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Effect of Acute Phase Reactants in Pathogenesis of Newly Diagnosed Type 2 Diabetic Patients and Patients under Treatment by Oral Hypoglycemic Drug for Minimum 5 Yrs

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Abstract

Acute phase response which is predominately cytokine-mediated is observed to be closely involved in the pathogenesis of type 2 diabetes. Since maximum world populations are at high risk of developing diabetes, we tested this hypothesis by estimating circulating acute phase proteins type 2 (T-2) diabetic patients and type 2 diabetic patients under oral hypoglycemic drugs for duration of at least 5 years.

The acute phase proteins, α1- antitrypsin, α1- acid glycoprotein, ceruloplasmin and fibrinogen were estimated in the plasma in newly diagnosed 25 T-2 cases and 25 T-2cases under oral hypoglycemic agent for at least 5 years Thirty normal controls to match the age and sex of the test groups were also studied. The levels of these proteins were correlated with their BMI and random plasma glucose values.

In comparison with the controls, the values of all the four proteins studied were significantly elevated in the T-2 patients ($p<.00001$) and reduced significantly except α1- acid glycoprotein and ceruloplasmin. Interestingly, no correlation was found with BMI or the degree of hyperglycemia in either of the types. A low grade inflammatory process is definitely implicated in the pathogenesis of type 2 diabetes. This line of pathological basis should be further explored for diagnosis, management and follow up

Keywords: α1- acid glycoprotein; α-1 antitrypsin; Fibrinogen; Ceruloplasmin

Introduction

Diabetes Mellitus is one of the most common major public health problems having worldwide distribution. It has now adopted epidemic proportions. This recent explosion of interest in the notion that chronic low grade inflammation and activation of the innate immune system are closely involved in the pathogenesis of type 2 diabetes mellitus was first proposed in 1997-98 [1]. Several studies after that have shown that circulating markers of inflammation, acute phase reactants or interleukin-6 (IL-6) are strong predictors of the development of type 2 diabetes [2,3]. α1- acid glycoprotein, α-1 antitrypsin, fibrinogen and ceruloplasmin are few of the acute phase reactants. The level of these inflammatory markers in the pathogenesis of type 2 Diabetes mellitus was of interest.

Recently, there in increasing evidence that an ongoing cytokine induced acute phase response which is sometimes called low grade inflammation, but part of a widespread activation of the innate immune system, is closely involved in the pathogenesis of type 2 diabetes mellitus and associated complications such as dyslipidemia and atherosclerosis. Elevated circulatory inflammatory markers such as C-reactive protein and interleukin-6 predict the development of type 2 Diabetes mellitus and several drugs with anti-inflammatory properties both lower both acute phase reactants and glycaemia and possibly decrease the risk of developing type 2 diabetes mellitus. Age, inactivity, certain dietary components, smoking, psychological stress and low birth weight are among the risk factors for type 2 diabetes mellitus, which are also known to be associated with activated innate immunity. Activated immunity may be the common antecedent of developing type 2 diabetes mellitus [4]. Other features of type 2 diabetes mellitus such as fatigue, sleep disturbance and depression are likely to be at least partly due to hypercytokinemia and activated innate immunity.

Material and Method

Patients with features of previously undiagnosed diabetes were examined by the physicians. Of the confirmed cases, patients with a history of chronic inflammatory diseases, episodes of recent acute inflammation, smokers, alcoholics, women on oral contraceptive pills or any other hormones, pregnant women and patients with clinical evidence of neuropathy, nephropathy, and retinopathy were not enrolled in the study. Twenty five (25) type 2 patients between the age limit of 30-60 yrs. of either sex gave their consent to participate in the study. Twenty five (25) type 2 diabetes mellitus patients who are under treatment of oral hypoglycemic drugs for at least 5 yrs. between the age limit of 30-60 yrs. were also chosen. Type 2 was decided based only on their age and their subsequent response to insulin and oral hypoglycemic, respectively. Thirty (30) individuals were chosen from attendants of the patients to serve as controls. All exclusion criteria of the test groups were applied to the control group also. The protocol was approved by the Institutional Ethics Committee. Age, weight and height were recorded and body mass index (BMI) was calculated. Blood was collected as a random sample before the initiation of therapy in the diabetic patients and the following estimations were carried out:

- Random plasma glucose (RBS): By the glucose oxidase method on Hitachi 917 autoanalyser using Roche Kits.
- Fibrinogen assay [5]: Fibrinogen in plasma was converted to fibrin in the presence of calcium chloride. The fibrin clot was collected and digested with sodium hydroxide. Protein content of the clot was determined by the biuret method.
- Ceruloplasmin assay [6]: At pH 5.4, ceruloplasmin catalysis the oxidation of paraphenylenedia-mine(PPD) to yield a coloured product which is believed to correspond either to Bandrowski's base or to Weuster's red. The rate of formation of the coloured oxidised product is proportional to the concen-tration of ceruloplasmin, if a correction is made for the nonenzymatic oxidation of PPD. Simultaneous estimations were carried out with and without sodium azide, which inhibits the nonenzymatic oxidation of PPD. The difference between the results of the two assays was proportional to the ceruloplasmin concentration.
- α-1 antitrypsin assay [7]: The proteolytic enzyme trypsin hydrolyses casein, with the formation of smaller peptides. The enzyme reaction after suitable interval of time is arrested by the addition of tri-chloroacetic acid (TCA) which precipitates 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,I t prevents the release of peptides by the proteolytic enzymes. Thus, the esti-mation 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 analysed by the method of Lowry et al. [8]. The final colour 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.
- α-1 acid glycoprotein [9]: After removing heat coaguable proteins with perchloric acid, 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. Statistics The data was analysed by the student's t test and the ANOVA test. Pearson's coefficient was applied for corre-lational analysis.

Results

The aim of the study was to examine inflammation as a pathogenetic cause in type 2 freshly diagnosed diabetes mellitus cases. The mean age (range), BMI and the number of males: females are presented in Table 1 the control group participants were so chosen as to cover the age range of the test groups. Table 2 lists the values of random blood sugar (RBS) and acute phase proteins in the three groups as mean ± SD. Test group T-2 had significant higher values of all the parameters in

comparison with the control group. It is noteworthy that although the levels of all the acute phase markers studied were higher in the T-2 patients. This can be further appreciated in Table 3 which depicts the significance levels (p values) of the test and control groups. After treatment by oral hypoglycemic drug for 5 yrs. the level of ceruloplasmin and α1 acid glycoprotein were quite under control which can be further again depicts by the p values of the test and control groups.

	Type 2 (n = 25)	Controls (n = 30)	Type2 under treatment(n=25)
Age	47.27±7.11(30-60 yrs)	43.97±14.06 (30-60 yrs)	51.32 ± 7.56(30-60yrs)
BMI	23.03±1.46	20.75 ±2.27	24.20 ± 2.40
Males : Females	15:10	17:13	16:09

n= number of subjects

Table 1: Patient Characteristics.

Parameters	Type 2 Mean ±SD	Controls Mean ±SD	Type2 under treatment Mean ±SD
Random blood Sugar (mg/dL)	192.26±35.20	93.20±7.00	193.61±33.65
α1 antitrypsin (mg/dL)	561.16±63.00	349.48±114.07	519.38±47.80
α1 acid glycoprotein(mg/dL)	180.93±31.94	102.41±22.13	87.10±17.69
Ceruloplasmin (mg/dL)	44.05±9.03	25.95±4.10	25.73±9.94
Fibrinogen (mg/dL)	571.25±82.26	334.34±42.19	581.74±79.09

Table 2: Levels of the acute phase proteins as Mean ± SD.

Parameters	T-2 v/s Controls	T-2UT v/s Controls	T-2 v/s T-2UT
Random blood Sugar (mg/dL)	< 0.0001*	< 0.0001*	0.972
α1 antitrypsin(mg/dL)	< 0.0001*	< 0.0001*	0.03
α1 acid glycoprotein (mg/dL)	< 0.0001*	0.005	< 0.0001*
Ceruloplasmin(mg/dL)	< 0.0001*	0.55	< 0.0001*
Fibrinogen(mg/dL)	< 0.0001*	< 0.0001*	0.682

T-2= Type 2 newly diagnosed patient

T-2 UT = Type 2 diabetic patient under treatment for minimum 5 yrs

p≤0.05 was considered significant *= statistically significant

Table 3: Significance (p value).

Discussion

The aim of this study was to examine inflammation as a pathogenetic cause in type 2 diabetes mellitus. Twenty-five type 2 newly diagnosed patients showed increased levels of α1-antitrypsin, α1-acid glycoprotein, ceruloplasmin and fibrinogen. The findings were in agreement with most of the authors who worked with acute phase proteins in type 2 diabetes [10-12]. The role of chronic low grade inflammation in the pathogenesis of type 2 diabetes seems possible beyond doubt. The most dreaded complication being that of development of atherosclerosis resulting in cardiovascular diseases. Fibrinogen is identified as an independent risk factor in the development of ischemic heart diseases.

Ceruloplasmin is known to have antioxidant action [13]. It is also an acute phase protein with a response of intermediate magnitude. Ceruloplasmin is known to stimulate cell proliferation and angiogenesis [14]. The higher levels of ceruloplasmin in type 2 as compared to controls may be due to an oxidative stress that is prevalent intype2 diabetes [15,16]. Eduardo Ehrenwald [17] showed a very interesting feature of ceruloplasmin. The intact human ceruloplasmin which is 132 KD molecules caused increased oxidation of LDL in vitro. Starkebaum G and Harlan JM et al also showed that increased serum ceruloplasmin could generate excess oxidized LDL, and cause vascular injury by generating free radicals such as hydrogen peroxide. These findings defined the earlier notions of the antioxidant activity of

ceruloplasmin. By further investigations Eduardo Ehrenwald et al. found that the holoceruloplasmin, which is seen in serum as a 132 KD molecule, has a prooxidant effect and the action was attributed to the copper ions present in ceruloplasmin. The commercially available ceruloplasmin is a degraded product containing either 115 KD fragment or 19 KD fragment or both. These had an antioxidant effect. The works done to show that ceruloplasmin as an antioxidant used these degradated products. The antioxidant action of a commercial ceruloplasmin was observed even in the system where holoceruloplasmin oxidized LDL [17]. Hence considering ceruloplasmin as an antioxidant in vivo is debatable. The LDL oxidizing action of ceruloplasmin could probably explain at least in part of the increased risk of IHD in type 2 diabetes. Also it could not be wrong to count ceruloplasmin as an acute phase reactant whose levels are increased in type 2 diabetes.

The values of various parameters when compared between controls and type 2 patients reveal a significant increase in type 2 patients (Table-2). Even the ceruloplasmin values, although not statistically significant, were slightly higher in the type 2 patients. The mean random blood sugar (RBS) values in Type 2 newly diagnosed diabetics was 192.26±35.20 mg/dl. In spite of this huge difference, the inflammatory markers levels were higher in the type 2 patients which go to prove that the glycemic status doesn't influence the inflammatory markers. This is in accordance with previous findings [18]. Evidence is available to say that inflammatory markers are elevated well before the clinical manifestation of hyperglycemia [19-22]. This also gives credence to the thought that activation of innate immunity is not related to hyperglycemia. But research has shown that decreasing plasma glucose levels decrease the concentration of acute phase reactants [23]. Also 2 hrs post load glucose values showed positive correlation with the inflammatory markers in few studies [18].

The underlying mechanism for the augmented acute phase response is not well understood and the stimulus for the response is unknown. A number of hypotheses have been put forward and these include insulin resistance, obesity, atherosclerosis, other diabetic complications and maladaptation of the normal innate immune response to environmental threats [24-26]. The most widely studied is the association of obesity, insulin resistance, type 2 diabetes and acute phase reactants. It has been shown that adipocytes secret a number of proinflammatory cytokines in the postprandial state [27-29]. The term 'diabecity' has received attention of late for obese diabetics [30]. The 'common soil' theory proposed, evaluates the involvement of inflammation in the pathogenesis of diabetes and atherosclerosis. Hyperglycemia and insulin resistance could promote inflammation and inflammation may be a factor linking diabetes mellitus to the development of atherosclerosis. Elevated glucose levels promote inflammation by increasing oxidative stress, by the formation of AGEs and increased TNF (kappa B) [31,32]. In this study, the mean BMI was found to be 20.75 ± 2.27 in control and 23.03 ± 1.46 in type 2 patients. No correlation was found between BMI and acute phase reactants. Hence it can be summarized that there could be multiple pathways involved in the activation of the innate immunity system and much work needed to be done to establish either a casual role in the development of mainly type 2 diabetes.

Having demonstrated that there is an inflammatory process going on in type 2 diabetes, we next thought of estimating inflammatory markers in patients on treatment(for at least 5 years) with oral hypoglycemic drugs. Many of the drugs have been shown to have anti-inflammatory effects. Statin drugs inhibits HMG-CoA reductase and prevent atherosclerosis and inhibit the acute phase response by diminishing the deposition of LDL particles rich in cholesterol and phospholipids in macrophages and smooth muscle cells [33]. Statins were found to reduce CRP levels and did not correlate with the reduction of the lipid levels suggesting that the in addition to their ability to reduce LDL, statins may also inhibit the acute phase response [34]. Freeman DJ et al showed that statin therapy also prevent diabetes mellitus. Pravastatin therapy in the West of Scotland Coronary Prevention Study resulted in a 30% reduction of risk of developing type 2 diabetes [35]. Salicylates in high doses have been known to lower glycosuria in diabetic patients [36]. Although earlier studies were contradictory, these studies has used lower aspirin doses (<3gm/day) and therapeutic duration was only for a few days. Hundal RS [37] reported that high doses of aspirin (7 gm/day) for 2 wks caused 25% reduction in fasting plasma glucose, 50% reduction in triglyceride and 15 % reduction of CRP concentration independently of the changes in the plasma insulin concentration. The recently introduced oral hypoglycemic agents thiazolidinedions (Glitazone) are peroxizome proliferators activated receptor γ (PRAR γ) agonist that have been regarded as insulin sensitizes through mechanisms such as altered transcription of insulin sensitive genes controlling lipogenesis, adipocytes differentiation , fatty acid uptake and GLUT 4 (Glucose Transporter 4) expression. They also have an anti-inflammatory action inhibiting cytokine production, macrophage activation and reducing CRP as well as WBC count in type 2 diabetic subjects [38-41].

Angiotensin Converting Enzyme Inhibitors (ACE inhibitors) are also known to decrease insulin resistance in either type 1 or type 2 diabetic patients with concomitant hypertension [42]. Torlone E et al.

demonstrated improved glycemic control in patients with arterial hypertension and type 2 diabetes using ACE inhibitors [43]. Insulin has a potent anti-inflammatory activity [32]. Insulin was found to be a rapid nonspecific and dose dependent inhibitors of the cytokine and glucocorticoids stimulation of acute phase protein, gene expression and exerted effect at the transcriptional levels. Insulin inhibition applied to all cell cytokines tested but to various degrees depending upon the particular acute phase gene [44].

In this study, of the 25 type 2 diabetic patients on treatment for at least 5 yrs, 8 patient were in sulfonylurea-metformin combination, 7 were on glitazone, 6 were on sulfonylurea alone, 2 were on glitazone-metformin combination and 2 were on metformin alone. When compared with newly diagnosed untreated group the levels of α1-antitrypsin, α1-acid glycoprotein and ceruloplasmin were statistically lower. No significant difference was found in the fibrinogen levels. The values of α1-acid glycoprotein and ceruloplasmin were comparable to those of the control group. The RBS values were similar to those of untreated group (193.61 ± 33.65 and 192.26 ± 35.30). It is interesting to note that α1-acid glycoprotein levels were quite low in under treatment patients in compare to type 2 diabetic and even control populations. Probably α1-acid glycoprotein is the most amenable acute phase protein to treatment modalities. Comparable ceruloplasmin levels in type 2 patients on treatment and controls again raise the question as to the 'prooxidant' or 'antioxidant' action of ceruloplasmin. No change in fibrinogen values suggest multiple pathway involvement that are poorly understood.

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