Original Article

Assessment of Thyroid Function Test Among Sudanese Patients with Chronic Myeloid Leukemia

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Abstract

Background: Chronic myelogenous leukemia (CML) is a prevalent hematological malignancy with many impacts on the body, including the potential for causing thyroid dysfunction. Previous research has shown that CML patients might develop thyroid dysfunction. **Objectives:** This study aims to assess thyroid hormone levels in CML patients. **Material and Methods:** In this cross-sectional study, 87 serum samples, obtained from 42 cases (who were diagnosed using the BCR-ABL mutation discovered by polymerase chain reaction molecular analysis and assessment of bone marrow and peripheral blood morphology) and 45 controls, were tested for thyroid hormone levels by using the enzyme-linked immunosorbent assay (ELISA) technique in Khartoum, Sudan, from September to December 2019. **Results:** Compared to the control group, CML patients had a significant increase in TSH (P value = 0.00) and no insignificant changes in T3 and T4 levels (P value > 0.05).When comparing the duration of disease across study cases, significant differences with a weak negative correlation for T3 (P value = 0.037) and T4 (P value = 0.007), but insignificant differences with a negative correlation for TSH (P value = 0.228) were observed. **Conclusion:** The study concluded that incidence of CML could have affected TSH levels in patients and should be evaluated routinely (3 to 6 months) throughout the duration of their follow-up. The patient's age, gender, medication, or stage of the disease do not affect the results of the thyroid function test.

Keywords: Chronic myeloid leukemia, Sudan, thyroid function test, tyrosine kinase inhibitors

Introduction

Chronic myelogenous leukemia is a malignant disorder that causes excessive proliferation and accumulation of abnormal white blood cells in the blood, bone marrow, and other organs.[1-4] The most prevalent risk factors include radiation exposure, cigarette smoking, and benzene exposure.[5-7] Men are more likely than women to have CML, and the average age of diagnosis differs by up to 65 years as observed in cancer registries of low- and middle-income countries from the end of the 1930s.[8,9] According to the European Treatment Outcome Study (EUTOS) registries, the median age of CML diagnosis in Western countries is between 56 and 57.[10] Chronic myeloid leukemia is the common leukemia in Sudan.[11] Pathogenesis of CML begins with a mutual translocation of the ABL and BCR genes from chromosomes 9 and 22, respectively, resulting in a truncated chromosome 22, the Philadelphia chromosome (Ph).[12,13] Tyrosine kinase inhibitors (TKIs) inhibit (turning off) the tyrosine kinase generated by the BCR-ABL1 gene in leukemia cells. TKIs significantly improve prognosis in CML patients.[14] Imatinib was the first and most extensively developed TKI for treating chronic myeloid leukemia (CML) and has evolved considerably since its discovery.[15-18] TKIs can cause thyroid disorders such as hypothyroidism and, less frequently, hyperthyroidism. However, the exact mechanism by which TKIs cause thyroid dysfunction is elusive and not thoroughly

Access this article online

Quick Response Code:

Website: https://journals.lww.com/mjby

DOI: 10.4103/MJBL.MJBL_1687_23

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Submission: 14-Nov-2023 **Accepted:** 15-May-2024 **Published:** 30-Sep-2025

How to cite this article: Ali MA, Elzein HO. Assessment of thyroid function test among sudanese patients with chronic myeloid leukemia. Med J Babylon 2025;22:844-7.

explained.[19,20] However, certain studies have suggested that TKIs can cause hypothyroidism through drug-induced thyroiditis, atrophy, obstruction of thyroidal iodine absorption, and decreased thyroid hormone production.[21-23] Thyroid function tests show multiple significant changes, according to Singha's research; subclinical hypothyroidism affects approximately 10% of the patients.[24] Thyroid diseases, such as thyrotoxicosis, hyperthyroidism, and hypothyroidism, can be a significant trigger for cancer; many studies propose that autoimmune and inflammation are risk factors for thyroid cancer.[25,26]

This study aims to assess thyroid hormone levels in CML patients for improving patient management by supporting oncologists in early diagnosis and therapy optimization.

Materials and Methods

This cross-sectional research was conducted in Khartoum state, Sudan, between September and December 2019. The study included 42 known patients with chronic myeloid leukemia who were diagnosed using the BCR-ABL mutation discovered by polymerase chain reaction molecular analysis and assessment of bone marrow and peripheral blood morphology) and 45 healthy controls.

The sample size required 80% statistical power to detect a 5% difference at $P = 0.05$. All the individuals come from similar socioeconomic backgrounds. Based on their medical history, males and females between the ages of 20 and 60 diagnosed with chronic myeloid leukemia were included in this study. The study excluded participants who had a history of thyroid disease or were currently receiving medication for thyroid dysfunction organ failure, undergoing radiation therapy, pregnancy, concurrent usage of oral contraceptive pills, or were on corticosteroids.

Statistical analysis

The SPSS software for Windows (version 16) was used for all statistical analyses. The data were shown as mean ± S.D. Tables and figures were used to express the results. We used a *t* test to compare the two groups. The results were expressed using tables and figures. Statistical significance was defined as P-value less than 0.05.

Ethical approval

After explaining the study's objectives to each participant, informed consent was acquired, and the Alzaiem Alazhari University Ethics Committee approved the study number MLEC/3609 on 22 August 22 2019. A structured questionnaire collected information of their medical history, sociodemographics, and clinical features.

After signing an informed consent form, 5 mL of blood was drawn from all the participants into a plain vacutainer container under septic conditions. All blood samples were centrifuged at 4000 rpm for 5 minutes after being allowed to clot at room temperature to obtain serum samples and then stored at –30 °C until the TSH, T3, and T4 tests were performed using the solid-phase sandwich enzyme-linked immunoassay (ELISA) method according to the manufacturer's guidelines (Fortress Diagnostics Ltd, Unit 9A, the Technology Park, Belfast Road, Co. Antrim, N Ireland, BT41 1QS); the normal range for TSH was 0.39–6.16 μIU/mL), T3: (0.6–1.85 ng/mL), and T4: (0.5–13.0 μg/dL).

Results

Table 1 illustrates the statistical significance of the mean ±SD of TSH (3.089 ± 2.3, P value > 0.00) and insignificant (P value > 0.05) findings for T3 and T4 in the case group (1.21 ± .28; 6.79 ± 1.46), respectively, compared with the control group (TSH was 1.25 ± .83, T3 = 1.93 ± .84, and 8.25 ± 3.26 for T4). The age distribution of the case group was 17 (40.1%) for those over 40 years of age and 25 (59.9%) for those between the ages of 21 and 40. The mean age is (38.33 ± 11). Table 2 demonstrates insignificant differences among the various age groups with a weak negative correlation for T3 and a positive correlation for T4 and TSH (P value = 0.44, 0.53, and 0.76). Table 2 also shows there are significant differences with a weak negative correlation for T3 (P value = 0.037) and T4 (P value = 0.007) and insignificant differences with a negative correlation for TSH (P value = 0.228) when compared with the duration of disease among study cases. The study included 22 (52%) men and 20 (48%) women. The mean ±SD of TSH, T3, and T4 in men was 2.80 ± 1.76, 1.8 ± 0.57, and 8.13 ± 3.11, respectively, compared to the mean ± SD in women (3.4 ± 2.84, 2.06 ± 1.07, and 8.4 ± 3.5, respectively). The results were insignificant, with P value of 0.4009, 0.352, and 0.813, respectively. It was reported that 35 patients (83%) and seven patients (17%), respectively, took Glivec (imatinib) and hydroxyurea as part of their disease treatment. Figure 1 displays the mean ±SD of TSH, T3, and T4 for patients who took Glivec (2.9 ± 2.4, 1.9 ± 0.9, and 8.2 ± 3.2) and hydroxyurea (3.6 ± 1.3, 1.96 ± 0.5, and 8.5 ± 4), and the results were statistically insignificant (P value = 0.517,

Table 1: Statistics and mean differences of T3, T4, and TSH and age

Variable	Patients (n = 84)	Control (n = 45)	*P* value
T3	1.21 ± .28	1.93 ± .84	0.05
T4	6.79 ± 1.46	8.25 ± 3.26	0.05<
TSH	3.09 ± 2.3	1.25 ± .83	0.000

Table 2: Correlation of age and duration with T3, T4, and TSH

		T3	T4	TSH
Age (year)	R	–.122	.099	.048
	P value	0.44	0.53	0.76
Duration	R	**-.323**	**-.408**	-.190
	P value	**.037**	**.007**	.228

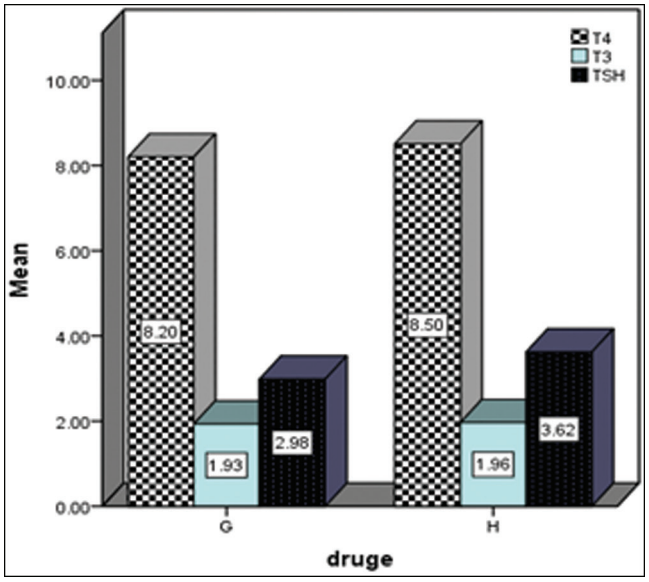

Figure 1: Mean differences of T3, T4, and TSH among drug groups

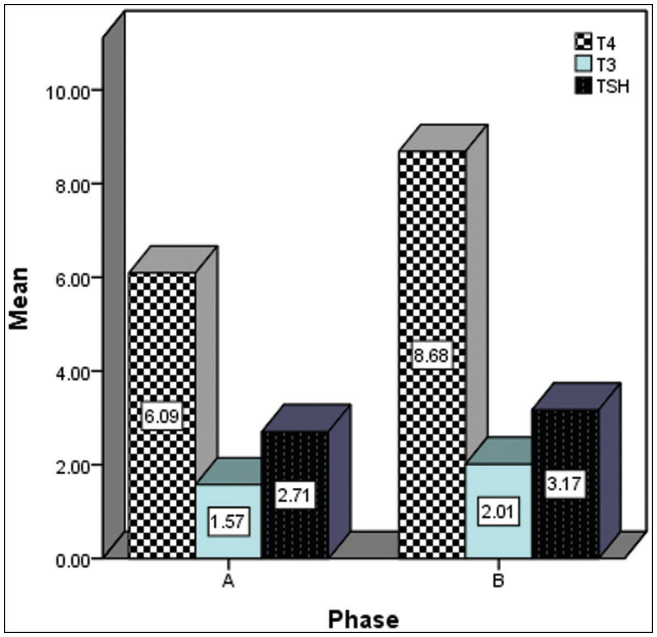

Figure 2: Mean of T3, T4, and TSH among phase groups. Phase A = accelerated phase. Phase B = chronic phase

0.928, and 0.826, respectively. According to the disease phase, there was a high incidence in 35 patients (or 83%) in the chronic phase and seven patients (17%) in the accelerated phase. The mean ±SD of TSH, T3, and T4 in patients in the accelerated phase were, respectively, 2.71 ± 1.59, 1.57 ± 0.53, and 6.09 ± 2.7, when compared to patients in the chronic phase (3.17 ± 2.47, 2.01 ± 0.88, and 8.68 ± 3.2) respectively. The results were statistically insignificant (*P* value <0.05), as shown in Figure 2.

Discussion

This study examined thyroid hormone levels in patients with chronic myeloid leukemia, revealing a significant increase in TSH hormone (*P* value = 0.00) compared to the control group. The results can signify subclinical hypothyroidism after 6 months, as shown in the studies by Malhotra *et al*. and Allahyari *et al*.,[27,28] which revealed that TSH levels increased considerably from the baseline (3.20 ± 0.978) after 6 months of medication. Moreover, there were insignificant results (T3 and T4) (*P* value > 0.05) compared to the control group. Thyroid dysfunction in patients with CML, which is most likely the outcome of metabolic syndrome, may be caused by endothelial dysfunction or damage. These substances most likely affect tyrosine kinases associated with vascular function, namely, VEGFR (vascular endothelial growth factor receptor); transient reduction in blood flow may occur more gradually, leading to steady degradation in thyroid levels, leading to hypothyroidism. The current study showed insignificant correlations (*P* value 0.44, 0.53, and 0.76), respectively, with the ages of the study patients. The T3, T4, and TSH levels have been tested, and their corresponding *P* value are 0.44, 0.53, and 0.76, respectively. However, there was an insignificant correlation for TSH (*P* value = 0.228) and a significant correlation for T3 and T4 (*P* value = 0.037 and 0.007) concerning the duration of the patient's disease. Thus, thyroid hormone levels appeared to have low impact on the patient's characteristics. They were, however, contrasting the length of disease of the study's subjects. When comparing the results with the gender, all *P* values (0.4009, 0.352, and 0.813, respectively) were >0.05 (insignificant). On the other hand, the results of evaluation of T3, T4, and TSH levels with the intake of both drugs hydroxyurea and imatinib Glivec were statistically insignificant (*P* value = 0.517, 0.928, and 0.826), respectively; these findings are consistent with those of Dora *et al*.[29] and disagree with the findings of the investigations by De Groot *et al*.[30] and Kim *et al*.[31] This study showed that T3, T4, and TSH levels were

statistically insignificant compared to those in accelerated and chronic phases of CML, with *P* value of 0.64, 0.214, and 0.054, >0.05, respectively. The small sample size and need for future investigation are limitations in the current study. Further research should be conducted using highly sophisticated techniques, instruments, and other parameters such as thrombopoietin TPO, Free T3, Free T4, and calcitonin.

Conclusion

The study results reveal that thyroid-stimulating hormone levels (TSH) were altered significantly in CML patients compared to the control group. However, other tests (T3 and T4) showed insignificant changes. Furthermore, the patient's age, gender, medication, or stage of the disease do not affect the thyroid function test (TFT); however, the duration of the disease has a strong correlation with thyroid hormone levels.

Acknowledgments

The authors extend their appreciation to all individuals involved in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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