Estimated Glomerular Filtration Rate in Pediatric Patients with β-Thalassemia Major: A Single-Center Observational Study at Dr. M. Djamil General Hospital, Padang, Indonesia

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ABSTRACT

Background: Patients with β-thalassemia major can experience impaired kidney function. Impaired kidney function can occur without symptoms and before serious manifestations appear, so early markers are needed to detect kidney damage. Estimated glomerular filtration rate (eGFR) is a calculation to detect early impairment of kidney function and is widely accepted as an indicator in determining overall kidney function. This study aims to determine the estimated glomerular filtration rate in pediatric patients with β-thalassemia major.

Methods: This research is a descriptive research. Data was taken from pediatric patients with β-thalassemia major who received routine transfusions at the pediatric polyclinic of Dr. M. Djamil General Hospital Padang from January 1st – July 31st 2023. Patients underwent hematology examination, serum ferritin, serum creatinine, and estimated glomerular filtration rate calculations using the Schwartz formula.

Results: A total of 55 children met the research criteria, consisting of 27 boys (49%) and 28 girls (51%). The median serum creatinine level was 0.5 (0.3-0.8) mg/dL with a mean estimated glomerular filtration rate of 167 mL/minute/1.73m².

Conclusion: Glomerular hyperfiltration occurs in the majority of β-thalassemia major patients, but a decrease in eGFR is found in some patients. Regular checks of kidney function in thalassemia sufferers are needed to monitor kidney function disorders.

1. Introduction

World Health Organization (WHO) identified thalassemia as the most common chronic genetic disease in 60 countries, especially in the Mediterranean, Middle East, and Southeast Asia. Thalassemia is a hereditary blood disease caused by reduced or absent expression of the globin chains that make up the hemoglobin molecule. Thalassemia is named based on the type of globin chain whose synthesis is disturbed. Lack of production of β globin chains in β thalassemia will cause accumulation of α globin chains. Morbidity and mortality due to thalassemia significantly contributes to the global health burden because an estimated 56,000 babies are born with thalassemia each year and more than half of them require regular blood transfusions. Around 300 million people worldwide are carriers of this hemoglobin disorder and 55 million of them are in Southeast Asia. Indonesia is one of the countries in the world’s thalassemia belt, namely a country with a high frequency of the thalassemia gene. Epidemiological research in Indonesia found that the frequency of the β thalassemia gene ranges from 3-10% and an estimated 2500 newborns with β thalassemia major each year.

Monitoring of the complications of thalassemia disease in various organs is done a lot, but very few monitor kidney complications. Clinical studies show
varying degrees of tubular dysfunction and glomerular filtration rate abnormalities are common findings in β-thalassemia patients. Chronic anemia, iron overload, and the use of iron chelation are thought to be related to the manifestation of kidney disorders. Impaired kidney function can occur without symptoms and before serious manifestations appear, so early markers are needed to detect kidney damage. A commonly used marker of kidney damage is serum creatinine levels. Creatinine examination cannot be used to detect kidney function disorders early because an increase in serum creatinine levels begins to appear when there has been a significant decline in kidney function.

The glomerular filtration rate is widely accepted as an indicator in determining overall kidney function. Estimation of glomerular filtration rate (eGFR) using creatinine or Cystatin C is an important step in early clinical discovery and follow-up of Kidney dysfunction that occurs in children and adults. Research conducted by Milo et al found that there was a decrease in the value of the glomerular filtration rate in patients with thalassemia major. Tameem et al also got a decrease in eLFG <90mL/minute/1.73m² in 32 patients (42.6%). This is different from the research conducted by Arman et al found that the estimated glomerular filtration rate was significantly increased in β-thalassemia major patients compared with controls. Research on kidney involvement in adults with β-thalassemia major has been reported, but there is not much data on children. There has been no research regarding the description of kidney function in thalassemia sufferers at Dr. M. Djamil General Hospital Padang until now. Researchers are interested in knowing the estimated glomerular filtration rate in pediatric patients with beta-thalassemia major at Dr. M. Djamil General Hospital Padang.

2. Methods

This study uses a descriptive method that aims to assess the estimated rate of glomerular filtration in pediatric patients with β-thalassemia major. This research was conducted at Dr. M. Djamil General Hospital Padang from January–July 2023. The population in this study were all patients who had been diagnosed with β-thalassemia major who came to the pediatric polyclinic at Dr. M. Djamil General Hospital Padang in the period January – July 2023. The inclusion criteria for this study were pediatric patients who received regular transfusions and received iron chelation therapy or not and were aged 2-18 years. Regular transfusion in β-thalassemia major is assessed by patients who receive transfusions of ≥ 8 PCR units per year. The exclusion criteria in this study were children with β-thalassemia major who suffered from systemic disorders (diabetes mellitus, heart failure, and liver disorders) and were known to suffer from kidney failure before the study began.

Heteroanamnesis and physical examination were performed on research subjects to rule out systemic abnormalities. Serum hemoglobin, ferritin, and creatinine levels were then checked. The eLFG calculation is carried out using the Schwartz formula with the formula: (eLFG) mL/min/1.73m² = Constant (K) x body height (cm) / serum creatinine (mg/dL). The Constant Factor is divided as (1) <1 year = 0.45; (2) 1-12 years = 0.55; (3) women aged 13-21 years = 0.55; (4) males aged 13-21 years = 0.70. Decreased renal function, normal renal function, and renal hyperfiltration are defined by eLFG <90 mL/minute/1.73m², 90-140 mL/minute/1.73m², and >140 mL/min/1.73m². Data were analyzed and processed descriptively to describe the characteristics of thalassemia major patients at the pediatric polyclinic of Dr. M. Djamil General Hospital Padang. Data were processed using the SPSS 25.0 program. The data is then presented in a frequency distribution table.

3. Results

The characteristics of pediatric patients with β-thalassemia major who were included in the study can be seen in Table 1. This study obtained data from 55 pediatric patients with β-thalassemia major at Dr. M. Djamil General Hospital Padang. The basic
Characteristics of pediatric patients with β-thalassemia major were 28 female patients (51%) and 27 male patients (49%) with a median patient age of 11 years (range: 2-17 years). The median serum creatinine level was within normal limits, namely 0.5 mg/dL with a range of 0.3-0.8 mg/dL. The mean hemoglobin level was 7.9 ± 0.89 g/dL. Serum ferritin levels were divided into 2 groups, namely <1000 and ≥1000 based on the administration of iron chelation therapy. Of the 55 patients, 6 (10.9%) had non-risk ferritin levels (<1000) and 49 (89.1%) had risky ferritin levels.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
<th>Median (Min-Max) / Mean (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>49 (27%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>51 (28%)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>11 (2-17)</td>
</tr>
<tr>
<td>Hemoglobin levels</td>
<td></td>
<td>7.9 (0,89)</td>
</tr>
<tr>
<td>Creatinine serum</td>
<td></td>
<td>0.5 (0,3-0.8)</td>
</tr>
<tr>
<td>Ferritin level (ng/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1000</td>
<td>6 (10.9%)</td>
<td></td>
</tr>
<tr>
<td>≥1000</td>
<td>49 (89.1%)</td>
<td></td>
</tr>
</tbody>
</table>

The estimated glomerular filtration rate in pediatric patients with β-thalassemia major who were included in the study can be seen in Table 2. Estimated glomerular filtration rate in pediatric patients with β-thalassemia major based on the Schwartz Formula showed that the majority of patients (78.2%) experienced glomerular hyperfiltration with a mean 167.14 ± 41.3 mL/min/1.73m². Of the 55 patients, 9 patients (16.4%) had normal eLFG values. Decreased eLFG was found in 3 patients (5.4%) with eLFG being below <90 mL/minute/1.73m².

<table>
<thead>
<tr>
<th>Estimated glomerular filtration rate</th>
<th>n (%)</th>
<th>Mean (±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (mL/minute/1.73 m²)</td>
<td></td>
<td>167,14 (41,3)</td>
</tr>
<tr>
<td>Decrease</td>
<td>3 (5,4%)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>9 (16,4%)</td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>43 (78,2%)</td>
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</tr>
</tbody>
</table>

4. Discussion

The characteristics assessed in this descriptive analysis study were age, hemoglobin levels, creatinine levels, serum ferritin, and estimated glomerular filtration rate. Thalassemia patients in this study consisted of 28 female patients (51%) and 27 male patients (49%) with a median age of 11 years (range: 2-17 years). The mean hemoglobin level in this study was 7.9 ± 0.89 g/dL. Thalassemia is a hereditary (hereditary) blood disease caused by genetic mutations that cause reduced or absent expression of the globin chains that make up the hemoglobin molecule. β-thalassemia major usually occurs between the ages of 6 months and 2 years and is characterized by severe anemia and stunted growth. Patients with β-thalassemia major require periodic and lifelong blood transfusions to maintain hemoglobin levels higher than 9.5 g/L and maintain normal growth. This study found a median serum creatinine of 0.5 mg/dL with a range of 0.3-0.8 mg/dL. This is in line with Siregar et al research which obtained a mean creatinine of 0.43 ± 0.06 mg/dL in pediatric patients with β-thalassemia major who received iron chelation therapy. Arman et al revealed that there was no correlation between Cystatin C, creatinine, and estimated glomerular filtration rate. Arman et al reported that creatinine is a marker that cannot be used for initial kidney function screening because an
The increase in creatinine only begins to appear when there has been a significant decline in kidney function. The literature states that creatinine levels in the blood will only increase if there is a decrease in the glomerular filtration rate <60 mL/minute/1.73m². The majority of patients in this study had ferritin levels ≥1,000 ng/mL (89.1%). This is almost in line with Mahmoud et al research which received a mean ferritin of 2820.55 ± 742.81 ng/mL which increased significantly compared to the control group. Arman et al research and Tameemi et al found that there was a significant correlation between serum ferritin and Cystatin C, indicating there was a relationship between iron excess and impaired kidney function.

Excess iron characterized by increased serum ferritin levels can occur in thalassemia patients due to the degradation process of erythrocyte cells from repeated transfusions and degradation of erythrocyte cells in patients. The mechanism of iron toxicity in the kidney occurs due to exposure to heme in the nephron when there is excess iron saturation. Blood transfusions cause the excretion of iron that is not bound to transferrin or heme elements in the nephron. This situation causes the formation of free radical reactive oxygen species which causes damage to the renal tubular membrane. Hemosiderin deposition in the kidneys can also cause tubular necrosis, cortical atrophy, and interstitial fibrosis, resulting in kidney injury in people with thalassemia. This study found that the majority of pediatric patients experienced glomerular hyperfiltration (78.2%) with a mean eLFG of 167 mL/minute/1.73m². This research is in line with Arman et al research which found that eGFR increased significantly in β-thalassemia major patients. Glomerular hyperfiltration in patients with thalassemia major is associated with chronic anemia in the patient. Chronic anemia causes a decrease in vascular resistance resulting in hyperdynamic circulation, increased plasma flow in the kidneys, and an increase in the glomerular filtration rate known as hyperfiltration. The state of glomerular hyperfiltration causes stretching of the glomerular capillary walls and damage to epithelial and endothelial cells. Disruption of glomerular function will eventually occur and in the long term will reduce the glomerular filtration rate. Several previous studies revealed that glomerular hyperfiltration is an early stage of kidney damage.

This study also found that 5.4% of patients experienced a decrease in eLFG. Kamel et al (2022) reported a decrease in eLFG <90 mg/minute/1.73m² in 26.8% of pediatric patients. Sari et al also reported a decrease in eFLG in patients receiving oral iron chelation therapy. Decreased eGFR can occur due to chronic anemia, iron overload, and the use of certain iron chelators. Chronic anemia will cause chronic hypoxia in tubular cells, which can result in apoptosis or the transition of epithelial cells to mesenchymal cells, resulting in tubulointerstitial damage, glomerulosclerosis, and renal fibrosis. Damage to tubular cells due to excess iron results in the migration of tubular cells to the interstitium, the release of cytokines and growth factor which causes tubulointerstitial scarring and glomerulosclerosis, which will further decrease the glomerular filtration rate.

β-thalassemia major is an inherited blood disorder characterized by inadequate production of β-hemoglobin. Hemoglobin β is one of the main components of red blood cells which is responsible for transporting oxygen throughout the body. In patients with β-thalassemia major, hemoglobin β deficiency causes severe chronic anemia. Although chronic anemia is the main manifestation of β-thalassemia major, various other complications can occur, including kidney damage. One of the common kidney abnormalities in β-thalassemia major patients is glomerular hyperfiltration. The glomerulus is a small structure in the kidney that is responsible for filtering blood and producing urine. Under normal conditions, the glomerulus filters the blood efficiently, allowing important substances such as water, electrolytes, and glucose to pass into the urine, while bulk substances such as proteins and red blood cells remain in the blood. In patients with β-thalassemia major, glomerular hyperfiltration occurs when the
glomerulus filters blood excessively. This can be caused by several factors. Chronic anemia in β-thalassemia major can cause increased blood flow to the kidneys. This excessive blood flow can overload the glomerulus and cause hyperfiltration. Chronic anemia can also cause structural damage to the glomerulus, which can increase its permeability and cause hyperfiltration. Increased intraglomerular pressure, which can be caused by various factors such as hypertension and excess fluid volume, can also cause hyperfiltration. Glomerular hyperfiltration in β-thalassemia major can have several negative consequences. Prolonged hyperfiltration can cause glomerular damage and a decrease in eGFR. eGFR is an important measure of kidney function. A decrease in eGFR indicates that the kidneys are no longer able to filter blood efficiently. Hyperfiltration can cause proteinuria, which is the leakage of protein into the urine. Proteinuria can cause further kidney damage and increase the risk of complications such as kidney failure. Hyperfiltration can cause activation of the renin-angiotensin-aldosterone system (RAAS), which can increase blood pressure. Hypertension can worsen kidney damage and increase the risk of cardiovascular complications. Although glomerular hyperfiltration is a common renal abnormality in β-thalassemia major, decreased eGFR does not always occur in all patients. Several factors can influence the development of decreased eGFR in β-thalassemia major patients. Younger patients with β-thalassemia major generally have better preserved eGFR than older patients. This is because kidney damage due to hyperfiltration takes time to develop. Patients with more severe anemia generally have a higher risk of decreased eGFR. The presence of other comorbidities such as diabetes mellitus and hypertension can worsen kidney damage in β-thalassemia major patients and increase the risk of decreased eGFR. Management of glomerular hyperfiltration and decreased eGFR in patients with β-thalassemia major focuses on effective treatment of anemia with blood transfusions or iron chelation therapy can help reduce glomerular hyperfiltration and protect the kidneys. Tight blood pressure control with antihypertensive drugs can help prevent further kidney damage, treatment of proteinuria with drugs such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) can help slow the decline in eLFG, regular monitoring of kidney function with blood tests and urinalysis is essential to detect a decline in eLFG early and initiate treatment right. Glomerular hyperfiltration and decreased eGFR are common renal complications in β-thalassemia major patients. Proper management can help prevent or slow kidney damage.22-25

Chronic anemia in β-thalassemia major causes increased intraglomerular pressure, which can enlarge glomerular pores and increase filtration of water and solutes. Excess iron in β-thalassemia major patients can accumulate in the kidneys and cause glomerular damage, which can worsen hyperfiltration and decrease eGFR. Chronic anemia and kidney damage in β-thalassemia major can disrupt the function of the renal tubules, which are responsible for the reabsorption of water and solutes from the glomerular filtrate. Impaired renal tubular function can worsen hyperfiltration and decrease eGFR. Glomerular hyperfiltration and decreased eGFR can cause various renal complications in β-thalassemia major patients. Hyperfiltration can cause proteinuria, which is the leakage of protein from the blood into the urine. Proteinuria can worsen kidney damage and increase the risk of kidney failure. Hyperfiltration can cause electrolyte imbalances, such as hypocalcemia (low calcium levels) and hyponatremia (low sodium levels). This electrolyte imbalance can cause muscle weakness, cramps, and heart problems. Glomerular hyperfiltration and decreased eGFR can lead to chronic renal failure, which is a serious and life-threatening condition. Patients with chronic kidney failure may require dialysis or a kidney transplant.23-25

This study has weaknesses, namely that it does not assess how long the patient was known to suffer from thalassemia and whether iron chelation therapy was given to the patient. Research conducted by Siregar et al reported that age, the length of time the child...
suffered from thalassemia, and the duration of iron chelation therapy was correlated with eLFG.\textsuperscript{18} Several other clinical studies have also found that iron chelation therapy can affect kidney function in β-thalassemia major patients although this manifestation is rare.\textsuperscript{7} The weakness of this research is that it also did not assess the nutritional status of the sufferers. Malnutrition in sufferers will affect serum creatinine levels. Creatinine is the end result of muscle metabolism so that if muscle mass is low then the creatinine value will also be low. Creatinine levels are influenced by age, gender, race, muscle mass, and nutritional status.\textsuperscript{25}

5. Conclusion

Most pediatric patients with β-thalassemia major show glomerular hyperfiltration but decreased eGFR is found in some children. Long-lasting glomerular hyperfiltration can result in decreased kidney function and kidney failure. Routine kidney function checks in thalassemia sufferers are needed to monitor kidney function disorders.

6. References


