ADENOSINE DEAMINASE ACTIVITY IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

BACKGROUND

Altered blood levels of adenosine deaminase may help in predicting immunological dysfunction in diabetic individuals. But very few studies exist on ADA activity in type 2 diabetes mellitus.

Aim of this study is to compare serum adenosine deaminase activity in type 2 diabetic patients with non-diabetic control.

MATERIALS AND METHODS

A comparative study design was used in data collection process. The study was conducted in 40 type 2 diabetes mellitus patients attending diabetic clinic or admitted in the medicine ward for metabolic control of diabetes in medical college, Calicut from January 2011 to January 2012. The adenosine deaminase (ADA) level in the serum is measured by endpoint method in these patients. The results were expressed as mean and standard deviation. The statistical significance of the differences between the values was assessed by ANOVA.

RESULTS

Among 40 diabetic patients, mean ADA level in the serum is 38.56, SD±6.72 (min 30, max 53). Mean ADA level in the serum in the control group is 22.04±4.625 (min 13, max 29).

CONCLUSION

ADA level in the serum is found to be increased indicating its role as an important immunoenzyme marker in the aetiopathology of type 2 diabetes mellitus.

KEYWORDS

Adenosine Deaminase, Type 2 Diabetes Mellitus, Adenosine, Insulin.

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BACKGROUND

Type 2 Diabetes mellitus, a group of disorders characterised by impaired insulin secretion, variable degrees of insulin resistance and increased glucose production. Although the prevalence of both type 2 and type 1 diabetes is increasing worldwide, the prevalence of type 2 is rising rapidly because of increasing obesity and reduced activity levels. In the early stages, despite insulin resistance glucose tolerance remains near-normal because the pancreatic beta cells compensate by increasing insulin output. As insulin resistance and compensatory hyperinsulinaemia progresses, islet cells are not able to maintain the hyperinsulinaemic state. Then IGT develops which is characterised by elevations in postprandial glucose. A further decrease in insulin secretion and an increase in hepatic glucose production lead to overt diabetes with fasting hyperglycaemias. Ultimately, beta cell failure occurs.[1]

Insulin acts on peripheral tissues to stimulate glucose transport, glycolysis, glycogenesis, and decreases gluconeogenesis and glycogenolysis. Previous work has been shown that adenosine, the purine nucleoside modulates the action of insulin in various tissues. In adipose tissue it increases the sensitivity to glucose transport and oxidation. In the skeletal muscle, adenosine is involved in the regulation of glucose transport just as in the adipose tissue, but the results are inconsistent.[2] In pancreas adenosine and analogues inhibit insulin release. The adenosine receptor A1R is involved in this process. However, a recent study has shown that other adenosine receptors might also be involved in insulin secretion since agonists of A_1R, A_2AR as well as A_3R reduced glucose stimulated insulin release. Also antagonists of the $A_{2B}R$ were able to counteract the inhibitory effect of an unselective adenosine agonist on insulin release. At present time, the mechanism behind these findings is unknown. In liver, adenosine stimulates cyclic AMP formation and regulates gluconeogenesis and glycogenolysis, most likely through the adenosine A_{2B} receptor subtype in hepatocytes.[3]

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Adenosine production and utilisation in mammalian tissues are primarily dependent on the activity of two utilising enzymes adenosine kinase and adenosine deaminase and producing enzyme 5′-nucleotidase.[4] In humans, the highest ADA activities found in thymus and other lymphoid tissues and the lowest in erythrocytes. It participates in the purine metabolism by degrading either adenosine or 2′-deoxyadenosine producing inosine or 2′-deoxyinosine. Even though ADA is a cytosolic enzyme, it may also appear on the cell surface (ecto-ADA). There is no much difference between the catalytic activity of ecto-ADA and cytosolic ADA. Ecto-ADA could have functions independent of its enzymatic activity in addition to these. Ecto-ADA bind and stimulate adenosine receptors -A1, A2B and a lymphocyte activation marker human CD26 (Dipeptidyl peptidase-4, DPP4).[5] DPP4 has been shown to be involved in the inactivation of incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide.[6]

ADA was considered as an excellent marker of cell mediated immunity. It has important role in lymphocyte proliferation and differentiation. It has got highest activity in T lymphocytes.[7] In patients having severe combined immunodeficiency, the role of adenosine deaminase in the cellular immunity was first identified.[8] The high activity of ADA reflects immunological disturbances observed in jaundice[9], leukaemia,[10] nephrotic syndrome,[11] tuberculosis,[12] and infectious mononucleosis.[13]

As ADA is associated with T-lymphocyte activity, its altered blood levels may furnish better insights on the role of cell-mediated immunity in the pathophysiology of type 2 DM.[14]

MATERIALS AND METHODS

A comparative study was conducted.

Inclusion Criteria

Study was conducted in patients attending diabetic clinic or admitted in the medicine ward for metabolic control of diabetes in medical college, Calicut from January 2011 to January 2012. Two study groups are selected.

Group 1

40 consecutive type 2 diabetic patients including both male and female of age group 30-60 years.

Group 2

30 non-diabetic subjects in the age group 30-60 years from bystanders of other patients or from medical or paramedical staff. Diabetes mellitus was diagnosed on the basis of FBS≥126 mg/dL or a patient already on antidiabetic medication.

Exclusion Criteria

Patients not giving written consent, individuals with diabetic complications, those with hypertension, those who are pregnant, subjects with history of infectious or alcoholic hepatitis, chronic renal disease, coronary artery disease, disease affecting immune system like rheumatoid arthritis, cancers like leukaemia, chronic infections like tuberculosis, nephrotic syndrome are excluded from the study.

RESULTS

The results were expressed as mean and standard deviation. The statistical significance of the differences between the values was assessed by ANOVA. Ethical approval of study was obtained. ADA activity is found to be elevated in diabetic patients compared to control. Other parameters like BMI, FBS, total cholesterol, VLDL and triglycerides are also significant.

Variable Mean±SD	Diabetic	Control	P value
Age	51.52±8.437	43.83±9.56	<0.0001
BMI (Kg/m^2)	23.23±1.843	21.26±2.105	<0.0001
FBS (mg/dL)	178.7±44.44	91.97±9.554	<0.0001
ADA (U/L)	38.56±6.722	22.04±4.625	<0.0001
TCL (mg/dL)	199.7±41.17	172.2±26.41	0.002
HDL (mg/dL)	42.75±7.192	42.8±6.895	0.977
LDL (mg/dL)	127.17±30.39	122.2 ± 16.56	0.418
VLDL (mg/dL)	29.27±12.08	22.83±5.213	0.008
TG (mg/dL)	148.82±61.31	113.7±25.94	0.004

Table 1. Clinical and Laboratory Data of 40 Diabetic Patients/Control

DISCUSSION

In diabetic patients, elevated ADA activity is significant. First of all it may be an important immunoenzyme marker in the aetiopathology of type 2 diabetes mellitus.

Disturbances of cell-mediated immunity in diabetes are believed to initiate from T-lymphocyte dysfunction. Resting human peripheral T-lymphocytes are devoid of insulin receptors, but upon activation of cells by specific antigens or mitogens these receptors emerge. Along with the insulin receptors two other growth factor receptors IL-2 & Insulin like growth factor (IGF-1) also appear on the T lymphocyte along with the intracellular signal transduction mechanisms and insulin degrading enzyme. In the stimulated T- cell insulin binds to its receptor and exerts classical effects on carbohydrate metabolism. Through its ability to enhance uptake of nutrients and increase intermediary cellular metabolism, insulin is believed to maintain the allo-activated state of T lymphocytes, enhance its responsiveness, and support the actions of immunoderived regulatory growth and differential factors. Since insulin enhances protein synthesis and energy requirements necessary for appropriate T-cell functions, defects in insulin action may lead to inappropriate immune responses in

diabetes.[15] It is also thought that deranged immunity in diabetic individuals may also originate from antibody dependant cellular cytotoxic responses, which target insulin.[16]

Elevated ADA in diabetic patients may associate with the insulin resistance. Insulin acts on peripheral tissues to stimulate glucose transport and metabolism and inhibit gluconeogenesis.[17] Adenosine acts directly to stimulate insulin activity via several processes such as glucose transport, lipid synthesis, pyruvate dehydrogenase activity, leucine oxidation and cyclic nucleotide phosphodiesterase activity.[18] In adipocytes and heart, adenosine potentiates insulin stimulated glucose transport. By enhancing the increase in GLUT-4 at the cell surface, adenosine potentiated contraction and insulin stimulated glucose transport in skeletal muscles. It raised the possibility that decreased adenosine production or action could play a causative role in insulin resistance.[2] Adenosine deaminase catalyses the deamination of adenosine to inosine contributing to the regulation of intracellular and extracellular concentrations of adenosine[19] and probably modulates energy metabolism.[20]

Free radical generation in diabetic patient is found to be associated with elevated ADA activity. In India prevalence of type 2 diabetes is increasing and makes it important to recognise, postpone, or even prevent the serious complications associated with it. The common pathogenic factor leading to insulin resistance, β-cell dysfunction and ultimately type 2 DM is the oxidative stress resulting in free radical production. It is also considered as an underlying cause of both microvascular and the macrovascular complications. Increased level of adenosine deaminase in diabetic patients could result in increase in hypoxanthine which oxidises to xanthine and uric acid with concomitant generation of superoxide anion radical ($O_2^{\cdot-}$). Also through downregulation of the inhibitory adenosine-c-AMP system plasma ADA amplifies the release of oxygen free radicals from neutrophils. Amelioration of oxidative stress might slow down apoptosis at the same time when it repairs the existing beta cells, could lead to the improvement of insulin secretion independently from conventional therapy.[21]

CONCLUSION

Altered ADA level in diabetics may help in predicting immunological dysfunction and might be one of the important biomarkers in predicting the disease. Elevated ADA in diabetic patients may associate with the insulin resistance. Adenosine deaminase activity could be regarded as a strong indicator of reactive oxygen species production due to oxidative stress in type 2 diabetic subjects, which could be modulated by antioxidants thereby reducing the rates of various micro and macrovascular complications associated with the disease.

REFERENCES

[1] Kasper DL, Fauci AS, Hauser S, et al. Harrison's principles of internal medicine. 19th edn. Vol. 2. McGraw Hill Professional 2015:2399-2404.

[2] Han DH, Hansen PA, Nolte LA, et al. Removal of adenosine decreases the responsiveness of muscle glucose transport to insulin and contractions. Diabetes 1998;47(11):1671-1675.

[3] Johansson S. Metabolic roles of adenosine. Thesis Karolinska Institute 2007.

[4] Kurtul N, Pence S, Akarsu E, et al. Adenosine deaminase activity in the serum of type 2 diabetic patients. Acta Medica 2004;47(1):33-35.

[5] Doležal T. Adenosine deaminase: review of physiological roles. Czech Republic: University of South Bohemia 2001.

[6] Lee JG, Kang DG, Yu JR, et al. Changes in adenosine deaminase activity in patients with type 2 diabetes mellitus and effect of DPP-4 inhibitor treatment on ADA activity. Diabetes Metab J 2011;35:149-158.

[7] Sullivan JL, Osborne WR, Wedgewood RJ. Adenosine deaminase activity in lymphocytes. Br J Haematol 1977;37(1):157-158.

[8] Giblett ER, Anderson JE, Cohen F, et al. Adenosine deaminase deficiency in two patients with impaired cellular immunity. Lancet 1972;2:1067.

[9] Goldberg DM. Serum adenosine deaminase in the differential diagnosis of jaundice. Br Med J 1965;1(5431):353-355.

[10] Grever MR, Coleman MS, Balcerzak SP. Adenosine deaminase and terminal deoxynucleotidyl transferase: biochemical markers in the management of chronic myelogenous leukemia. Cancer Res 1983;43(3):1442-1445.

[11] Mishra OP, Garg R, Ali Z, et al. Adenosine deaminase activity in nephrotic syndrome. J Trop Pediatr 1997;43(1):33-37.

[12] Pettersson T, Ojala K, Weber TH. Adenosine deaminase in the diagnosis of pleural effusions. Act Med Scand 1984;215(4):299-304.

[13] Koehler LH, Benz EJ. Serum adenosine deaminase: methodology and clinical applications. Clin Chem 1962;8(2):133-140.

[14] Prakash MS, Chennaiah S, Murthy YSR, et al. Altered adenosine deaminase activity in type 2 diabetes mellitus. JIACM 2006;7(2):114-117.

[15] Stentz FB, Kitabchi AE. Activated T-lymphocytes in type 2 diabetes: implications from in vitro studies. Curr DrugTargets 2003;4(6):493-503.

[16] Fovenyi J, Totpal K, Thaisz E, et al. Non-specific cellular immunity in type I and type II diabetes. Exp Clin Endocrinol 1984;83(2):203-206.

[17] Joost HG, Steinfelder HJ. Modulation of insulin sensitivity by adenosine. Effects on glucose transport, lipid synthesis, and insulin receptors of the adipocyte. Mol Pharmacol 1982;22(3):614-618.

[18] McLane MP, Black PR, Law WR, et al. Adenosine reversal of in vivo hepatic responsiveness to insulin. Diabetes 1990;39(1):62-69.
[19] Patel B, Taviad D, Malapati B, et al. Serum adenosine deaminase in patients with type-2 diabetes mellitus and its relation with blood glucose and glycated haemoglobin levels. International Journal of Biomedical Research 2014;5(09):556-558.
[20] Bottini E, Gerlini G, Lucarini N, et al. Evidence of selective interaction between adenosine deaminase and acid phosphatase polymorphisms in fetuses carried by diabetic woman. Hum Genet 1991;87(2):199-200.
[21] Siddiqi SS, Ahmad J, Islam N, et al. A study on the modulation of adenosine deaminase (ADA) activity in monocytes of type 2 diabetic patients by antioxidants. JIACM 2011;12(2):113-116.