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FETUIN-A INTERCONNECT THE INSULIN, INSULIN RESISTANCE WITH TYPE 2 DIABETES.

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ABSTRACT

Introduction: Type 2 diabetes is a major metabolic disorder due to loss of insulin sensitivity in target cells, results hyperglycemia. The most common clinical features associated with type 2 diabetes are polyuria, polydipsia, and polyphagia and weight loss. The other long term medical complications related with type 2 diabetes are retinopathy, neuropathy, foot ulcer, nephropathy, cardiovascular disease and hypertension. Insulin resistance is one of the most important causes of type 2 diabetes. Fetuin-A is a multifunctional protein which block the auto phosphorylation of beta subunit of insulin receptor and produces insulin resistance. This is the connecting link between insulin resistance and type 2 diabetes. Aim: The present study evaluate the interconnection of fetuin-A , insulin and insulin resistance in type 2 diabetes patients. Materials and Methods: Blood samples were collected from 88 subjects (44 type 2 diabetes and 44 healthy controls). Insulin, HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) and Fetuin-A were determined using conventional methods. Results: Insulin, HOMA-IR and Fetuin-A were significantly higher in type 2 diabetes patients as compared to healthy controls with p=<0.001.Conclusion: Our results suggest that Fetuin-A inhibit insulin action by blocking the auto phosphorylation of beta subunit of insulin receptor in type 2 diabetes patients.

INTRODUCTION

In India, diabetes is the most important pathological state affecting more than 62 million people in India. Diabetes in India is multi-factorial factors including genetic defect, environmental factor, obesity, urban migration and changes in life style. Various factors are responsible for the development of diabetes. These factors include autoimmune destruction of the beta cells of pancreas and insulin resistance in cell. The metabolic defects in carbohydrate, lipid and protein due to impaired action of insulin on target tissues cause's clinical abnormalities in diabetic patients. The major symptoms of diabetes are hyperglycemia with polyuria, polydipsia, weight loss, and polyphagia. The other long-term medical complications of diabetes include retinopathy with loss of vision, nephropathy results renal failure, peripheral neuropathy with risk of foot ulcers, cardiovascular abnormalities and sexual dysfunction. The clinical evidences for cardiovascular disease, peripheral arterial, and cerebrovascular disease are higher in diabetes patients. Diabetic patients also suffering for hypertension and abnormalities of lipoprotein metabolism [1].

In various types of diabetes, type 2 diabetes is more common about more than 90% as compared to type 1 diabetes and gestational diabetes. WHO Diabetes Country Profiles 2016 predicted 97,300 diabetes deaths & 285,600 deaths to high blood glucose in India. Prevalence of diabetes is 7.5%, overweight 23.9%, obesity 6.5% and physical inactivity 15.1% [2]. In normal healthy person, insulin is essential for transport of glucose and regulation

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of normal blood glucose level. Insulin resistance is a state in which the cellular response for insulin decreased which effects the insulin- mediated glucose homeostasis. Insulin acts by the binding to the insulin receptor and acts on the insulin like growth factor–1 (IGF-1) receptor. The binding of insulin to the receptor produces signaling pathways within target cells for regulation of metabolism. Insulin sensitivity and release, both are inversely related to each other. Insulin resistance results in increased insulin release to maintain normal glucose and lipid homeostasis. The mathematical relation between sensitivity and release is hyperbolic. Failure of the beta cell dysfunctions is related to insulin sensitivity results, abnormal insulin levels, higher fasting glucose (HFG), impaired glucose tolerance and type 2 diabetes Insulin resistance results from inherited and acquired causes. Hereditary causes includes genetic alteration of insulin receptor, glucose transporter, and signaling proteins. Acquired causes include physical inactivity, diet, medications, hyperglycemia, increased free fatty acids, and the aging. Due to the above factors insulin resistance in insulin target tissues including liver, skeletal muscle and adipose tissue shows progressive results towards type 2 diabetes [3]. During insulin resistance, liver and muscles are unable to take glucose and stored it in the form of glycogen. At the same time liver initiates the gluconeogenesis to maintain normal cells functions. This causes hyperglycemia [4,5]. Fetuin-A, also called Alpha 2-Heremans Schmid Glycoprotein (AHSG), is a multifunctional plasma protein with a molecular weight 60 kDa.It's half-life is several day. Fetuin-A is synthesized by multiple tissues during fetal life. In adults liver is the major site for fetuin-A synthesis. Fetuin-A act as a physiological inhibitor of insulin receptor tyrosine kinase. This interconnect the fetuin-A with insulin resistance, metabolic syndrome (MetS) and type 2 diabetes.HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) is used for measured insulin resistance by fetuin-A [6,7].

The present study evaluate the interconnection between Fetuin-A, insulin and insulin resistance in type 2 diabetes patients.

MATERIAL AND METHODS:

The present study was conducted after the approval of Research Advisory Committee (PCMS/OD/2016/3158) Ethical Committee (PCMS/OD/2016/3159) of People's College of Medical Science and Centre for Scientific Research and Development (CSRD), People's University Bhopal. This study consist of 44 healthy control and 44 with type 2 diabetes mellitus, during the period of Jan-Dec 2017. Informed written consent was obtained from all study subjects.

Study Design: This is a hospital based Analytical Cross sectional study.

Source of data: The blood samples collected from diabetic and non- diabetic persons under the supervision of Physician who attended their routine checkup in the Department of Medicine, during the period Jan – Dec 2017 at People's Hospital Bhopal.

Sample size: All Patients admitted in study period and meeting the inclusion criteria.

A) Inclusion criteria: 1.Patients diagnosed with type 2 diabetes, according to ADA (American Diabetes Association) value for FBG, HbA1c and lipid profile were taken into consideration for selection of patients.
2. Patients newly diagnosed with type 2 diabetes are take.
3. Age between upto70 years.

B) Exclusion criteria: 1.Patients with diagnosis of any other disease other than type2 diabetes like acute myocardial infarction, renal failure, liver disease, critical illness, tuberculosis, carcinoma and any severe infection.
2. Pregnant woman.
3. Patients with anemia.
4. Patients above 70 years will be excluded.

Biochemical Investigations: Insulin by solid phase enzyme linked immunoassay, Insulin resistance was measured by HOMA-IR (FPIXFPG/22.5) and serum Fetuin-A was measured by sandwich-ELISA using thermofisher kit.

Statistical Analysis:

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%).Significance is assessed at 5 % level of significance.

RESULT:

In our study we observed that the insulin, insulin resistance (HOMA-IR) and Fetuin-A level were significantly higher in type 2 diabetes patients as compared to controls ($p<0.001$)

Parameters	Groups	Mean	Std.Deviation	"p" value
Insulin(mu/l)	Controls	11.31	3.53	p<0.001
	Patients	30.43	3.06	
HOMA-IR	Controls	2.51	0.83	p<0.001
	Patients	16.04	6.11	
FetuinA(microg/ml)	Controls	264.40	6.49	p<0.001
	Patients	335.30	6.64	

P value=0.05 significant, P value=0.001 highly significant

DISCUSSION

Type 2 diabetes is indicated by imbalance of glucose, fat and protein metabolism because of decreased insulin secretion, higher insulin resistance in skeletal muscle, liver, adipose tissue and combination of both .In our study we found that significant high level insulin, insulin resistance and fetuin-A in type 2 diabetes as compared to healthy controls. Our study coincide well with the studies carried out by Joachim HI et al(2006) [8], Vandana Saini(2010) [9], Aiyun Song et al(2011) [10], Lamyaa Ismail Ahmed et al(2014) [11]' Sudhanshu Shekhar et al (2016)[12], Shatha Rouf Moustafa (2016)[13] and Karel A. Erion et al (2017) [14]. They found that hyperinsulinemia may be related with development of obesity and in the beta-cell dysfunction that increase the risk of type 2 diabetes. They also observed that insulin resistance is also responsible for the clinical changes in type 2 diabetes.Fetuin-A is responsible for insulin resistance by blocking insulin receptor auto phosphorylation in type 2 diabetes. In our study population, hypercholesterolemia, hypertriglyceridemia and hyperinsulinemia were significantly observed. These factors may be causes hepatic production of fetuin-A in type 2 diabetes patients. The gene which encode Fetuin-A is located on chromosome 3q27, related with regulation of glucose and fat metabolism. This is graphed as a type 2 diabetes and metabolic syndrome sensitivity locus. Genetic analysis of fetuin-A gene indicates that single nucleotide polymorphisms were related with type 2 diabetes. Higher expression of gene which encode fetuin-A related with fatty liver by increased fat accumulation in the liver. This observation indicated correlation of fetuin-A with fatty liver. Elevated level of fetuin-A is a marker of coronary disease in diabetes patients. This suggested that fetuin-A may be connect fatty liver and coronary disease with type 2 diabetes. In type 2 diabetes fetuin-A also affects the functions of beta-cells. The beta cell dysfunction causes higher fasting glucose in type 2 diabetes. This observation interconnect the fetuin-A with insulin resistance and type 2 diabetes. This indicates that fetuin-A may be an important marker for type 2 diabetes.

SUMMARY AND CONCLUSION

The type 2 diabetes increased in all over the world, as well as in India. The important risk factor of type 2 diabetes is insulin resistance. Recently, studies indicates the correlation of fetuin-A with insulin resistance and its multifactorial diseases, such as metabolic syndrome and type 2 diabetes. Disturbance of glucose metabolism related with impaired fasting glucose and impaired glucose tolerance. Both are important risk factor for type 2 diabetes and cardiovascular disease. Insulin resistance connect the Fetuin-A with type 2 diabetes. However, more work is required to be carried out in order to correlate the severity and duration of disease and uncover the mechanisms between elevated Fetuin-A and insulin resistance and type 2 diabetes.

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