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Role of ceruloplasmin as a low grade chronic inflammatory marker and activated innate immune system in pathogenesis of diabetes mellitus

Abstract

Aim: Ceruloplasmin is a late acute phase protein and one of the very prominent low grade chronic inflammatory markers. It is a circulating blue multicopper oxidase that contains >95% of copper in plasma. Pathogenesis of type 2 diabetes is observed to be associated closely with acute phase response which is predominately cytokine-mediated. The role of inflammation in type 1 diabetes is contradictory. By estimating circulating ceruloplasmin in type 2(T-2) and type 1(T-1) diabetic patients, I tried to establish this hypothesis.

Method: Newly diagnosed twelve T-1 cases, twenty-five T-2 cases and twenty-five T-2 cases under oral hypoglycemic agent for at least 5 years were chosen and were estimated the level of ceruloplasmin. By matching the age and sex of the test groups, thirty normal controls were also studied.

Result: In comparison with the controls, newly diagnosed T-1 and T-2 cases showed significantly higher levels of the ceruloplasmin. T-2 cases had little higher values of ceruloplasmin when compared to the T-1 cases. Levels are significantly reduced and found almost same level as control in T-2 cases after treating by oral hypoglycemic drugs for at least 5years. Interestingly, no correlation was found with Basal Metabolic Rate (BMI) or the degree of hyperglycemia in either of the types.

Conclusion: A low grade inflammatory process is definitely implicated in the pathogenesis of both type 1 and type 2 diabetes mellitus. This line of pathological basis should be further explored for diagnosis, management and follow up.

Keywords: diabetes mellitus, type 2 diabetes mellitus, ceruloplasmin, innate immunity, chronic inflammation

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Introduction

Ceruloplasmin is one the important components of the multicopper oxidase family of enzymes. Three types of spectroscopically distinct copper sites are present in this evolutionarily conserved group of proteins.[1] The signature sequences encompassing the amino acid ligands for copper are highly conserved among all multicopper oxidases. The substrates, the number of type I coppers and precise mechanism of intramolecular electron transfer differ from protein to protein.[2] Unique members of this family of enzymes, which include the well characterized protein laccase and ascorbate oxidase, are present in bacteria, fungi, yeast, plants, worms, parasites and mammals. Manganese, iron, nitrate, bilirubin, phenol and ascorbate are the known substrates of the multicopper oxidase.[2]

Human ceruloplasmin is approximately 65 kb of DNA localized to chromosome 3q23-q24 and encoded in 20 exons encompassing.[3] A processed pseudogene encoding the carboxyl terminal 563 amino acids has been identified and mapped by somatic cell hybridization to chromosome 8.[4] The presence of this sequence in the human genome must be considered in the design of any molecular diagnostic testing for aceruloplasminemia, although this pseudogene is not expressed. In hepatocytes, the human ceruloplasmin gene is expressed as two transcripts of 3.7kb and 4.2kb, which arise from use of alternative polyadenylation sites within the 3' untranslated region.[5] In the liver, abundant expression of these transcripts results in the 1046-amino acid protein detected in serum. Nucleoside and amino acid sequence comparisons suggest that serum ceruloplasmin and serum clotting factors V and VIII constitute a family of structurally related proteins.[6] Ceruloplasmin is an acute phase reactant and due to result of elevated gene transcription in hepatocytes, the concentration in serum is increased during inflammation, infection and trauma which are mediated by cytokines.[7]

Recently, there in increasing evidence that for the development of type 2 diabetes mellitus and also associated complications such as dyslipidemia and atherosclerosis are closely associated with ongoing cytokine induced acute phase response which is sometimes called low grade inflammation, but part of a activated innate immune system.[8] The role of acute phase reactants in the development of type 1 diabetes mellitus is not very clear. High plasma levels of circulatory inflammatory markers such as C-reactive protein and interleukin-6 are predicted to be associated with the development of type 2 diabetes mellitus and both acute phase reactants and glycaemia are reduced by lot of drugs which have properties to fight against inflammation and possibly decrease the risk of developing type 2 diabetes mellitus.[8] Acute phase reaction is a general reaction to inflammation, comparable to the increase in temperature or leukocyte count and is not specific for any given disease. A small protein known as Leucocytic Endogenous Mediator (LEM) which is released from the site of injury probably triggers all these changes.[8] Levels of the individual acute phase proteins in plasma rise at different rates. First; the levels of C-reactive protein and α–1 antichymotrypsin rise, then within the first 12 hrs, α–1 acid glycoprotein followed by α-1 antitrypsin, haptoglobin, C4 and fibrinogen levels rise and finally there is a rise of C3 and ceruloplasmin levels. All levels reach their maximum within

2-5days.[8] Out of the all risk factors for development of type 2 diabetes mellitus factors like age, inactivity, certain dietary components, smoking, psychological stress and low birth weight are considered as highly associated with, that are also considered to be involved with activated innate immunity. For developing type 2 diabetes mellitus activated immunity may be consider as common antecedent. All of other associated signs and symptoms 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.[9]

Rapid front line defense of the body against environmental threat such as microbial infections, physical or chemical injuries is the natural or innate immune system.[10] A series of reactions are activated followed by, that prevent ongoing damage of tissue, isolate and demolished infective agents and activate repair mechanism to restore homeostasis.[11]

A prominent segment of activated innate immunity is a series of sentinel cells such as macrophages, antigen presenting β cells and dendritic cells and probably also; intestinal epithelial cells, endothelium, kupffer cells in liver, adipocytes and others. These act as devices to detect troubles. A number of germ line-encoded (i.e. monoclonal) pattern recognition receptors (PRPs) on and in these cells detect conserved molecular structures (pathogen associated molecular patterns) that are characteristic of a class of harmful agents. The most researched PRPs are probably the family of at least 10 tolls like receptors (TLRs) which are situated on the cell surface as transmembrane receptors.[12] binding to PRP cause activation of nuclear factor Kappa β signaling pathways. This induces immune response genes, those for inflammatory cytokines which are considered as main mediators of low grade chronic inflammation and acute phase response.[13] Acute phase reactant secretion from the liver is stimulated by cytokines. These also have positive impact on the brain to release adrenocorticotropic hormone and therefore secretion of cortisol from the adrenal gland leads to activation of sympathetic nervous systems leads the release of catecholamine's. Acute phase response can be aggravated by psychological stressful situation via innervations of cells which produce cytokine and stimulation of the sympathetic nervous system and adrenergic receptors on macrophages. Recently it has been appreciated that a very prominent second function of innate immunity is to motivated the adaptive immune response.[14]

Ceruloplasmin is one of the very prominent acute phase reactant and the association of this inflammatory marker in the pathogenesis of type 1 and type 2 diabetes mellitus was of interest.

Subjects and method

Study design, inclusion and exclusion criteria

1. To detect the elevation of ceruloplasmin, if any, in newly diagnosed untreated type 1 diabetes mellitus patients, in newly diagnosed untreated type 2 diabetes mellitus patients and in patient of type 2 diabetes mellitus under treatment for at least 5 years.
2. Compare the levels in newly diagnosed untreated type 2 diabetes mellitus patient with type 2 diabetes mellitus patients under treatment for at least 5 years.
3. Compare the inflammatory markers of newly diagnosed untreated type 1 diabetes mellitus with newly diagnosed untreated type 2 diabetes mellitus patients.

Subject was selected from various private clinics in Mangalore, India. At first physicians examine the glycemic status of the patients. Written informed consents were obtained from all participants in the study.

Estimation of serum ceruloplasmin

Principle

Ceruloplasmin assay in serum was carried out by the method of Sunderman and Nomoto.[15] At pH 5.4, ceruloplasmin catalyzes the oxidation of PPD to yield a coloured product which is believed to correspond either to Bandrowski's base or to Weurster's red. The rate of formation of coloured oxidized product is proportional to the concentration of ceruloplasmin, if, a correction is made for the nonenzymatic oxidation of PPD. Therefore simultaneous assay were carried out with and without sodium azide, which inhibited the enzymatic oxidation of PPD. The difference between the results of the two assays is proportional to ceruloplasmin concentration.

Statistics

The data was analyzed by the student's t test and the ANOVA test. Pearson's coefficient was applied for correlational analysis (Table 1) (Table 2)

Group I = Type 1 diabetes mellitus patient (newly diagnosed)

Group II = Type 2 diabetes mellitus patient (newly diagnosed)

Group III = Type 2 diabetes mellitus patient (under treatment for at least 5 years)

Group IV = Control

n = number of subjects

SD = Standard Deviation

BMI= Body Mass Index

RBS= Random Blood Sugar

*denoted significant value

Table 1 The anthropometric data of the subjects participated in the study are presented in Table 1

	Group I(n=12) (Mean ± SD)	Group II (n=25) (Mean ± SD)	Group III (n=25) (Mean ± SD)	Group IV(n=30) (Mean ± SD)
Age (yrs)	18.33 ± 7.64	48.22 ± 7.11	51.32 ± 7.56	44.97 ± 15.06
BMI	19.50 ± 1.23	24.03 ± 1.46	24.20 ± 2.40	21.75 ± 2.27
RBS (mg/dl)	338.25 ± 50.97	193.26±35.30	193.61±33.65	94.20±7.00

Table 2 Comparison of level of ceruloplasmin (mg/dl) between different groups in Table-3 (p value < 0.05 is considered significant.)

	Level(mg/dl)	Level(mg/dl)	p value
Comparison between Group I and Group IV	40.69 ±9.85(I)	26.95 ±4.10(IV)	< 0.0001*
Comparison between Group II and Group IV	45.05 ± 9.03(II)	26.95 ± 4.10(IV)	< 0.0001*
Comparison between Group III and Group IV	25.73 ± 9.94(III)	26.95 ± 4.10(IV)	0.55
Comparison between Group I and Group II	40.69 ± 9.85(I)	45.05 ± 9.02(II)	0.19
Comparison between Group II and Group III	45.05 ± 9.03(II)	25.73 ± 9.95(III)	< 0.0001*

Discussion

This study was setup for detection whether pathogenicity of type 1 diabetes mellitus and type 2 diabetes mellitus is related with low grade chronic inflammatory process with activated innate immunity or not by detecting the level of ceruloplasmin which is considered as a very prominent inflammatory marker. Increased ceruloplasmin was shown in twenty-five type 2 newly diagnosed patients. Our findings were in supporting with various authors who researched on acute phase proteins in type 2 diabetes.[16–18] The importance of chronic low grade inflammation with activated innate immune system in the pathogenesis of type 2 diabetes seems possible out of doubt. The most dreaded and brutal complication being that of development of atherosclerosis resulting in cardiovascular diseases in which fibrinogen is determined as a sole risk factor in the production and manifestation of ischemic heart diseases.

Ceruloplasmin is also an acute phase reactant with a response of intermediate magnitude and is known to have antioxidant action.[19] and also known to stimulate cell proliferation and angiogenesis.[20] May be due to an oxidative stress that is prevalent in type2 diabetes the levels of ceruloplasmin in newly diagnosed type 2 are high as compared to controls.[21,22] Eduardo Ehrenwald showed a very interesting characteristic of ceruloplasmin that the intact human ceruloplasmin which is 132KD molecules produced elevated oxidation of LDL *in vitro*.[23] Starkebaum G and Harlan JM et al also mentioned that excess oxidized LDL could be generated by increased serum concentration of ceruloplasmin and produce vascular injury by producing free radicals like hydrogen peroxide. The earlier notions of the antioxidant activity of ceruloplasmin can be defined and supported by these findings.[24] By further extensive investigations Eduardo Ehrenwald et al. found that the holoceruloplasmin has a prooxidant effect and the action was attributed to the copper ions present in ceruloplasmin. These holoceruloplasmin is seen in serum as a 132KD molecule. The commercially available ceruloplasmin which had an antioxidant effect, is mainly a degraded product containing either 115KD fragment or 19KD fragment or both. The works done to show that ceruloplasmin used these degraded products as an antioxidant. Even in the system the antioxidant action of a commercial ceruloplasmin was observed where holoceruloplasmin oxidized LDL.[23] Hence it's quite debatable for considering ceruloplasmin as an antioxidant in vivo. 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 and important parameter whose levels used to increase in case of low grade chronic inflammatory condition as well as in activated innate immunity as seen in type 2 diabetes.[23]

The values of ceruloplasmin when we compare between controls and type 2 patients reveal a significant elevated in type 2 patients (Table 3). The mean random blood sugar (RBS) values in Type 2 newly diagnosed diabetics was 192.26 ± 35.20mg/dl. In spite of this huge difference, which go to prove that the glycemic status doesn't influence the inflammatory markers. This is in accordance with previous findings. Evidence is available to say that before the clinical manifestation of hyperglycemia appears[25–28], inflammatory markers used to elevate well. This also gives credibility and support to the thought that activation of innate immunity is not related to hyperglycemia. But research has shown that the concentration of ceruloplasmin.[29] used to decrease by decreasing plasma glucose levels. Also the inflammatory markers showed positive correlation with 2 hrs post load glucose values in few studies.[30]

Table 3 The compare of mean value of ceruloplasmin in groups in Table 3

	Group I (Mean ± SD)	Group II (Mean ± SD)	Group III (Mean ± SD)	Group IV (Mean ± SD)
Ceruloplasmin(mg/dl)	40.69 ± 9.85	45.05 ± 9.03	25.73 ± 9.94	26.95 ± 4.10

Although number of hypotheses has been put forward but the underlying procedure for the augmented acute phase response is not well studied and the stimulus for the response is not known. Some of few hypotheses included resistance of insulin, obesity, atherosclerosis, other complications related to diabetes and maladaptation of the normal innate immune response to environmental threats.[31–33] The most widely studied is the association of obesity, insulin resistance type 2 diabetes and acute phase reactants. It has been studied that in the postprandial state.[34–36] adipocytes secret a number of proinflammatory cytokine. The term 'diabecity' has received attention.[37] of late for obese diabetics. The involvement of inflammation in the pathogenesis of diabetes and atherosclerosis is proposed and evaluated by 'common soil' theory. Inflammation can be promoted by hyperglycemia and insulin resistance and inflammation may be a factor linking diabetes mellitus to the development of atherosclerosis. Increased levels of glucose stimulated inflammatory reaction by increasing oxidative stress.[38] by the formation of AGEs and increased Tumor Necrosis Factor (kappa B).[39] In our present study, the mean BMI was found to be 20.75±2.27 in control and 23.03±1.46 in new type 2 diabetic patients. No association was found between BMI and the level of ceruloplasmin. 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 production of mainly type 2 diabetes.

Having demonstrated that low grade inflammatory process is involved with the pathogenesis of type 2 diabetes, we next thought of estimating the level of ceruloplasmin in patients on treatment(for at least 5 years) with oral hypoglycemic drugs. Many of the drugs have anti-inflammatory effects. Statin drugs inhibits HMG-CoA reductase and prevent atherosclerosis and inhibit the acute phase response.[39] Statins though found to reduce CRP levels but 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.[40] Freeman DJ et al showed that statin medication also prevent diabetes mellitus. 30% reduction of risk of developing type 2 diabetes mellitus was resulted by Pravastatin therapy which was shown in the West of Scotland Coronary Prevention Study.[41] Salicylates in high doses have been known to lower glycosuria in diabetic patients.[42] 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 reported that 25% decrease in fasting plasma glucose, 50% decrease in triglyceride and 15 % decrease of CRP concentration independently of the changes in the plasma insulin concentration are caused by high doses of aspirin (7gm/day) for 2 weeks duration of treatment.[43] Thiazolidinedione (Glitazone)is a widely used peroxisome proliferators activated receptor γ(PRAR γ) agonist agents 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.[44–47]

In type 1 as well as in type 2 diabetic patients, Angiotensin Converting Enzyme Inhibitors (ACE inhibitors) are also known to decrease insulin resistance with concomitant hypertension.[48] Torlone E et al.[49] demonstrated that using ACE inhibitors improved glycemic control in patients with arterial hypertension and type 2 diabetic patients.[49] Insulin has a potent anti-inflammatory activity which 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 specific acute phase gene.[50]

In our present 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. The levels of α1-antitrypsin, α1-acid glycoprotein and ceruloplasmin were statistically lower when compared with newly diagnosed untreated group. The levels of fibrinogen did not show any significant difference. The values of ceruloplasmin were comparable to those of the control group. The values of RBS were similar to those of untreated group (193.61±33.65 and 192.26±35.30). By compare ceruloplasmin levels in type 2 patients on treatment and controls again raise the question as to the 'prooxidant' or 'antioxidant' action of ceruloplasmin.

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.[51] 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 it has been shown that adipocytes secret a number of proinflammatory cytokines.[52] In case of late for obese diabetics the term 'diabecity' has received attention. 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, by the formation of AGEs and increased TNF (kappa B) is used to cause by elevated glucose level.[53] 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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None.

Conflict of interest

The author declares that there is no conflict interest.

Refereneces

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