# Studies on lipid peroxidation and non-enzymatic antioxidant status as indices of oxidative stress in patients with chronic myeloid leukaemia

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## ABSTRACT

**Introduction: Chronic myeloid leukaemia (CML) is a myeloproliferative disorder of the haematopoietic cell. Free radicals can be important causative agents of a number of human diseases, including cancer and leukaemia. Thus, antioxidants, which control the oxidative stress state, represent a major line of defense for regulating the overall true state of health. The relationship between non-enzymatic antioxidant status and the levels of well-known markers of oxidative stress that are measured as lipid peroxides reflects better health indices. The aim of this study was to evaluate the plasma levels of lipid peroxidation products and non-enzymatic antioxidant status as indices of oxidative stress, disease progression and early responses to chemotherapeutic agents in chronic myeloid leukaemia patients.**

**Methods: The study included 128 CML patients and 50 age- and gender-matched healthy control volunteers. Indices of oxidative stress were evaluated as lipid peroxidation and non-enzymatic antioxidant status using the spectrophotometric method.**

**Results: There was a significant increase in the plasma levels of lipid peroxidation products in CML patients as compared to the healthy volunteers. The plasma levels of lipid peroxidation products continued to rise significantly as the disease progressed. The non-enzymatic antioxidant status was found to be significantly decreased in CML patients as compared to the healthy participants. The plasma levels of non-enzymatic antioxidant status continued to decrease significantly during the disease progression.**

**Conclusion: It can be concluded that plasma lipid peroxidation and non-enzymatic antioxidant status reflect oxidative stress in CML patients, and may be used as indices for oxidative stress, disease progression and early responses to different therapeutic modalities.**


**Keywords: chronic myeloid leukaemia, oxidative stress, response marker**

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## INTRODUCTION

Chronic myeloid leukaemia (CML) is a pleuripotent stem cell disorder that is characterised by the neoplastic proliferation of progenitor cells of the haematopoietic system. CML is characterised by a chromosomal abnormality that is known as the Philadelphia (Ph) chromosome. The resulting break point cluster region-Abelson (BCR-ABL) fusion on the Ph chromosome is transcribed into a chimerical ribonucleic acid (RNA) and then translated into a fusion tyrosine kinase protein of varying sizes of P210 to P190 kDa. CML has an incidence rate of 1–1.5 cases per 100,000 per year in the western countries, whereas the incidence of CML is not well known in India.

Free radicals are responsible for deoxyribonucleic acid (DNA). lipid and protein damage, or oxidative stress, and play an important role in the development and progression of many human diseases including cancer.[1-3] Therefore, there is a need for an index to quantify the damage or the oxidative stress. Oxidative stress is evaluated in terms of thiobarbituric acid reactive substances (TBARS) and total lipid hydroperoxides (LOOH). On the other hand, reduced glutathione (GSH) and total thiols (T-SH) have been studied as markers of non-enzymatic antioxidant status. The levels of these parameters have been shown to be valuable as indicators or biomarkers of oxidative stress and disease progression in a number of pathophysiologies.[2-5] Increased levels of lipid peroxidation products have been found in the plasma of patients with gynaecological malignancies,

**Table I. Plasma levels of lipid peroxidation products and non-enzymatic antioxidant status in CML, CML-CP and CML-AP patients as well as healthy subjects.**

| | Healthy Subjects (n = 50) | CML | | CML-CP | | CML-AP | |
|---|---|---|---|---|---|---|---|
| | | Group I (n = 83) | Group II (n = 45) | Group I (n = 62) | Group II (n = 36) | Group I (n = 21) | Group II (n = 9) |
| TBARS (n mole MDA/ml) | 3.18 ± 2.50 | 5.74 ± 3.83*** | 5.02 ± 2.90** | 4.51 ± 2.51* | 4.05 ± 1.44Ψ | 9.37 ± 4.75*** | 8.91 ± 3.96*** |
| LOOH (m mole/ml) | 0.36 ± 0.25 | 0.59 ± 0.38** | 0.64 ± 0.37*** | 0.50 ± 0.31*** | 0.55 ± 0.30** | 0.86 ± 0.44* | 1.00 ± 0.41*** |
| GSH (μ mole/ml) | 1.11 ± 0.53 | 0.79 ± 0.36*** | 0.82 ± 0.28*** | 0.88 ± 0.36** | 0.89 ± 0.27** | 0.55 ± 0.22*** | 0.55 ± 0.12*** |
| T-SH (m mole/ml) | 480.09 ± 233.72 | 315.11 ± 141.69*** | 367.88 ± 114.69** | 333.81 ± 123.51*** | 391.15 ± 109.63* | 259.90 ± 177.48*** | 274.79 ± 87.10** |

Values are mean ± SD of number of subjects as mentioned in parenthesis.
*p-value < 0.05; **p-value < 0.01; ***p-value < 0.001; Ψ p-value > 0.05
CML: chronic myeloied leukaemia; CP: chronic phase; AP: accelerated phase; TBARS: thiobarbituric acid reactive substances; LOOH: total lipid hydroperoxides; GSH: reduced glutathione; T-SH: total thiols

breast cancer, squamous cell carcinoma, colon cancer and various types of leukaemia.[2,6-12] Decreased levels of non-enzymatic antioxidant status in plasma have been found in various diseases including cancers.[4,7,13-15] To the best of our knowledge, there are no studies in the literature on the indices of oxidative stress as a response to different therapeutic agents. Therefore, the plasma levels of lipid peroxidation and non-enzymatic antioxidant status were prospectively studied as indices of oxidative stress, disease progression and early responses to different chemotherapeutic agents in chronic myeloid leukaemia patients.

## METHODS

There were 128 CML patients in this study and 50 age- and gender-matched healthy volunteers. The mean age of the patients was 36.76 ± 11.34 years, whereas the mean age of the healthy volunteers was 32.52 ± 5.66 years. 83 CML patients were offered the generic hydroxyurea, CYTODROX (Cipla Limited, Mumbai, India) treatment while 45 were given the (Generic Imatinib Mesylate, Cipla Limited, Mumbai, India) IMATIB, and they have been categorised as Group I and Group II, respectively. The decision about the choice of medication was dependent on affordability. The patients were followed up periodically for their response to the treatment and the side effects encountered. The standard haematological response criteria were used to assess the therapy.

Blood samples were taken from the patients and the healthy volunteers following an overnight fasting period in $K^2$ ethylenediaminetetraacetic acid (EDTA) vials. In this way, the possible influence of dietary factors on the level of free radicals was avoided. The plasma layer was separated by centrifugation at 3000 rpm per 15 minutes. The lipid peroxidation product (TBARS) in the plasma was evaluated using a slightly modified spectrophotometric (MultiScan, Thermo Electron Corporation, Waltham, MA, USA) method based on the reaction between malondialdehyde (MDA) and thiobarbituric acid (TBA).[16] Absorbance was measured spectrophotometrically at a wavelength of 532 nm with a molar extinction coefficient $\varepsilon\ 532 = 1.56 \times 10^5\ M^{-1}\ cm^{-1}$. The total LOOH level in plasma was evaluated using the ferrous oxidation in xylenol orange Fox-2 assay by the spectrophotometric method.[17] Non-enzymatic antioxidant status in the form of reduced GSH and T-SH was measured by using a 5,5'-dithiobis (2-nitrobenzoic acid) (DTNB) spectrophotometric method.[18,19] The plasma levels of TBARS and LOOH were expressed as n mole MDA/ml and mM/ml, respectively. Plasma GSH was expressed as μ mol/ml, while plasma T-SH was expressed as mM/ml.

The findings were expressed as the mean ± standard deviation. Statistical analyses were performed using the GraphPad InStat version 3.00 for Windows XP (GraphPad Software, San Diego, CA, USA). The differences were compared using an unpaired Student's *t*-test. A value of $p < 0.05$ was considered to be statistically significant.

## RESULTS

In Group I, the mean plasma TBARS and LOOH levels in CML, CML-chronic phase (CP) and CML-accelerated phase (AP) were significantly higher than in the healthy volunteers (Table I). The mean plasma TBARS and LOOH levels in those with no response (NR) and partial haematological response (PHR) were significantly higher than in those who had complete haematological response (CHR) (Table II). Furthermore, CML-CP patients who were converted into CML-AP had higher TBARS and LOOH levels than CML-CP patients who

**Table II. Plasma levels of lipid peroxidation products, non-enzymatic antioxidant status and haematological responses achieved in CML-CP patients during follow up.**

| | CHR | | PHR | | NR | |
|---|---|---|---|---|---|---|
| | Group I (n = 16) | Group II (n = 31) | Group I (n = 20) | Group II (n = 2) | Group I (n = 13) | Group II (n = 0) |
| TBARS (n mole MDA/ml) | 3.30 ± 0.84 | 3.18 ± 0.96 | 5.19 ± 1.52$^{*}$ | 5.17 ± 0.06$^{*}$ | 7.21 ± 3.75$^{***}$ | - |
| LOOH (m mole/ml) | 0.53 ± 0.26 | 0.40 ± 0.19 | 0.72 ± 0.38$^{\Psi}$ | 1.17 ± 0.75$^{***}$ | 0.94 ± 0.45$^{*}$ | - |
| GSH (µ mole/ml) | 0.99 ± 0.31 | 0.80 ± 0.30 | 0.70 ± 0.30$^{**}$ | 0.42 ± 0.10$^{\Psi}$ | 0.54 ± 0.34$^{**}$ | - |
| T-SH (m mole/ml) | 422.49 ± 222.96 | 349.67 ± 71.15 | 309.56 ± 109.8$^{*}$ | 288.41 ± 11.32$^{\Psi}$ | 225.65 ± 69.40$^{*}$ | - |

Values are mean ± SD of the number of subjects as mentioned in parentheses.
$^{\Psi}$ p-value > 0.05; $^{*}$p-value < 0.05; $^{**}$p-value < 0.01; $^{***}$p-value < 0.001.
TBARS: thiobarbituric acid reactive substances; LOOH: total lipid hydroperoxides; GSH: reduced glutathione; T-SH: total thiols; CHR: complete haematological response; PHR: partial haematological response; NR: no response

did not convert into CML-AP, whereas the plasma levels of TBARS and LOOH continued to rise significantly in those who later converted to CML-AP (Table III). In Group II, the mean plasma TBARS and LOOH levels in CML, CML-CP and CML-AP were significantly higher than those in the healthy volunteers (Table I). The mean plasma TBARS and LOOH levels in patients with PHR were significantly higher than in those who had CHR (Table II). CML-CP patients who did not progress to CML-AP exhibited small changes in their levels of plasma TBARS and LOOH during a follow-up period of 12 months (Table III).

In Group I, the non-enzymatic GSH and T-SH values in CML, CML-CP and CML-AP were significantly lower than in the healthy volunteers. (Table I) The mean plasma GSH and T-SH levels in NR and PHR were significantly lower than in those who had CHR (Table II). CML-CP patients who converted into CML-AP had lower mean plasma GSH and T-SH values than CML-CP patients who did not convert to CML-AP (Table III). In Group II, the plasma levels of GSH and T-SH in CML, CML-CP and CML-AP were significantly lower than in the healthy volunteers (Table I). The mean plasma GSH and T-SH levels in patients with PHR were not significantly lower than in those who had CHR (Table II). CML-CP patients who did not convert into CML-AP demonstrated a one-minute alteration in their plasma GSH and T-SH levels during the follow-up period of 12 months (Table III).

## DISCUSSION

Chronic myeloid leukaemia is the most common form of chronic leukaemia in India. The aetiology of CML is not well known, and of late, free radicals have been implicated in the pathogenesis of leukaemia.[11] It is therefore important to find new and reliable indices that would enable the early diagnosis and prognosis of this form of pathology.

In recent years, researchers have focused on the pathological role of free radicals in a variety of diseases, among which the most important ones are neurodegenerative diseases, aging and cancers.[2,3,20] High levels of oxidative stress result in the peroxidation of cell membrane lipids by generating lipid peroxides that can decompose into multiple mutagenic carbonyl products. TBARS and LOOH are well-characterised lipid peroxidation end products. They are considered to be mutagenic and carcinogenic.[21] They can also modulate the expression of genes that are related to tumour promotion.[22] The levels of TBARS and LOOH reflect the extent of lipid peroxidation.

In the present study, significantly increased lipid peroxidation, measured in terms of the plasma levels of TBARS and LOOH, were observed in patients with CML and its various phases (CML-CP and CML-AP) as compared with healthy volunteers. This could be attributed to the increased formation or inadequate clearance of free radicals by the cellular antioxidants. The present observations are in agreement with other reports on haematological malignancies, including various human cancers.[6,9,11,12,23,24]

Antioxidants have been shown to inhibit both the initiation and promotion in carcinogenesis as well as counteract cell immortalisation and transformation.[25] The actions of different antioxidants show different patterns during neoplastic transformation, and tumour, cancer or leukaemic cells exhibit abnormal activities of the antioxidant enzymes as well as the concentrations of non-enzymatic antioxidants, when compared with their appropriate normal cell counterparts.[8,26-28]

Cellular non-enzymatic antioxidants are also known as free radical scavengers that protect a cell against toxic

**Table III. Follow up plasma levels of lipid peroxidation products and non-enzymatic antioxidant status.**

| | Follow-up (months) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 | | 4th | | 8th | | 12th | |
| | Group I (n=49) | Group II (n=33) | Group I (n=49) | Group II (n=33) | Group I (n=49) | Group II (n=33) | Group I (n=49) | Group II (n=33) |
| TBARS (n mole MDA/ml) | | | | | | | | |
| CML-CP not progressed to CML-AP | 4.18 ± 2.64 | 4.03 ± 1.48 | 4.27 ± 2.19 | 3.29 ± 1.05 | 4.56 ± 2.64 | 3.94 ± 1.74 | 5.19 ± 2.51 | 3.76 ± 1.67 |
| CML-CP progressed to CML-AP | 6.39 ± 3.52$^{*}$ | - | 7.69 ± 3.13$^{***}$ | - | 8.51± 3.50$^{***}$ | - | 9.54 ± 4.18$^{***}$ | - |
| LOOH (m mole/ml) | | | | | | | | |
| CML-CP not progressed to CML-AP | 0.42 ± 0.27 | 0.52 ± 0.30 | 0.44 ± 0.21 | 0.45 ± 0.32 | 0.45 ± 0.19 | 0.42 ± 0.21 | 0.55 ± 0.25 | 0.43 ± 0.24 |
| CML-CP progressed to CML-AP | 0.65 ± 0.33$^{*}$ | - | 0.76 ± 0.35$^{**}$ | - | 0.79 ± 0.31$^{***}$ | - | 0.87 ± 0.41$^{**}$ | - |
| GSH (µ mole/ml) | | | | | | | | |
| CML-CP not progressed to CML-AP | 0.94 ± 0.36 | 0.80 ± 0.20 | 0.76 ± 0.33 | 0.78 ± 0.30 | 0.65 ± 0.31 | 0.66 ± 0.22 | 0.63 ± 0.29 | 0.69 ± 0.34 |
| CML-CP progressed to CML-AP | 0.68 ± 0.33$^{*}$ | - | 0.60 ± 0.24$^{\Psi}$ | - | 0.45 ± 0.18$^{*}$ | - | 0.28 ± 0.17$^{***}$ | - |
| T-SH (m mole/ml) | | | | | | | | |
| CML-CP not progressed to CML-AP | 358.66 ± 137.55 | 397.58 ± 112.40 | 349.94 ± 136.62 | 345.96 ± 70.50 | 325.18 ± 150.74 | 332.57 ± 62.53 | 326.74 ± 107.23 | 348.52 ± 94.94 |
| CML-CP progressed to CML-AP | 289.75 ± 124.57$^{\Psi}$ | - | 278.03 ± 109.76$^{\Psi}$ | - | 240.91 ± 109.33$^{\Psi}$ | - | 222.38 ± 113.95$^{\Psi}$ | - |

Values are mean ± SD of number of subjects as mentioned in parentheses.
$^{\Psi}$ p-value > 0.05; $^{*}$p-value < 0.05; $^{**}$p-value < 0.01; $^{***}$p-value < 0.001.
TBARS: thiobarbituric acid reactive substances; LOOH: total lipid hydroperoxides; GSH: reduced glutathione; T-SH: total thiols; CHR: complete haematological response; PHR: partial haematological response; NR: no response; SD: standard deviation

free radicals.[29] Reduced GSH is the chief constituent of the thiol pool and a vital intracellular scavenger of free radicals.[20,29] Therefore, decreased GSH levels may reflect a depletion of non-enzymatic antioxidant reserves.[29] On the other hand, total T-SH plays a prominent role in the antioxidant defense system, and in the reactions of catalysis, regulation, electron transportation and in preserving the correct structure of proteins.[22,30] Decreased levels of total T-SH have been reported in various pathophysiologies, including cancers.[8,31-33]

To the best of our knowledge, there is no available studies on plasma non-enzymatic antioxidants status in patients with leukaemia that is measured in the form of reduced GSH and total T-SH. In this study, a significant depletion of GSH and total T-SH was observed in patients with CML and its different phases (CML-CP, CML-AP) as compared with healthy volunteers. The low levels of plasma reduced GSH and T-SH in patients with CML, which provides some evidence that free radical generation in the haematopoietic cells is high compared to their normal counterparts.

The Ph chromosome is the hallmark of CML and produces a fusion protein, BCR-ABL. The resultant protein causes a perturbation of the stem cell function through an unclear mechanism that involves increased tyrosine kinase activity. It has been demonstrated that BCR-ABL is associated with increased levels of free radicals in the haematopoietic cell lines compared to their non-transformed parental cell lines. In addition, the levels of free radicals have been shown to increase with an increase in the level of activity of the tyrosine kinase protein, and both play an important physiological role in the signal transduction pathway as second messengers. In the CML stable phase, free radicals therefore have the potential to lead additional mutations that could contribute to the progression of CML.[34] Other studies have shown that the levels of lipid peroxidation increased continuously with disease progression and the aging process, whereas a defective non-enzymatic antioxidant defense system was found as the disease progressed.[8,9,11,13,14,19,20]

The authors believe that free radicals may play an important role in the pathophysiology of CML, and that

high levels of free radicals may cause oxidative stress in haematopoietic cells if the antioxidant defense system is not influential. Oxidative stress may occur in patients with CML due to the high number of mature and immature myeloid series cells as well as other unknown factors.

The chemotherapeutic treatment options for patients in the chronic phase of CML included conventional treatment with hydroxyurea and a contemporary, more effective treatment option with imatinib mesylate, a tyrosine kinase inhibitor. The responses to these therapeutic modalities were monitored in CML patients on the basis of clinico-haematological parameters, such as haematological responses and cytogenetic remission. This underlies the need to identify more early and reliable response biomarkers that reflect the intrinsic behaviour of CML neoplastic cells. To the best of our knowledge, there are no studies at present that focus on oxidative stress indices as response markers in CML.

In Group I of our study, hydroxyurea treatment did not show a marked reduction in the plasma levels of TBARS and LOOH as the disease progressed. On the other hand, the plasma levels of GSH and T-SH remained below the levels at diagnosis and did not show any increment with hydroxyurea treatment during the follow-up period. Hydroxyurea is an inhibitor of ribonucleotide reductase, which inhibits DNA synthesis. Thus, it does not interact with intrinsic proliferative factors such as, the BCR-ABL pathway, as well as other signal transduction pathways, even though some patients on hydroxyurea have achieved complete haematological remission. This validates its role as a cytotoxic drug, but it is unable to alter the natural course of the disease.

In Group II, imatinib mesylate caused a remission in all the parameters studied. Imatinib mesylate down-regulated the BCR-ABL proliferative pathway of CML and played an important role in achieving a survival advantage in CML because imatinib mesylate can change the natural course of CML.[35] Thus, these intrinsic biochemical parameters can predict the response to treatment modalities, but further studies are required in order to establish the precise role of free radicals in imatinib mesylate treatments and imatinib mesylate failure or resistance in CML.

Thus, it can be concluded that in CML patients, the plasma lipid peroxide levels and non-enzymatic antioxidant status may accurately reflect the magnitude of oxidative stress, proliferative signal transduction, disease phenotype, disease progression and the responses to chemotherapeutic modalities. It is suggested that these parameters may serve as biomarkers for oxidative stress, disease progression and responses to chemotherapeutic regimens in patients with CML. Further studies are required to confirm the precise role of oxidative stress in the pathobiology of CML and its responses to various tyrosine kinase inhibitors, including imatinib mesylate.

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