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Correlation between Serum H_2S Level, Oxidative Stress, and Antioxidant Defence in Acute Coronary Syndrome

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Abstract: ***Introduction: A number of recent literatures suggest a potential role of H_2S and oxidative stress in regulating cardiovascular pathophysiology. Aims and Objective: This study aimed to evaluate the serum levels of hydrogen sulfide (H_2S), total oxidative stress (TOS) and total antioxidant defence (TAD) in the patients with acute coronary syndrome (ACS) and explore their correlation. Materials and Methods: Fifty two ACS patients and an equal number of healthy controls were included and serum H_2S, TOS and TAD levels were measured. Results: The results showed significantly higher serum H2S and TOS levels and significantly lower TAD levels in ACS patients compared to controls. Positive correlation was observed between H2S and TOS, while negative correlation was found between H2S and TAD in the serum of ACS patients. These findings suggest that increased H2S levels are associated with oxidative stress and decreased antioxidant defence in ACS. Conclusion: The present study has revealed the increase in serum H_2S levels in the patients with acute coronary syndrome as the total plasma oxidative stress increases with the subsequent reduction of total antioxidant defence.***

Keywords: H_2S; Oxidative stress; Antioxidant defence; Acute Coronary syndrome; Kolkata

1. Introduction

Hydrogen sulfide (H_2S) is recently discovered to be the third gasotransmitter, joining the ranks of the other two gasotransmitters, namely nitric oxide (NO) and carbon monoxide (CO). H_2S is involved in the regulation of vascular tone, myocardial contractility and neurotransmission in cardiovascular system. [1] H_2S has been involved in regulating cardiovascular pathophysiology in experimental models. However, there is paucity of information regarding the levels of H_2S in health and cardiovascular disease. [1]

Interestingly, it was found that the vessels displayed enhanced reactivity to exogenous H_2S donors suggesting that H_2S donor therapy may be efficacious in patients suffering from acute coronary syndrome. Though research investigating endogenous H2S biosynthesis and bioavailability in a wide variety of cardiovascular disease states including hypertension, obesity and metabolic syndrome have been performed however further studies are required to definitely understand the role of the endogenous H2S in the acute coronary syndrome.

The term oxidative stress refers to the scenario of serious imbalance between production of reactive species and antioxidant defence. Oxidative stress can result from: 1. Decreased antioxidants, 2. Increased production of ROS/RNS.

The majority of cardiovascular disease results from complications of atherosclerosis. An important initiating event for atherosclerosis may well be the transport of oxidized low - density lipoprotein (Ox - LDL) across the endothelium into the artery wall. [2] This is likely to occur at the sites of endothelial damage which are caused by Ox - LDL itself as well as physical or chemical forces and infection. [3] Endothelial cells, smooth muscle cells (SMCs), and macrophages are the sources of oxidants for the oxidative modification of phospholipids. Ox - LDL can damage endothelial cells and induce the expression of adhesion molecules such as P - selectin [4] and chemotactic factors such as monocyte chemoattractant protein - 1 (MCP - 1) and macrophage colony stimulating factor (mCSF). [5, 6] These processes lead to the tethering, activation, and attachment of monocytes and T lymphocytes to the endothelial cells. [7] Endothelial cells, leukocytes, and SMCs then secrete growth factors and chemoattractants which effect the migration of monocytes and leukocytes into the subendothelial space. [8] Monocytes ingest lipoproteins and morph into macrophages; macrophages generate reactive oxygen species (ROS), which convert Ox - LDL into highly oxidized LDL. Now oxidized LDL is taken up by macrophages to form foam cells. Foam cells combine with leukocytes to become the fatty streak, and as the process

continues foam cells secrete growth factors that induce SMC migration into the intima. SMC proliferation, coupled with the continuous influx and propagation of monocytes and macrophages, converts fatty streaks to more advanced lesions and ultimately to a fibrous plaque that will protrude into the arterial lumen. Later, calcification can occur and fibrosis continues, yielding a fibrous cap that surrounds a lipid - rich core. This formation may also contain dead or dying SMCs. In acute coronary syndromes (eg, myocardial infarction), when fibrous plaques rupture, the formation and release of thrombi may ultimately occlude vessels.

Several studies posit an important role of H_2S in atherosclerosis pathogenesis involving both its development and attenuation of consequences of ischemic vascular remodeling and tissue ischemia reperfusion injury. [9, 10] H_2S has been shown to decrease oxidation of low - density lipoprotein (LDL) as well as uptake of oxidized LDL by macrophages involving antioxidant responses. [9, 11, 12] Furthermore, H_2S impairs the migration of monocytes into the subendothelial layer via reduction of expression of ICAM - 1 and monocyte chemotactic protein - 1 (MCP - 1). [9, 13] H_2S has also been found to inhibit foam cell formation and vascular smooth muscle cell proliferation. [14] Lastly, H_2S reduces vascular calcification in the rat model via down - regulation of alkaline phosphatase activity and osteopontin gene down - regulation. [15] Together, these findings suggest that changes in plasma - free H_2S levels could affect several different pathophysiological responses involved in atherosclerotic vessel disease.

Responses to both exogenous and endogenously produced H_2S have been extensively studied in the vasculature, showing tissue specific effects. H_2S has been shown to have cardioprotective properties. Ischemia is a restriction in blood supply which results in damage or dysfunction of tissue. Ischaemic preconditioning is a technique used to produce resistances to ischaemia by repeated but short episodes of ischaemia. This process was first identified in a study on dog coronary arteries by Murry *et al*., (1986) where ischaemic preconditioning was shown to protect the myocardium against a subsequent ischaemic insult. Bian*et al*., (2006) demonstrated that endogenous H_2S contributed to the ischemic preconditioning mechanism providing cardioprotection subsequent to an ischaemic insult. In addition, exogenous administration of H_2S has been shown to protect myocytes and their contractile activity by directly scavenging oxygen - derived free radicals and reducing the accumulation of lipid peroxidation products. [16]

In the present study, the levels of H_2S, total oxidative stress and antioxidant defence in serum of patients suffering from acute coronary syndrome will be assayed and compared with the control volunteers to elucidate if there is any association of the above and the other clinico - biochemical parameters.

Aims and Objective

The current study was aimed to evaluate the serum H_2S, total oxidative stress (TOS) and total antioxidant defence (TAD) levels in the patients with acute coronary syndrome and to find out if there is any correlation among these parameters.

2. Materials and Methods

This case control study was conducted in the department of Biochemistry and Cardiology, NRS Medical College, Kolkata, India. Fifty two diagnosed acute coronary syndrome patients ranging from 20 to 70 years of age, consisting 44 males and 8 females, were enrolled for the study along with similar number of age matched healthy volunteers as controls (40 males and 12 females). The Institutional Ethics Committee approved the study. Pregnant mothers, Patients with endocrine disorders, renal failure, malignant disease were excluded from the study.

Measurement of H_2S concentration in serum:

Serum H_2S levels were estimated following methods described earlier [17 - 19] with further modification and standardization in our laboratory. [20] This spectrophotometric method involves the reaction of sulfide with N, N - dimethyl - p - phenylenediamine sulfate in the presence of the oxidising agent Fe^{3+} in hydrochloric acid to form methylene blue which is read at 670nm.

Estimation of Total Oxidative Stress (TOS) in serum:

It is a simple colorimetric test based on the principle of Free Oxygen Radical Test (FORT) modified and standardised in our laboratory [21 - 24]. Hence we have used a different chromogen (N, N - dimethyl - p - phenylenediaminesulphate).

Principle: This test is based on iron catalysed breakdown of hydroperoxides (ROOH) into alkoxyl (RO•) and peroxyl (ROO•) radicals which reacts with the chromogen (N, N - dimethyl - p phenylenediamine sulphate) towards formation of a coloured compound, the absorbance of which is photometrically detectable. The intensity of the colour correlates directly with the quantity of radical compounds and it can be related to the oxidative status of the sample.

$$\mathbf{R - OOH + Fe^{2+} \rightarrow R - O^{\cdot} + OH^{-} + Fe^{3+}}$$

$$\mathbf{R - OOH + Fe^{3+} \rightarrow R - OO^{\cdot} + H^{+} + Fe^{2+}}$$

$$\mathbf{RO^{\cdot} + ROO^{\cdot} + 2CrNH_2 \rightarrow RO^{-} + ROO^{-} + [Cr - NH_2^{+\cdot}]}$$

Estimation of Total Antioxidant Defence (TAD) in serum: It is also a simple colorimetric test based on the principle of Free Oxygen Radical Defence (FORD) test, modified and standardized in our laboratory. [21]

Principle: The test uses preformed stable and colored radicals and determines the decrease in absorbance that is proportional to the antioxidant concentration of the sample according to the Lambert - Beer law. In the presence of an acidic buffer (pH = 5.2) and a suitable oxidant ($FeCl_3$), the chromogen (N, N - dimethyl - p - phenylenediaminesulphate) forms a stable and colored radical cation that is photometrically detectable at 505 nm. Antioxidant compounds in the sample by reducing the radical cation of the chromogen quench the color and thus produce a discoloration of the solution, which is proportional to their concentration. The absorbance values obtained for the samples are compared with a standard curve obtained using Trolox (6 - hydroxy - 2, 5, 7, 8 - tetramethylchroman - 2 - carboxylic acid), a permeable cell derivative of vitamin E commonly used as an antioxidant.

Chromogen (no color) + Fe^{3+} + H^+ → chromogen$^{\cdot+}$ (purple)
Chromogen$^{\cdot+}$ (purple) + AOH → chromogen (no color) + AO

3. Results

The serum H_2S level in the patients (42.15 ± 9.706 micromol/l) is significantly higher (P< 0.001) than the healthy controls (21.042 ± 9.747 micro mol/l).

The serum total oxidative stress (TOS) in the patients (31.81 ± 5.62 milimol/ l of H_2O_2) is also significantly higher (P<0.001) than the healthy controls (13.49 ± 6.33 mili mol/l of H_2O_2).

The serum total antioxidant defence (TAD) level in patients (143.65 ± 101.286 millimol/l equivalent of trolox) was found to be significantly lower (P<0.001) than those of controls (342.5 ± 165.883 millimol/l equivalent of trolox).

Serum H_2S level shows significant positive correlation with TOS (r= 0.379, P= 0.006) and significant negative correlation of with TAD (r= - 0.579, P<0.001) in the serum of the patients.

Table 1: Clinical & biochemical parameters of patients and controls

Variable	Patient (N=52)	Control (N=52)	P value
Age (years)	57.19 ± 9.265	56.09 ± 11.652	NS
Sex (M/F)	44/8	40/12	
Height (m)	1.64 ± 0.068	1.61 ± 0.095	NS
Weight (kg)	66.69 ± 8.523	62.38 ± 10.792	NS
Body mass index (BMI)	24.94 ± 2.966	24.00 ± 3.265	NS
TOS (mM of H_2O_2/l)	31.81 ± 5.623	13.49 ± 6.334	<0.001
TAD (mM of /l equivalent of Trolox)	143.65 ± 101.286	342.5 ± 165.883	<0.001
Serum H_2S (Micro mol/L)	42.15 ± 9.706	21.042 ± 9.747	<0.001

Serum H_2S Levels In Study Subjects:

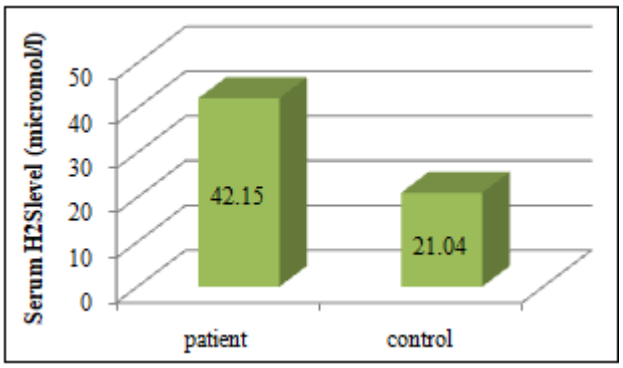

Figure 1: Comparison of serum H2S levels in patients and controls

Serum Total Oxidative Stress (TOS) In Study Subjects:

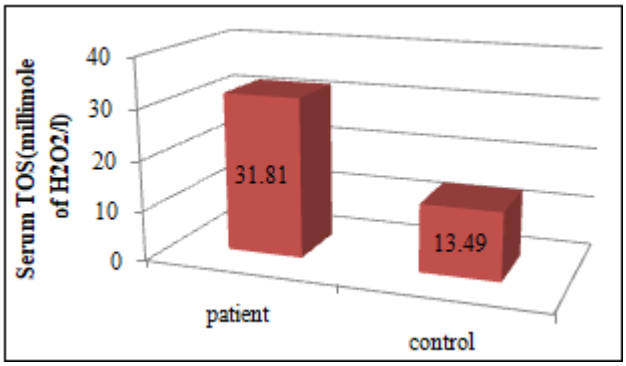

Figure 2: Comparison of serum total oxidative stress (TOS) in patients and controls

Serum Total Antioxidant Defence (TAD) In Study Subjects:

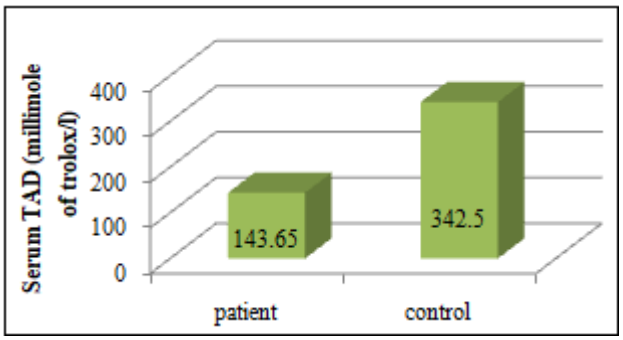

Figure 3: Comparison of serum total antioxidant defence (TAD) in patients and controls

Correlation Analysis:
Serum H_2S level shows significant positive correlation with TOS (r= 0.379, P= 0.006), as shown in figure 4.

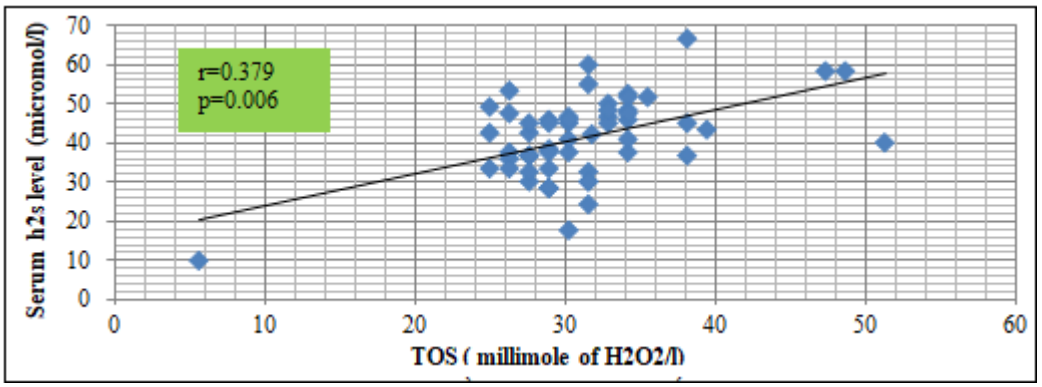

Figure 4: Scatter plot showing correlation between serum H2S levels and TOS values in patients

The serum H_2S level shows significantly negative correlation with level of total antioxidant defence (TAD) in serum (r= - 0.579, P<0.001) as shown in figure 5.

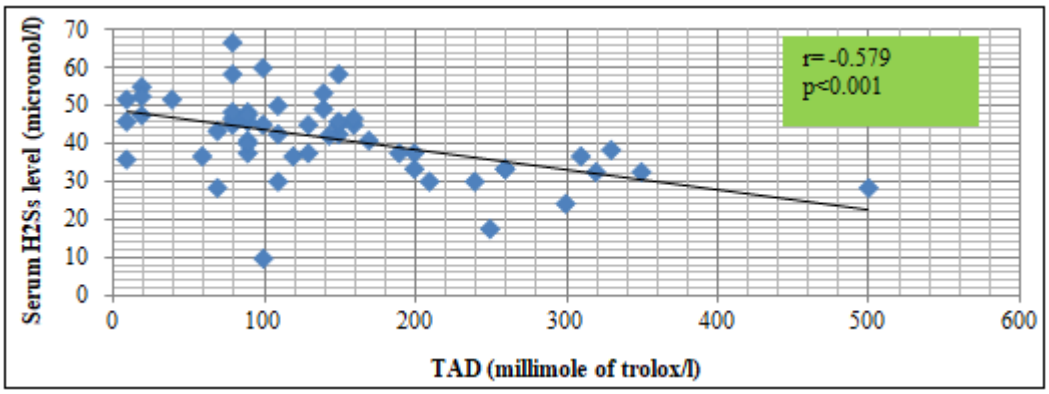

Figure 5: Scatter chart showing correlation between serum H_2S level and TAD values in patients

4. Discussion

The current study was aimed to find out if there is any relationship between serum H_2S levels with total oxidative stress and total antioxidant defence.

Acute coronary syndrome has already being established as a disease associated with oxidative stress. However, most of the studies have been conducted with different methods consisting of some of the oxidative stress parameters in the tissues or in plasma. [25] So the availability of speedy and easy assays which measures the combined effect of the standard oxidative stress and antioxidant defences in blood is of essential significance to provide an index of ability to withstand oxidative damage. At present, sophisticated methods like HPLC (High Performance Liquid Chromatography) and immunochemical determinations have become more and more common standard.

But comprehensive studies with total oxidative stress and total antioxidant defence status in this condition are limited. We have developed two simple colorimetric methods for assay of total oxidative stress (TOS) and total antioxidant defence (TAD) in our laboratory using a single chromogen (N, N - dimethyl - p - phenylenediaminesulphate) based on the FORT (Free Oxygen Radical Test) and FORD (Free Oxygen Radical Defence) test principles. [21, 22, 24] The serum total oxidative stress (TOS) in the patients in our study is 31.81 ± 5.62 milimol/ l of H_2O_2, which is significantly higher (P<0.001) than the healthy controls which is 13.49 ± 6.33 milimol / l of H_2O_2 (Figure - 2).

Our study has shown that the total serum antioxidant levels in the patients is 143.65 ± 101.29 milimol/l equivalent of trolox (trolox is 6 - hydroxyl - 2, 5, 7, 8 - tetramethyl chroman - 2 - carboxylic acid, a water soluble analogue of vitamin - E). This is significantly (P<0.001) reduced compared to the control subjects which is 342.5 ± 165.88 milimol/l equivalent of trolox (Figure - 3). The patients in our study have increased oxidative stress and decreased antioxidant defence. This observation also agrees with the previous reports. [26 - 28]

We have also found significant positive correlation between H_2S with the total oxidative stress (TOS) in serum of the patients (r= 0.379, P= 0.006, Figure - 4). A significant negative correlation of serum H_2S levels with the levels of total antioxidant defence (TAD) in the serum of the patients in this study (r= - 0.579, P<0.001, Figure - 5) supports the fact that hydrogen sulfide plays a protective role in acute coronary syndrome by contributing to the antioxidant defence mechanisms.

Cells can be protected from oxidative stress through numerous mechanisms with intracellular glutathione dependent or independent pathways serving as primary mediators. [29] Evidence in simple uni or multicellular organisms reveals that sulfur containing substances dimethylsulphoniopropionate and dimethylsulfide act as endogenous scavengers of reactive oxygen species in marine algae. [30] However, in more complex organisms it has been observed that H_2S exerts its antioxidant effect not directly but through induction of glutathione metabolism responses.

[31] This is confirmed by a recent study by Hamar et al demonstrating that H_2S itself is an antioxidant. [32]Jha et al. has also shown that hydrogen sulfide protects hepatocytes from ischemia reperfusion (I/R) injury through up regulation of intracellular antioxidants. [33] Likewise, Calvert et al has reported that exogenous H_2S confers cardioprotection against I/R injury through Nrf - 2 induction. [34] Conversely, it has been shown that oxidative stress is increased by decreased endogenous production of H_2S in hypoxic pulmonary hypertensive rats. [35] Moreover, H_2S enhances the activity of cysteine and cystine transporters to increase the level of substrates for glutathione (GSH) production. H_2S produced by 3 - mercaptopyruvatesulfurtransferase (3 - MST) along with catalase may also directly suppress oxidative stress in mitochondria. H_2S also attenuates oxidative injury in astrocytes by H_2O_2 by increasing glutamate uptake. [36] H_2S can also inhibit peroxynitrite - mediated tyrosine nitration of neuronal proteins, suggesting that H_2S has the potential to act as an inhibitor of peroxynitrite - mediated processes *in vivo*. [37] Evidence also indicates that H_2S increases the ability of the antioxidant enzyme superoxide dismutase to scavenge superoxide and increase the level of GSH biosynthetic enzyme γ - glutamylcysteine synthase. [38] It is well known that H_2S modulates mitochondria function, as it is a potent and reversible inhibitor of cytochrome C oxidase. Through this ability to blunt cellular respiration, which in turn reduces mitochondrial ROS production and decreases mitochondrial uncoupling, H_2S can elicit cytoprotection. [39] The majority of evidence suggests that H_2S production and bioavailability potently regulates cellular redox status through antioxidant defense responses besides direct antioxidant activity.

Our study results elicit a significantly positive correlation of plasma H_2S levels with plasma total oxidative stress and negative correlation with total antioxidant defence values. This may be due to the possibility of H_2S functioning as an antioxidant and reveals a protective role of this gasotransmitter. In a situation of oxidative stress the H_2S synthesizing activity is induced to combat the oxidative challenge. The reverse situation occurs when the antioxidant levels are adequate.

5. Limitations of the Study

Large scale study especially at the tissue level is required in the direction to find out the exact pathophysiological role of H_2S in acute coronary syndrome in order to draw a conclusion whether H_2S modifiers can be used for preventive and therapeutic purposes.

6. Conclusion

Patients with acute coronary syndrome have increased serum total oxidative stress and decreased total antioxidant defence. Increased serum H_2S levels are positively associated with increased oxidative stress levels and inversely associated with decreased serum antioxidant defence levels. This may be due to a protective role of serum H_2S in a patient suffering from acute coronary syndrome, where the H_2S playing a role of antioxidant. However the increased amount H_2S generated in this situation may lead to an adverse consequences and the balance of H_2S is more important which should be evaluated with more extensive study.

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