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Association of Health Hazardous Low Grade Chronic Inflammatory Process with Freshly Diagnosed type 1 Diabetes Mellitus in Adolescent Age Group.

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Abstract

It's very contradictory view point about the role of acute phase responsewhich used to mediate by cytokine in case of type 1 diabetes mellitus, although the association between cytokine mediated acute phase response and type 2 diabetes mellitus is almost well established. This study has to evaluste this hypothesis by determination of acute phase reactant in type 1 (T-1) diabetic patients as in adolescent population throughout the world, the incidence of type 1 diabetes is not negligible.

In 12 newly diagnosed cases of type 1 diabetes mellitus, I determined the level of α1- antitrypsin, α1- acid glycoprotein ceruloplasmin and fibrinogen which are considered to be very sensitive and reliable parameters in group of acute phase proteins. Matching the age and sex of cases we also took 30 normal controls.The levels of these proteins were correlated with their body mass index (BMI) and random plasma glucose values.

Except α1- acid glycoprotein the control group shows much lower level of rest of parameters in comparison of type 1 diabetes mellitus cases. From the finding of this study we can guess a bit of prediction that low grade inflammatory reaction is definitely associated in development of type 1 diabetic condition.

It is concluded that the association between low grades inflammatory condition and development of type 1 diabetes mellitus obviously need further study and follow up.

Keywords: *Type 1 diabetes; Chronic inflammation; Acute phase response; Ceruloplasmin; Fibrinogen*

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Introduction

Diabetes Mellitus is one of the most common major public health problems having worldwide distribution [1]. It has now adopted epidemic proportions. It is a syndrome with metabolic disorders and disturbed hyperglycemic condition either due to resistance to insulin, inadequate insulin secretion to compensate or deficiency of insulin secretion [1].

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Synergistic effects of immunologic, genetic and environmental factors that destroy the β-cells of pancreas are considered as aetiological factor for development of diabetes mellitus type 1 [1]. Due to autoimmune process that occurs over month and years used to destroy the normal cell mass of β cell of pancreas considered as a main factor for developing type 1 diabetes in individual with genetic susceptibility although may have normal β cell mass at birth. Infection and some environmental stimulation are thought to be responsible for this autoimmune process [1]. Before diabetic condition become clinically overt immunological markers considered as a triggering event in majority of individual. Insulin secretion is gradually decreasing due to progressive decline of β cell mass, although maintain of normal glucose tolerance. About almost 80% destruction of β cell mass used to causes the appearance of clinical sign and symptom of diabetes mellitus. At this point of time the number of residual functioning β cells is insufficient to maintain the glucose tolerance. The triggering factor for transition from impaired glucose tolerance to frank diabetes are very frequently associated with requirement of more amount of insulin that may occur in infections or puberty. A"Honeymoon" phase may ensure following the initial clinical presentation of type 1 diabetes, during which time a modest dose of insulin or rarely without insulin glycemic control can be achieved. Anyhow when the remaining β cells are destroyed by the progressive autoimmune process, residual cells stop this fleeting phase of endogenous insulin production [2].

The location of major susceptibility gene for diabetes mellitus type 1 is human leukocyte antigen region (HLA region) on chromosome no 6 and this inheritance is mainly is of polygenic variety which used to account for 40% to 50% of genetic risk for developing of type 1 diabetes mellitus [3]. Class II major histocompatibility complex (class II MHC) is encoded by genes which are situated in this region [3]. The strongest association is with the cell surface receptor protein HLA-DQ locus within this region and this locus is again subdivided into α and β loci. The haplotypes DQ A1* 0301, DQ B1* 0302, DQ A1* 501 and DQ B1* 201 have the strongest association with type1 diabetes that have shown after refinement in genotyping of HLA loci [3]. It has been found that susceptibility of type 1 diabetes mellitus is directly related to the amino acid in position 57 of the N-terminal β-1 domain of the HLA-DQ β chain although analysis of DNA sequence from patients with type 1 diabetes mellitus has not so far shown unique class II sequenceDQ beta polymorphisms are thought to be determined by the specificity and extent of an autoimmune response against pancreatic islets insulin secreting cell [3]. For the development of type 1 diabetes mellitus these polymorphisms are necessary but not sufficient in themselves. This signify either the role for environmental factors in clinical expression of the disease in genetically susceptible persons or existence of the specific type1 diabetes mellitus related genes or involvement of more than one HLA-D gene which are controlling the intensity of destruction process of β-cell (which appears to be mediated by cytokines) [4].

An infection or toxic insult to persons whose immune system is generally predisposed to develop a vigorous autoimmune response either against molecule of β cell resembling the viral protein or against altered pancreatic β cell antigens is felt to develop immune mediated type 1 diabetes mellitus [5]. Although other types of islets cell are inexplicably spared from the autoimmune process though they are functionally and embryological similar to β cells and expresses maximum of the similar proteins in β cells. By the process called "Insulitis" the pancreatic islets are infiltrated with leucocytes [5].

Islet cell auto antibodies, proliferation of T lymphocytes when stimulated by islets protein, release of cytokines within the insulitis, activated lymphocytes in the islets, peripanceatic lymph nodes and systemic circulation are all well-known abnormalities in both the humoral and cellular types of immune system was identified in type1 diabetes mellitus [6]. β cells are seen to be susceptible by some cytokines like tumor necrosis factor α (TNF α), interferon and interleukin 1(IL 1) [6]. Formation of nitric oxide metabolites, apoptosis and direct cytotoxic T cell (CD8+ T cell) cytotoxicity are some precise mechanism of death of β cell involves [6]. The autoimmune process including insulin, glutamic acid decarboxylase (GAD), ICA-512/IA-2 (homology with tyrosine phosphate) and phogrin (insulin secretary granular protein) used to targeting pancreatic islets molecule. Islets gangliosides and carboxypeptidase H are other less clearly defined autoantigens. Question used to raise the process of destruction of β cells because none of the autoantigens are β cell specific except insulin. According to current theories one β cell molecule is initiated by an autoimmune process which then migrates to other islets molecules as the immune mechanism that demolished β cells and form secondary autoantigens [6]. β cells of normal subjects do not

differ the β cells of individuals who develop type 1 diabetes mellitus since by a recurrence of the autoimmune process of type1 diabetes mellitus transplanted islets are destroyed [6].

A low grade inflammatory reaction is considered as an acute phase reaction which is associated with increase leukocyte count and temperature and is not specific for any given disease [7]. All these changes are triggered by a small protein known as Leucocytic Endogenous Mediator (LEM) which used to release from the site of injury [7]. Plasma levels of the individual acute phase proteins rise at different rates. The levels of C-reactive protein and α-1 antichymotrypsin rise first, and then level of α-1 acid glycoprotein rises within 12 hours followed by the level of α-1 antitrypsin, haptoglobin, C4 and fibrinogen andfinally C3 and ceruloplasmin [7]. Within 2-5 days [7] levels of all the parameters reach their maximum. Measurement of these proteins with the largest and earliest rises eg C-reactive protein (CRP) can be used in monitoring the progress of inflammation or its response to treatment but these changes which are caused by increased synthesis in the liver don't aid in the diagnosis of the cause of inflammation [7]. Decrease in the synthesis of prealbumin, albumin and transferrin are accompanied by increase in synthesis of acute phase reactants (APR) (so called negative acute phase reactants), so that in total only a slight rise plasma protein occurs [7].

Therefore nonspecific changes in level of individual proteins occur in inflammatory process which may mask changes attributable to a specific disease [8]. The widely explored hypothesis in the notion that chronic low grade inflammation followed by activation of the innate immune system is closely involved in the pathogenesis of type 2 diabetes mellitus was first proposed in 1997-98[9]. After that several studies have shown that circulating markers of inflammation, acute phase reactants or interleukin-6 (IL-6) are strongly associated with the pathogenicity for development of type 2 diabetes [10] but the role of acute phase reactants in case of type 1 diabetes mellitus is not very clear. The present study was to detect the level of these inflammatory markers in the pathogenesis of type 1 Diabetes mellitus. Out of all inflammatory markers α1- acid glycoprotein, α-1 antitrypsin, fibrinogen and ceruloplasmin were of interest.

Material and Methods

Patients sample and experimental design: First physicians examine the patient of previously undiagnosed diabetes in adolescent age groups and out of all confirmed cases, patients with a history of chronic inflammatory diseases, episodes of recent acute inflammations, patients with clinical evidence of neuropathy, nephropathy, and retinopathy were not enrolled in the study [11]. Twelve (12) Type 1 patient of either sex gave their consent to participate in the study. Thirty (30) individuals of almost same age group were chosen to serve as controls. The control groups were applied the same exclusion criteria like of test groups. Institutional Ethics Committee of Kasturba Medical College, Mangalore, India approved the total test protocol. Body mass index (BMI) was calculated after recording of weight and height of each and every patients as well as controls. Random blood samples were collected before the initiation of therapy in the diabetic patients estimation of the following parameterswere carried out:

1. Random plasma glucose (RBS): Detection of RBS by Trinder's glucose oxidase method on Hitachi 917 autoanalyser (Germany) using Roche Kits. [12]
2. Fibrinogen estimation: In presence of calcium chloride fibrinogen in plasma was converted to fibrin. The fibrin clot was collected and digested with sodium hydroxide. Protein content of the clot was determined by the biuret method [13]
3. Ceruloplasmin estimation: Paraphenylenediamine (PPD) is oxidized to yield a coloured product which is believed to correspond either to Bandrowski's base or to Weuster's red. This process is catalyzed by ceruloplasmin at pH 5.4. The rate of formation of the coloured oxidized product is proportional to the ceruloplasmin concentration, if a correction is made for the nonenzymatic oxidation of PPD. Simultaneous estimations were carried out with and without sodium azide. Sodium azide inhibits the nonenzymatic oxidation of PPD. The ceruloplasmin concentration is proportional to difference between the results of the two assays. [14]

4. α-1 antitrypsin estimation: Casein used to hydrolyzed by proteolytic enzyme trypsin with the formation of smaller peptides. Trichloroacetic acid (TCA) arrested the enzymatic reaction after suitable interval of time with the precipitation of the proteins, but the peptides are soluble in the acid. The TCA soluble fragments are a measure of proteolytic activity of this enzyme. When the inhibitor is added to the preincubated mixture, it prevents the release of peptides by the proteolytic enzymes. Thus, the estimation of TCA soluble components in the presence and absence of inhibitor is a measure of inhibitory activity against proteolytic enzymes. The TCA soluble fragments were analyzed by the method of Lowry et al [15]. The final color formed is a result of the reaction of the peptides with copper ions in alkali and reduction of the phosphomolybdic reagent by the presence of tyrosine and tryptophan present in the treated peptides.
5. Estimation of α-1 acid glycoprotein: By application of perchloricacid heat coaguable proteins used to remove and the orosomucoid which remains in the solution was precipitated by phosphotungstic acid and estimated by determining its carbohydrate content by reaction with its tyrosine residues with folin ciocalteau reagent. [16]

With the application of the student's t test and the ANOVA test the data was analyzed. For correlation analysis Pearson's correlation coefficient was applied.

Results

By the whole study, aim was to see whether low grade of chronic inflammation is a pathogenic cause in type 1 diabetes mellitus cases or not. In table 1 the mean age (range), BMI and the number of males: females are presented. The control group participants were so chosen as to cover the age range of the test groups. Lists the values of random blood sugar (RBS) and acute phase proteins in both groups as mean ± SD are denoted in table 2. In comparison with the control group test group T- 1 had significant higher values of all the parameters which can be further supported by depicts the significance levels (p values) of the test and control groups which are denoted in table 3.

	Controls Mean ± SD (n = 30)	Type 1 Mean ± SD (n = 12)
Age	43.97 ± 14.06 (30-60 yrs)	47.27 ± 7.11 (30-60 yrs)
BMI	20.75 ± 2.27	23.03 ± 1.46
Males : Females	17 : 13	05 : 07

Mean ± SD, n= number of subjects

Table 1: *Characteristics of Patients.*

Parameters	Controls Mean ± SD (n = 30)	Type 1 Mean ± SD (n = 12)
Random blood Sugar (mg/dL)	93.20 ± 7.00	338.25 ± 50.97
α1 antitrypsin (mg/dL)	49.48 ± 114.07	495.70 ± 32.77
α1 acid glycoprotein (mg/dL)	102.41 ± 22.13	94.87 ± 23.31
Ceruloplasmin (mg/dL)	25.95 ± 4.10	40.69 ± 9.85
Fibrinogen (mg/dL)	334.34 ± 42.19	434.65 ± 46.36

Mean ± SD, n = number of subjects

Table 2: *Levels of the acute phase reactants.*

Parameters	T-1 v/s Controls
Random blood sugar (mg/dL)	< 0.0001*
α1 antitrypsin(mg/dL)	0.0002
α1 acid glycoprotein (mg/dL)	0.275
Ceruloplasmin (mg/dL)	< 0.0001*
Fibrinogen (mg/dL)	< 0.0001*

T-1 = Type 1 newly diagnosed patient

P ≤ 0.05 was considered significant

*= statistically significant

Table 3: *Significance (p value).*

Discussion

Various contradictory reports were found previously regarding the level of acute phase reactant levels in Type 1 diabetes. Mohamed., *et al*. [17] has denoted that acute phase proteins and serum sialic acid are not elevated in type 1 diabetes. Increased level of CRP, α1-acid glycoprotein and fibrinogen in Type 1 patients are shown in the report by Gomes., *et al*. [18], Elia., *et al*. [19] also found increased fibrinogen levels, factor VII and whole blood viscosity. Defeo., *et al*. [20] also found almost found similar reports. In the present study, an increased level of α1-antitrypsin, ceruloplasmin and fibrinogen were found in type 1 patients. In both type 1 and type 2 diabetic patients the course of the disease and resulting complications are almost similar. Out of that the most dreaded complication being that of development of atherosclerosis resulting in cardiovascular diseases.

Out of the presently studied parameters for the development of ischemic heart diseases [21] fibrinogen is identified as an independent risk factor. The risk of developing atherosclerosis remains the same irrespective of the patients being type 1 or type 2. Hence there should have been some mechanism which links the pathogenicity of type 1 and type 2 diabetes. After infusion of insulin to non-diabetics as well as type 1 and type 2 diabetics Barrazzani., *et al*. [22] studied its role in fibrinogen production. It was seen in non-diabetics and type 1 diabetic individual that suppression of fibrinogen production occurs due to insulin replacement activity. In insulin resistant type 2 diabetics, despite the maintenance of euglycemia and euaminoaciduria fibrinogen production and its plasma concentration increased. From these interesting phenomena they postulated that an altered response to insulin causes hyperfibrinogenemia in type 2 diabetic patients. If this hypothesis is appropriate, it doesn't explain hyperfibrinogenemia in type 1 diabetics where the basic pathology is insulin deficiency. Hence there should have some other stimulators which stimulate increased fibrinogen synthesis in type 1 patients leading to risk of cardiovascular disease. Based on clinical risk factor in patient with type 1 diabetes and validated using euglycemic-hyperinsulinemic clamp studies an insulin resistance syndrome score [23] was developed and with this insulin resistance syndrome score fibrinogen levels were significantly associated.

This may explain high level of plasma fibrinogen in type 1 diabetes by this phenomena. But since the type subjects in this study were newly diagnosed, it still does not answer the above findings. Hence the mechanism of increased fibrinogen synthesis needs to be proved further and further specific studied needed. Ceruloplasmin is also an acute phase protein with a response of intermediate magnitude and also is known to have antioxidant action [24] Stimulate of cell proliferation and angiogenesis [25] used to done by ceruloplasmin. Oxidative stress which used to prevalent in type 1 diabetes [26,27] may be played as prominent role for these higher level of ceruloplasmin in contrast to control group. A very interesting feature of ceruloplasmin was showed by Eduardo Ehrenwald [28] that in vitro intact human ceruloplasmin which is 132 KD molecules caused increased oxidation of LDL. Starkebaum and Harlan., *et al*. also showed excess oxidized LDL could be generated by increased serum ceruloplasmin and cause vascular injury by generating free radicals such

as hydrogen peroxide [29]. The antioxidant activity of ceruloplasmin was defined by these findings. By further investigations Ehrenwald., *et al*. [30] shown that the holoceruloplasmin has a prooxidant effect and the action was attributed to the copper ions present in ceruloplasmin. These holoceruloplasmin used to seen in serum as a 132 KD molecule. The commercially available ceruloplasmin had an antioxidant effect and is a degraded product containing either 115 KD fragment or 19 KD fragment or both. As an antioxidant ceruloplasmin used these degraded products. The antioxidant action of a commercial ceruloplasmin was observed even in the system LDL used to oxidize by holoceruloplasmin. Hence it is debatable whether ceruloplasmin acts as an antioxidant *in vivo* or not. The action of ceruloplasmin as an agent to oxidize LDL could probably explain at least in part of the increased risk of IHD in type 1 diabetes. (As well as in type 2 diabetics also).

It is still not well understood what are the underlying mechanism for the augmented acute phase response and the stimulus for the response is unknown. Lots of hypotheses have been predicted and put forward and these include insulin resistance, obesity, atherosclerosis, other diabetic complications and maladaptation of the normal innate immune response to environmental threats [31-33]. The association of obesity, insulin resistance, type 2 diabetes and acute phase reactants are few of all that are most widely studied. In the postprandial state [34-35] it has been shown that adipocytes secret a number of proinflammatory cytokines. In case of late for obese diabetics the term 'diabecity' has received attention [36].

The 'common soil' theory proposed, evaluates the involvement of chronic low grade inflammation in the pathogenesis of atherosclerosis as well as in diabetes. This low grade chronic inflammation can be promoted by hyperglycemia and insulin resistance and inflammation may be a vital factor linking diabetes mellitus to the development of atherosclerosis. Promotion of these chronic low grade inflammation by increasing oxidative stress [37], by the formation of AGEs and increased TNF (kappa B) [38] is used to cause by elevated glucose level. In this present study, the mean BMI was found to be 19.5 ± 1.23 in type 1 patient and 24.03 ± 1.46 in type 2 patients and no proper correlation was found between acute phase reactants and BMI. That's why it can be concluded that for activation of the innate immunity system there could be multiple pathways involved and much work needed to be done to establish either a casual role in the development of mainly type 2 diabetes and could be type 1 diabetes also.

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