Evaluating the relationship of serotonin and ferritin levels with (P53) gene expression in Beta thalassemia patients

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Abstract
Objective:Beta thalassemia is an inherited blood disorder that affects the synthesis of the beta chain of hemoglobin, resulting in production of deficient RBCs. Iraq is among the countries where this disorder is prevalent. Beta thalassemia patients need frequent transfusions of healthy blood throughout life in order to mitigate the symptoms and can suffer from iron overload complications as a result . Serotonin is a neurotransmitter also considers a hormone is a natural chemical that intestines and brain produce. It helps the body send messages between nerve cells and affects mood and emotions. P53 the tumor protein is a regulatory protein that is often mutated in human cancers. P53 has been described as "the guardian of the genome" because of its role in conserving stability by preventing genome mutation. Aim:The aim of this study is to determine the relationship of serotonin and ferritin levels with (P53) gene expression in transfusion dependent β-thalassemia major patients. Methods:The present study is conducted at Thalassemia hematology center in Al-Kut women &children Hospital in Wasit province / Iraq. The study involve 85 samples, 55 specimens of β-thalassemia major patients and 30 blood samples as control. Measurements of serotonin and P53 was by using enzyme-linked immunosorbent assay (ELISA). Ferritin was measured automatically by Cobas e 411 device . Results:The results of the present study revealed reduced serotonin level in β-TM patients and shown a significant correlation (P≤0.02) in patients when compared with control. Serum ferritin showed a major increased level in blood transfusion dependent β-TM patients and its presented significant correlation (P≤0.001) in patients group when compared with control group. P53 showed increased level in β-TM and it's correlated positively in patients (P≤0.01) when compared with control. Serotonin and P53 showed no significant correlation(P>0.05) with ferritin level when compared between the same group of β-thalassemia patients.
Keywords: B-thalassemia major, serotonin, ferritin, P53.

1. Introduction

The term "thalassemia" is derivative from the Greek words (Thalassa) meaning sea because of the high prevalence of the disease in the countries bordering the Mediterranean Sea and (Heam) meaning blood, and refers to disorders associated with imperfect synthesis of α-globin or β-globin subunit of hemoglobin (Daraghmeh ,2016). The first medical explanation of thalassemia syndrome is credited to the Detroit pediatricians Thomas B. Cooley and Pearl Lee. The real term thalassemia is invented by George Whipple (Honar ,2014). The thalassemia syndrome are named according to the globin chain affected or the abnormal hemoglobin produced. Therefore, b-globin gene mutations give b- thalassemia as a result and a-globin mutations cause a-thalassemia. Moreover, the thalassemias are characterized by their clinical severity (phenotype) (Weatherall & Clegg ,2001). The foundation management for patients with β- thalassemia major is based on permanent transfusion and iron chelation. The purposes of transfusion are to correct anemia and defeat ineffective erythropoiesis (Makroo & Bhatia ,2014). β- Thalassemia major is the most severe form which causes hemolytic anemia, poor growth, delayed sexual maturation and skeletal abnormalities during infancy (Mohssin *et al.*,2015).Ferritin, the iron storage protein, has an important role in iron metabolism. Its ability to impound the iron offers ferritin the double function of iron detoxification and iron standby (Hoffbrand *et al.*,2005). Iron overload signifies a serious complication in transfusion dependent β-thalassemia patients. Free iron catalyzes the creation of highly reactive oxygen species, which leads to membranes, DNA and protein damage, this process results to cellular death, tissue necrosis and inflammatory response in multiple organs mostly liver, heart, and endocrine glands. Definitely organs failure due to sever iron overload preform the main cause of death in patients with β- thalassemia major dependent blood transfusions regularly (Cappellini *et al.*, 2006). Serotonin or (5-Hydroxytryptamine) is a biogenic amine best renowned for its role as a neurotransmitter. It is widely accepted that serotonin (5-HT), a neurotransmitter involved in the ruling of

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emotion, mood, sleep and aggression, plays a key role in the beginning and course of depression (Maes & Meltzer , 1995). & (Neumeister *et al.*,2004). The behavioral and neuropsychological processes controlled by serotonin include mood, reward, perception, anger, aggression, sexuality, appetite, memory, and attention, among others. Indeed, it is difficult to find a human behavior that is not regulated by serotonin (Airan *et al.*, 2007). Youths with thalassemia experience stress, anxiety and depression which constituted 18.8 %, 60.9 % and 59.4 % (Khamoushi *et al.*, 2015). Some of the previous studies showed that 80% of patients with Thalassemia major have at least one psychiatric disorder.

The P53 protein is a transcription factor identified as the "guardian of the genome" because of its serious function in protective genomic integrity. The TP53 gene is mutated in about half of all human malignancies, including those of the breast, colon, lung, liver, prostate, bladder, and skin (Marei *et al.*, 2021). P53-dependent apoptosis contributes to cell death induced by chemotherapy (Zhang *et al.*, 2013). P53 realized as a good anticancer agent and thus provided a new technique for targeting cancer (Patwari *et al.*,2012). The P53 tumor suppressor protein is a gatekeeper of cellular fate in multicellular organisms. p53 is activated in response to genotoxic stress and initiates cell cycle arrest apoptosis via pathways involving transactivation of p53 target genes (Murray-Zmijewski *et al.*,2008).

2. Methodology

A cross sectional study design has been conducted on β-thalassemia major patients who are registered in Thalassemia hematology center in Al Kut women &children Hospital in Wasit province / Iraq, for regular blood transfusion and treatments in the period from February 2022 to May 2022.The study involve 85 samples, 55 specimens of blood samples have been collected from β-thalassemia major patients, in age ranged from 2-34 years and 30 blood samples have been collected from totally healthy individuals , who have no history of thalassemia disease or any other hematology disease and clinical complications , in age ranged from 18-45 years.

Blood collection

3 ml of venous blood were collected by vein puncture from β- thalassemia major patients and control in gel tubes arranged and labeled, and left to clot in room temperature for 30 minutes, and then it was centrifuged for 5 minutes at 4000 RPM for serum separation. , hemolysis has been avoided by taking the necessary precautions and ignoring hemolysis samples. Serum was collected and distributed by micropipette into eppendorf tubes and give the same number, and the samples were frozen in (-20°C) in deep freezer until the assay was done. Those specimens were then processed by using enzyme-linked immunosorbent assay (ELISA) to investigate serotonin level and P53 level in β- thalassemia major patients and control. Ferritin level in was measured automatically by Cobas e 411 device.

3. Results and Discussion

This study included 55 patients of β-thalassemia major with age ranged (2-34) years , the mean is (15.7±0.7) and 30 control of healthy individuals with age ranged (18-45) years , the mean is (31.2±0.8), as shown in table (1).

Table (1): The age distribution of patients and control.

Groups	NO.	Age-Range	Mean ±SD
Patients	55	2-34	15.7±0.7
Control	30	18-45	31.2±0.8

A study found the patients age were generally < 10 years (73 patients 46.5%) and there was no patient above the age of 30 years (Abdul- Karim *et al.*,2005) These conclusions can be explained due to increasing disease load and shortened life expectancy in thalassemia patients (Al-Ali & Faraj, 2016).The most common cause of death was heart disease, followed by infection, liver disease and malignancy. Another study showed that patients who follow entirely to treatment usually predictable to live at least until their mid- forties (Modell *et al.*,2000).

4. Laboratory Findings

In the control Serum ferritin ranged from (97-371) ng/ml with the mean (237.6±7.2), P53 ranged from (1.6-2.8) with the mean (1.8±0.2) and Serotonin ranged from (1.6-3.7) with the mean (2.8±0.6) , as shown in table (2).

Table (2): Lab. data of the control in this study includes serum ferritin,P53 and Serotonin .

Item (Control)	No.	Range	Mean±SD
ferritin ng/ml	30	97-371	237.6±7.2
P53	30	1.6-2.8	1.8±0.2
Serotonin	30	1.6-3.7	2.8±0.6

In total number of β-thalassemia patients (55), Serum ferritin ranged from (705-16270) ng/ml with the mean (3362.6±3.1), P53 ranged from (1.67-2.83) with the mean (2.0±0.3), and Serotonin ranged from (1.56-4.17) with the mean (2.4±0.7) , as shown in table (3).

Table (3): Lab. data of thalassemia patients includes serum ferritin , P53 and Serotonin .

Item (patients)	No.	Range	Mean±SD
Ferritin ng/ml	55	705-16270	3362.6±3.1
P53	55	1.67-2.83	2.0±0.3
Serotonin	55	1.56-4.17	2.4±0.7

Correlation of biochemical parameters in patients and control.

Estimation of P53 level in β- thalassemia patients , shows significant increase concentration(2.0 ±0.3) in patients and there is a significant correlation (P≤0.01) respectively when compared with control as shown in table (4).

Table (4): Correlation of P53, serotonin and serum ferritin in patients and control.					
Item	patients and control	N	Mean±SD	Std. Error Mean	P value
P53	Patients	55	2.0 ±0.3	0.04	0.01
	Control	30	1.8±0.2	0.04	
Serotonin	Patients	55	2.4±0.7	0.1	0.02
	Control	30	2.8±0.6	0.1	
Ferritin	Patients	55	3362.6±3.1	428.7	0.001
	Control	30	237.6±7.2	13.2	

This result also agreed with the investigation that observed a higher expression of p53 and p21 in β-thalassemia patients as compared to controls, P53 expression powerfully correlated with GDF15 expression at the mRNA in β- thalassemia major. GDF15 has two p53 response elements in the organizer region and p53 binding stimulates GDF15 in the erythroid compartment, P53 may thus contribute to GDF15 elevation in beta thalassemia (Athiyarath *et al.*,2012).

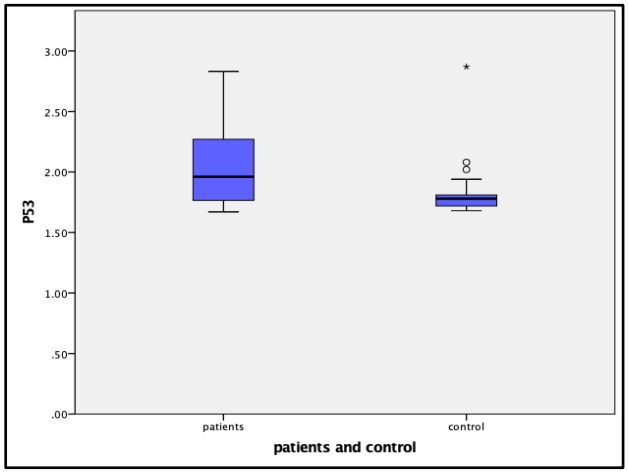

Figure (1): Boxplot of P53level in patients and control.

Evaluation of Serotonin in β- thalassemia major patients shows a significant decreased serotonin level (2.4±0.7), and the results in table (4) reveals a significant correlation (P≤0.02) respectively in patients when compared with healthy controls. Depression is a popular psychiatric disorder in numerous chronic diseases and β-thalassemia is no exception. The prevalence of various degrees of depression in patients with β-thalassemia was 30.8% in Iranian study, this prevalence was not significantly altered between males and females; furthermore, age was not significantly connected with the BDI score as an indicator of depression (Shafiee et al.,2014).

The level of serotonin decreases in individuals who suffer from psychological disorders and depression, therefore the level of this hormone is reduced in thalassemia patients with depression and anxiety. Anemia is well-known to be related with depression both in community and medical populaces. In a previous study the association of both depression and antidepressant intake with hemoglobin level was examined, concluded that both depression and antidepressant intake were related with lower hemoglobin level. In specific, as SSRI or SNRIs intake was likewise associated to lower hemoglobin level, these classes must be used through caution in depressed individuals at risk for anemia (Vulser et al.,2020).

Estimation of serum ferritin in thalassemia patients demonstrated a significant increase in β-TM patients (3362.6±3.1), and the data in table (4) reveals a significant correlation (P≤0.001) respectively in patients group when compared with control group . Transfusion iron overload is directly related with the number of blood transfusions. One unit of transfused blood contains about 200-250 mg of iron. At all events, patients who obtain more than 10 to 20 units of blood are at a significant danger of iron overload (Remacha et al., 2013). Serum ferritin acts as a buffer between iron deficiency and overload, and since the body cannot disregard iron itself, even with treatment, it is an specifically important measure of iron levels (Majd et al.,2015). The result of current study agreed with previous study that indicated serum ferritin levels were particularly very high in both the β- thalassemia major and β- thalassemia intermediate groups (Attafi & Rasheed,2022).The present result agreed with the study that found higher serum ferritin levels were a significant interpreter for mortality , As baseline , serum ferritin levels increased the risk of death (Shah et al.,2022).

Correlation between biochemical parameters according to serum ferritin level in patients.

The data showed in table (5) revealed that P53 have no significant correlation (p > 0.05) with serum ferritin level when compared between the two categories of β-thalassemia patients more and less than 3000 (ng/ml) of ferritin level .P53 acting a title role in tumor suppression (Kastenhuber & Lowe, 2017). The p53 gene is mutated in above half of all human cancers and nearly in each sort of cancers (Donehower et al.,2019). Patients with β-thalassemia major with period more than 10 years at a risk of tumors especially with liver origins (Abdulhadi et al.,2022).

Various human researches reported that excess iron have a role in the expansion of liver cancer (Kowdley, 2004).Ferritin, an iron storage protein, shows an important role in iron homeostasis and an extensive range of physiologic processes. Ferritin level is unsuitably regulated in several cancer cells. In specific cases for example breast cancer, colon cancer and testicular seminoma, ferritin level is increased in tumor tissue when compared with equivalent normal tissue; in other cases with liver cancer, a decrease in ferritin is reported (Torti, F.& Torti, S. ,2002). Normally, cancer cells need a high

amount of iron for proliferation and therefore, are vulnerable to iron deficiency. Consequently, iron chelators are presently being tested for the treatment of several types of cancers including solid tumors and blood cancers (Corcé et al.,2016). Such as, deferoxamine presented an antitumor effect in patients with advanced HCC (Hepatocellular Caecinoma) (Yamasaki et al., 2014).

Table (5): Correlation between P53 and Serotonin according to serum ferritin level in patients .

Item	Ferritin level ng/dl	N	Mean±SD	Std. Error Mean	P value
P53	<3000	35	2.0±0.3	0.05	0.1
	=>3000	20	1.9±0.2	0.06	
Serotonin	<3000	35	2.3±0.7	0.1	0.4
	=>3000	20	2.5±0.8	0.1	

A study conducted in USA, investigated the ability of p53 to regulate ferritin. Real time reverse transcription-PCR confirmed no difference in levels of ferritin H mRNA in the existence and absence of p53. Because these results proposed that transcriptional mechanisms were not responsible for the p53-dependent increase in ferritin (Zhang et al.,2008).

The data presented in table (5) verified that serotonin have no significant correlation ($p > 0.05$) with serum ferritin level when compared between the two categories of β-thalassemia patients more and less than 3000 (ng/ml) of ferritin level. Serotonin (5-HT) has customary roles as a key neurotransmitter in the central nervous system and as a controlling hormone monitoring a wide-ranging of physiological functions .Possibly the utmost standard-defined functions of 5-HT (serotonin) are mainly in the control of mood, sleep,and anxiety (Jones et al.,2020). Beta thalassemia major is a chronic genetic blood disorder. Patients are reliant on blood transfusion. Depression, anxiety, and stress can make their condition very difficult. A study conducted in Egypt estimated the prevalence of anxiety and depression between individuals afected by thalassemia indicated that 32.1% and 16.1%, of patients reported suffering from clinical and borderline levels of depression (Yahia et al.,2013). Another study conducted in palastine demostrated that a majority of thalassemia patients(78.5%) , which have elevated levels of the iron storage protein ferritin had moderate to severe depression (55.8%) of the contributors had severe depression while (22.7%) had moderate depression (Sarhan et al.,2022). Astudy has found that depression severity was associated to greater levels of iron in multiple brain regions of patients with major depressive disorder (Yao et al.,2017).

Several studies found no significant relationship between depression and level of ferritin (Armony-Sivan et al.,2012). A study conducted in Najaf Governorate indicated an inverse correlation between the level of ferritin and depression as the correlation coefficient (- 0.158) and ($P<0.05$), (Hashim ,2020).

A sufficient quantity of iron is mainly essential for the synthesis of serotonin, a neurotransmitter that plays a substantial role in mood disorders and impulsivity (Yi et al.,2011). Iron also plays a part in monoamine neurotransmitter function as a co-factor for the manufacture of neurotransmitters, including serotonin (Roberts & Fitzpatrick ,2013).

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