2005; 149(1):119–7.

13. Satoh N, Naruse M, Usui T. Leptin-to-Adiponectin Ratio as a Potential Atherogenic Index in Obese Type 2 Diabetic Patients. Diabetes Care 2004; 27 (10): 2488-2.

14. Banks WA, Coon AB, Robinson SM, Moinuddin A, Shultz JM, Nakaoke R, Morley JE. Triglycerides induce leptin resistance at the blood-brain barrier. Diabetes 2004; 53(5): 1253-7.

15. Seung-Hyun Ko. The Adiponectin/Leptin Ratio and Metabolic Syndrome in Healthy Korean Adult Males. Korean Diabetes J 2010; 34(4): 220–1.