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Research Article

Assessment of Lipid Peroxidation and Micronutrients Level in Chronic Myeloid Leukemia Patients from Punjab Pakistan

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Abstract

Background: At the cellular level, Hematopoietic stem cells are the source of CML, and aberrant tyrosine kinase activity and clonal growth are caused by the BCR-ABL translocation. Antioxidant systems typically control the generation of ROS, but when they are dysregulated, disease progression occurs, underscoring their potential as therapeutic modulators.

Objective: To estimate the level of lipid peroxidation and micronutrients in chronic myeloid leukemia (CML) patients.

Methodology: Blood samples (5.0 ml) of 60 diagnosed chronic myeloid leukemia (CML) patients treated with tyrosine kinase inhibitors (TKI's) and blood samples (5.0 ml) of 50 healthy individuals as a control group was taken from vein in clotted gel vial from Oncology department, Mayo Hospital Lahore. Antioxidants, micronutrients, serum electrolytes and complete blood profile was examined.

Results: serum malondildehyde (MDA) level in CML patients was 4.32 ± 0.61mM while in healthy individuals, it was 0.75 ± 0.51mM which reveal that serum malondildehyde (MDA) level was elevated significantly ($p = 0.000$) in CML patients as compared to control group. vitamin A level in disease persons was 0.39 ± 0.06 µg/mL and in control group, it was 1.98 ± 0.29 µg/mL which point out that Vitamin A in disease persons was lower significantly ($p = 0.001$) as compared to control group. Serum vitamin C level in CML patients was 0.34 ± 0.28 µg/mL and in healthy individuals it was 1.50 ± 0.65 µg/mL.

Conclusion: Present study concluded that lipid peroxidation level increased in CML patients due to which serum MDA level was also increased while serum micronutrients level declined while oxidative stress level declined in patients treated with drugs.

Keywords: CML; Antioxidants; Imatinib; TKI's; Micronutrients

Introduction

The Philadelphia (Ph) chromosome, which arises from a reciprocal translocation among chromosomes 9 and 22, causes the BCR-ABL fusion gene to form, and is a characteristic of chronic myeloid leukemia (CML), a persistent myelo-proliferative neoplasm [1]. A chimeric protein with constitutive tyrosine kinase activity, p210, is encoded by the BCR-ABL oncogene. This abnormal kinase promotes unchecked proliferation, leukemogenesis, and the advancement of illness by activating many signaling pathways, such as JAK/STAT, MAPK, PI3K, and Hedgehog [2,3]. Additionally, BCR-ABL signaling contributes to genomic instability and the progression of illness by inducing reactive oxygen species (ROS) via the PI3K/mTOR and PI3K/AKT routes. From a clinical perspective CML develops in three stages: blastic, rapid, and chronic. Tyrosine kinase inhibitors (TKIs), which have transformed patient outcomes, constitute the foundation of the present standard of care. Oxidative stress is a key factor in the pathways underlying BCR-ABL kinase mutations, gene amplification, and other genetic changes that lead to resistance to TKIs, which continues to be a significant clinical issue [4,5]. The significance of assessing ROS levels in CML patients and its consequences for treatment response are highlighted by this context [6].

The Philadelphia chromosome, t(9;22)(q34;q11), is the molecular hallmark of CML and is found in about 95% of CML patients as well as a subset of other leukemias, such as adult acute lymphoblastic leukemia (ALL) and infrequent cases of acute myeloid leukemia. An 8.5 kb mRNA encoding the 210 kDa fusion protein (p210 BCR-ABL) is produced when the translocation combines the 5′ segment of the BCR gene on chromosome 22 with the 3′ segment of the ABL gene on chromosome 9. Though variations like p190 and p230 have been reported and are linked to certain hematologic characteristics, such as monocytosis and neutrophilia, respectively, the majority of CML cases express either b2a2 or b3a2 transcripts [7]. The human illness phenotype is replicated in vitro and in animal models by the BCR-ABL fusion protein, which confers growth factor independence and leukemogenic conversion.

According to epidemiology, CML makes up 15% of adult leukemias, with a typical age of onset of 45 to 55 years and an annual incidence of 1-2 cases per 100,000 people [4]. Nonspecific indications like weight loss, exhaustion, bleeding, splenomegaly, and test results showing leukocytosis, anemia, and thrombocytosis are frequently seen in patients. Without adequate therapy, CML usually develops into an accelerated phase, a chronic phase, and finally a blastic disaster, which is similar to acute leukemia. Both lymphoid and myeloid phenotypes of blastic transformation are possible, and the lymphoid subtype's response to treatment frequently resembles that of ALL [7].

At the cellular level, Hematopoietic stem cells are the source of CML, and aberrant tyrosine kinase activity and clonal growth are caused by the BCR-ABL translocation. Molecular testing for BCR-ABL transcripts is required since approximately 5% of cases lack identifiable Ph chromosomes, even though the diagnosis is typically simple based on blood counts and cytogenetics. Worldwide, the polymerase chain reaction (PCR) is the gold standard for tracking therapy response and is the most sensitive technique for identifying residual disease [8].

Indirect indicators of ROS burden include biomarkers like oxidized proteins and lipid peroxidation products (such malondialdehyde). Both TKI resistance and CML pathogenesis have been linked to high levels of oxidative stress. Antioxidant systems typically control the generation of ROS, but when they are dysregulated, disease progression occurs, underscoring their potential as therapeutic modulators.

Allogeneic stem cell transplantation (SCT) and interferon-α have historically been used to treat CML. A subgroup of patients experienced significant cytogenetic responses from interferon therapy, and some of them experienced long-lasting remissions, especially when paired with cytarabine [9]. Even though SCT has dangers including graft-versus-host disease, it is still a potentially curative treatment, particularly for younger patients with HLA-matched donors. Better donor matching and lower-intensity training regimens improved results over time, improving tolerability while preserving the effects of graft-versus-leukemia [10].

The treatment of CML was completely changed by the introduction of imatinib mesylate, a specific BCR-ABL tyrosine kinase inhibitor. In randomized trials, imatinib outperformed interferon-based regimens, exhibiting high rates of hematologic and cytogenetic responses, long-lasting remissions, and a favorable safety profile [11]. Higher dosages may produce deeper and quicker molecular responses, according to dose-escalation studies [12]. Imatinib resistance persists despite these developments, especially in more advanced stages of the disease. BCR-ABL amplification, kinase domain mutations, and pharmacokinetic variability are examples of

resistance mechanisms. As a result, current initiatives concentrate on tackling ROS-mediated mechanisms of resistance, investigating second- and third-generation TKIs, and optimizing dosage [13].

Methodology

Place of work

The whole experimental work was done in the Biochemistry Lab, School of Biochemistry and medical Lab Technology, Faculty of Allied Health Sciences, Minhaj University Lahore.

Blood/data collection

Blood samples (5.0 ml) of 60 diagnosed chronic myeloid leukemia (CML) patients treated with tyrosine kinase inhibitors (TKI's) and blood samples (5.0 ml) of 50 healthy individuals as a control group was taken from vein in clotted gel vial from Oncology department, Mayo Hospital Lahore. Blood was further process for the estimation of Complete Blood Count (CBC) by hematology analyzer, Reduced Glutathione (GSH) [14], Catalase (CAT) [14], Superoxide Dismutase (SOD) [1], Malondialdehyde (MDA) [15] Estimation of Nitric oxide (NO) [1], Estimation of micronutrients (Vitamin A, Vitamin C and Vitamin E) [16] and Electrolytes concentration by flame photometer (Na^+, K^+, Cl^-).

Serum separation

Blood sample was centrifuged at 4000 rpm for 10 minutes and serum was separated. The serum was preserved at -20°C till further analysis.

Results

Descriptive statistics of age in both genders in CML patients

The results in Table 1 shows the clear picture of demographic data (age) of CML patients. There were total sixty (60) patients of CML. Data were collected from both genders. The mean age of the male participants was 37.69 ± 11.81 years where as female participants was 32.54 ± 6.73 years. The minimum age of males was 25 years and the maximum age of males was 65 years. In case of female, the minimum age was 20 years and the maximum age was 60 years.

Table 1: Descriptive statistics of age in both genders in CML patients*.

Variable	Gender	n	Minimum	Maximum	Mean ± S.D
Age	Male	38	25.00	65.00	37.69 ± 11.81
	Female	22	20.00	60.00	32.54 ± 6.73

*n = no. of observation, ± S.D = standard deviation.

Determination of gender frequency in CML patients

Table 2 depicted that out of 110 participants, 50 (100 %) individuals were taken as healthy or control while 60 (100 %) individuals were diagnosed CML patients. Out of 50 healthy individuals, 30 (60 %) were males and 20 (40 %) were females. Same as 60 CML patients, 38 (66 %) were males and 22 (34 %) were females. Data presented in table 3 demonstrated the mean value and comparison of BCR-ABL percentage level and antioxidant status among CML patients and healthy individuls. Table 3 showed that binding cluster region-abelson (BCR-ABL) percentage in CML patients was 85.76 ± 12.32 and in control group it was 21.93 ± 9.24 which shows that level of BCR-ABL was elevated significantly (p = 0.000) in CML patients rather than control group.

Table 2: Determination of gender frequency in CML patients*.

Variables		Frequency (Control)	Frequency (patients)	Total	p-value
Gender	Male	30 (60 %)	38 (66 %)	66	0.00
	Female	20 (40 %)	22 (34 %)	34	
	Total	50 (100 %)	60 (100 %)	100	

*Level of significance = $p \leq 0.05$.

Table 3: Determination and comparison of BCR-ABL percentage level and Antioxidant status in CML patients with healthy individuals.

Variables	Control (n = 50)	Patients (n = 60)	p-value
BCR-ABL (%)	21.93 ± 9.24	85.76 ± 12.32	0.000
MDA (mM)	0.75 ± 0.51	4.32 ± 0.61	0.000
GSH (mg/dL)	6.8 ± 1.52	0.59 ± 0.16	0.000
Catalase (mM)	1.35 ± 0.71	2.49 ± 0.35	0.001
SOD (µM/mL)	0.96 ± 0.11	5.84 ± 0.51	0.005
NO (µM/L)	3.47 ± 2.37	8.9 ± 0.76	0.000
AGE's (U/mL)	1.71 ± 0.04	2.71 ± 0.26	0.000
AOPP (ng/mL)	0.73 ± 0.11	3.95 ± 0.77	0.000
Malondialdehyde $CH_2(CH_2O)$ (MDA) = Normal Range = 1.0-3.0 mM/mL. Glutathione C10H17N3O6S (GSH) = Normal Range = 8.0-12.0 mg/dL. Catalase = Normal Range = 1.0-5.0 mM. Superoxide dismutase NaO_3P (SOD) = Normal Range = 0.1-0.6 mM/mL. Level of significance = $p \leq 0.05$; n = no. of observation			

Table 3 predicted that serum malondildehyde (MDA) level in CML patients was 4.32 ± 0.61mM while in healthy individuals, it was 0.75 ± 0.51mM which reveal that serum malondildehyde (MDA) level was elevated significantly (p = 0.000) in CML patients as compared to control group. serum glutathione (GSH) level in CML patients was 0.59 ± 0.16 mg/dL whereas in healthy persons it was 6.8 ± 1.52 mg/dL which showed that serum glutathione (GSH) level was raised significantly (p = 0.000) in CML patients as compared to healthy group. The results showed that the serum catalase level in chronic myeloid leukemia patients was 2.49 ± 0.35 mM while in control group it was 1.35 ± 0.71 mM which represent that serum catalase level was higher in CML patients in contrast to healthy group significantly (p = 0.001). Results showed that serum superoxide dismutase (SOD) level in CML patients was determined as 5.84 ± 0.51 mM and in control group; it was 0.96 ± 0.11mM. Hence serum superoxide dismutase (SOD) level was increased significantly (p = 0.005) in CML patients as compared to healthy individuals. Serum nitric oxide (NO) level in CML individuals was determined as 8.9 ± 0.76 µM/L and in healthy group it was 3.47 ± 2.37 µM/L. Results indicated that serum nitric oxide (NO) level was significantly (p = 0.000) increased in CML patients as compared to control. serum advance glycation end products (AGE's) level in CML patients was determined as 2.71 ± 0.26 U/mL and in control group was 1.71 ± 0.04 U/mL which represent that serum advance glycation end products (AGE's) level was significantly (p = 0.000) higher in CML patients as compared to control group. serum advance oxidation protein product (AOPP) level in patients of CML was 3.95 ± 0.77 ng/mL and in healthy individuals, it was 0.73 ± 0.11 ng/mL which reveal that serum advance oxidation protein product (AOPP) level patients of CML was significantly (p = 0.000) higher than healthy individuals. The results existed in table 4 reveals the level of micronutrients (Vitamin A, C & E). Table 4 showed that vitamin A level in disease persons was 0.39 ± 0.06 µg/mL and in control group, it was 1.98 ± 0.29 µg/mL which point out that Vitamin A in disease persons was lower significantly (p = 0.001) as compared to control group. Serum vitamin C level in CML patients was 0.34 ± 0.28 µg/mL and in healthy individuals it was 1.50 ± 0.65 µg/mL (Table 4). Results showed that vitamin C level was dropped significantly (p = 0.001) in CML patients than healthy individuals. serum tocopherol (Vit.E) level in disease persons was 1.34 ± 0.57 µg/mL and in control group was 5.61 ± 1.13 µg/mL which reveal that vitamin E level in disease persons was decreased significantly (p = 0.000) as compared to control group (Table 4).

Table 5 demonstrated the serum electrolytes level in CML patients and comparison with normal persons. Serum Potassium (K^+) level in CML patients was 3.20 ± 0.33 mM/L and in control group, it was 3.96 ± 0.57mM/L (Table 5). Which shows that serum Potassium (K^+) level in CML patients was lowered non – significantly (p = 0.1) than control group. serum sodium (Na^+) level in CML patients was 137.22 ± 2.24 mM/L and in healthy individuals, it was 142.72 ± 4.87 mM/L which reveal that serum sodium (Na^+) level in patients was decreased non-significantly (p = 0.000) in contrast to

Table 4: Determination and comparison of Micronutrients status in CML patients with healthy individuals.

Variables	Control (n = 50)	Patients (n = 60)	p-value
Vitamin A or Ratinol (**µg**/mL)	1.98 ± 0.29	0.39 ± 0.06	0.001
Vitamin C or Ascorbic acid (**µg/mL**)	1.50 ± 0.65	0.34 ± 0.28	0.001
Vitamin E or tocopherols (**µg/mL**)	5.61 ± 1.13	1.34 ± 0.57	0.000
Level of significance = p ≤ 0.05; n = no. of observation			

Table 5: Determination and comparison of serum Electrolytes status in CML patients with healthy individuals.

Variables	Control (n = 50)	Patients (n = 60)	p-value
K^+ (mM/L)	3.96 ± 0.57	3.20 ± 0.33	0.361
Na^+ (mM/L)	142.72 ± 4.87	137.22 ± 2.24	0.011
Cl^- (mM/L)	109.84 ± 1.29	102.52 ± 1.01	0.182
Potassium Normal Range = 3.5-5.4 mM/L. Sodium Normal Range = 135-155 mM/L. Chloride Normal Range = 102-109 mM/L. Level of significance = p ≤ 0.05; n = no. of observation			

healthy individuals. Serum chloride (Cl^-) level in CML individuals was 102.52 ± 1.01 mM/L and in healthy group it was 109.84 ± 1.29 mM/L which reveals that serum chloride (Cl^-) level, was dropped in CML individuals non-significantly (p = 0.01) than healthy group (Table 5).

Table 6 revealed the picture of complete blood count (CBC) level in CML patients and also compared with the healthy persons. Level of heamoglobin in disease persons was 10.64 ± 1.96 g/dL and it was in healthy individual's 14.64 ± 1.21 g/dL (Table 5). Which indicated that level of haemoglobin in disease persons was lowered significantly (p = 0.000) than healthy individuals. Red blood cells in CML patients was 3.18 ± 0.89 and in healthy group it was 5.61 ± 0.98 which reveal that RBC's in CML patients was dropped significantly (p = 0.000) as compared to healthy group. platelets in chronic myeloid leukemia was 279.38 ± 64.42 and it was 165.76 ± 12.69 in control group which expose that platelets higher in CML patients significantly than control group. White blood cells in chronic myeloid leukemia patients was 74.92 ± 6.63 and in healthy group it was 11.28 ± 2.31 which indicated that WBC's highly raised in chronic myeloid leukemia patients significantly (p = 0.001) as compared to healthy group. Neutrophils in disease persons was 56.36 ± 11.25 and in healthy individuals it was 13.02 ± 4.21 which indicated that neutrophils significantly (p = 0.000) greater in disease persons than healthy individuals. Lymphocytes in disease persons were 34.48 ± 7.42 and in healthy group it was 13.68 ± 5.97. Calculations show that lymphocytes in disease persons increased significantly (p = 0.000) as compared to healthy group. Eosinophils in CML patients was 2.26 ± 0.68 and in control group it was 0.92 ± 0.04 which demonstrations that eosinophils higher significantly (p = 0.000) in CML patients than in control group. Monocytes in patients were 5.68 ± 1.09 and in healthy individuals it was 5.57 ± 1.21. Results revealed that monocytes in patients was significantly (p = 0.000) greater than healthy individuals. Basophils in disease persons was 1.54 ± 0.36 and in control individuals it was 0.51 ± 0.21 which exposed that basophils in disease persons was high significantly (p = 0.000) than control individuals (Table 6).

Table 6: Determination and comparison of Complete Blood Count (CBC) status in CML patients with healthy individuals.

Variables	Control (n = 50)	Patients (n = 60)	p-value
Heamoglobin (g/dL)	14.64 ± 1.21	10.64 ± 1.96	0.000
RBCs $(\times 10)^6$/uL	5.61 ± 0.98	3.18 ± 0.89	0.000
Platelets $(\times 10)^3$/uL	165.76 ± 12.69	279.38 ± 64.42	0.000
WBCs $(\times 10)^3$/uL	11.28 ± 2.31	74.92 ± 6.63	0.001
Neutrophils (%)	13.02 ± 4.21	56.36 ± 11.25	0.000
Lymphocytes (%)	13.68 ± 5.97	34.48 ± 7.42	0.000
Eosinophils (%)	0.92 ± 0.04	2.26 ± 0.68	0.000
Monocytes (%)	5.57 ± 1.21	5.68 ± 1.09	0.000
Basophils (%)	0.51 ± 0.21	1.54 ± 0.36	0.000

Discussion

A main remedial innovation shows tyrosine kinase inhibitors adenosine triphosphate competitive TKI's in CML disease persons and optimum responders have close to existence probability. In experimental repetition, suggestions are continue for lifetime cure, achieved in disease persons with so called MUD (molecular undetectable disease) more than ten years ago that challenged for long time the perception that tyrosine kinase inhibitors may not stationary. Tyrosine kinase inhibitors interruption may be estimated prospectively [17].It was described that imatinib, nilotinib and dasatinib may be clogged in disease persons had DMR's (deep molecular responses) for long time. Deep molecular responses score of assessable RT-qPCR (reverse transcriptase polymerase chain reaction) sensitivity known as MR4, MR4.5, and MR5 (molecular response) [18].

Recently diagnosed chronic myeloid leukemia patients in chronic phase with positive philadelphia chromosomes have initial cure of imatinib, dasatinib, nilotinib and bosutinib drugs. After usage of interferon alpha treatment, imatinib is also successful for the treatment of chronic myeloid leukemia patients of positive Philadelphia chromosomes in acute phase or chronic phase. Imatinib, dasatinib, bosutinib, ponatinib are selected as first-line treatment for chronic myeloid leukemia patients with positive Philadelphia chromosomes in chronic or acute phase. The chronic myeloid leukemia patients of chronic phase that are resistant to first line treatment shows nilotinib best results. Now, there are many choices of bcr-abl1 tyrosine kinase inhibitors presented for chronic myeloid leukemia patients as prior treatment reliant on clinical and patient aspects. In Western countries, the recently detected CML (chronic myeloid leukemia) patients in chronic phase with positive Ph-chromosomes have existence probability nearer to age compliment of characters in overall inhabitants [19].

Sometimes, reproductive side effects are noted before clinical treatment in animal studies included from rats and rabbits. 400 mg dose capacity of bosutinib require daily for cure CP, AP, AB State of chronic myeloid leukemia. Imatinib sales out by Novartis as Gleevec and it is also recommended as STI-571 which is phosphorylase suppressor designed chemically 4-N-2-benzamide methane sulforate. The mode of action of imatinib drug in chronic myeloid leukemia is 2-phenyl aminopyrimidine that perform unique inhibition function of tyrosine kinase. According to mechanism, this compound sound with active site of tyrosine kinase inhibitors that result to slow down its activity. A lot of tyrosine kinase enzymes present in our body, for example insulin receptors. The imatinib is only used for tyrosine kinase domain in BCR-ABL, and in platelet-derived growth factor [20].This drug also used to slow down the BCR-ABL function. The TKI active site is responsible to binding with energy currency Adenosine Triphosphate.

This process, enzymaticactivity suppresses the function of Imatinib. In CML the treatment with imatinib is go through ITRR, introduced on 01 Jan, 2020 inside nucleus. It is the site where it does not perform their normal function against the apoptosis [21].Ahmed., *et al*. [22] demonstrated that serum MDA level was elevated (4.22 ± 2.11) in chronic myeloid leukemia patients as compared to control subject (2.63 ± 0.62) significantly [23]. Malonedaldelyde is the end product of (Lipid peroxidation) MDA also regulated the gene aspects related to neoplasm contents. The serum MDA level consider as the measurement of lipid peroxidation. It was hypothesized that higher level of lipid peroxidation may cause malignancy or these malignant cells originate a large amount of reactive oxygen species activity [24]. In present study, serum level of MDA is higher in CML patients than healthy volunteers. The mean serum GSH level was significantly dissimilar to control one. In this study, due to increase of reactive oxygen species in hematopoitic cells. In hematopoietic cells, the serum GSH level was decreased. In leukemia patients, decrease level of GSH (0.79 ± 0.30) as compared to control subjects (1.25 ± 0.54). In present study, the serum GSH level decreases in CML patients than healthy group and shows highly significant statistically. A major biological function of glutathione is operating as non-enzymatic reducing promoter. On the top of protein GSH support to retain cysteine thiol as a reduced position. GSH play an important role in the formation and destruction of DNA. GSH assists as a reducing agent in oxidation reaction resultant reacted GSH; in that way decreased GSH levels may reproduce exhaustion of non-enzymatic antioxidant standby [24].Rasool., *et al*. described that elevated serum CATALASE level (4.07 ± 0.84) was observed than healthy volunteers (0.73 ± 0.67*) significantly. It was proposed that CAT is usually found in tissues in small quantity. The aggregation of ROS increases and the antioxidant level must be decreases. The antioxidant enzyme level like CAT is decrease in lymphocytes of chronic myeloid leukemia patients as compare to healthy subjects. In present study, the serum CAT level is highly elevated in CML patients than healthy individuals, which is significant statistically. Galuat., *et al*. evaluated that the serum NO level was elevated in chronic myeloid leukemia patients (42.43 ± 5.79 mmol/liter) as compared to healthy volunteers (14.26 ± 2.76 mmol/liter). Serum NO level decreases by using imatinib and statistically significant. After ima-

tinib therapy, a significant decrease was observed in serum level of NO in chronic myeloid leukemia patients. In present study the serum NO level increased in CML patients as compared to healthy volunteers and statistically significant. Kuan and Michael, 2018 described that the mean serum SOD level were elevated (16.99 ± 7.61**) in chronic myeloid leukemia patients as compared to control group (11.69 ± 4.34), which was statistically significant. SOD is a higher cellular defense mechanism against superoxides in the cells. The serum SOD level may be exalted due to change in gene aspects in hematopoietic cells. In present study, the mean serum SOD level increases in leukemia patients than control subjects which is statistically significant [25].

Conclusion

Present study concluded that lipid peroxidation level increased in CML patients due to which serum MDA level was also increased while serum micronutrients level declined while oxidative stress level declined in patients treated with drugs. Further studies are required to investigate the genetic behavior of the genes involved in the progression of chronic myeloid leukemia (CML).

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