

## **Disease Knowledge and Treatment Adherence Among Thalassemia Patients: A Literature Review**

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### **I. Introduction**

A literature review is defined by Hart (2018) as an analysis, critical evaluation, and synthesis of existing knowledge relevant to a research problem. The aim of this chapter is to expand our understanding about disease knowledge and treatment adherence among adult patients with thalassemia. Previous studies on this topic were examined to identify gaps in the nursing literature and present what is already known about relevant issues from a nursing perspective.

#### **Data Search Strategy**

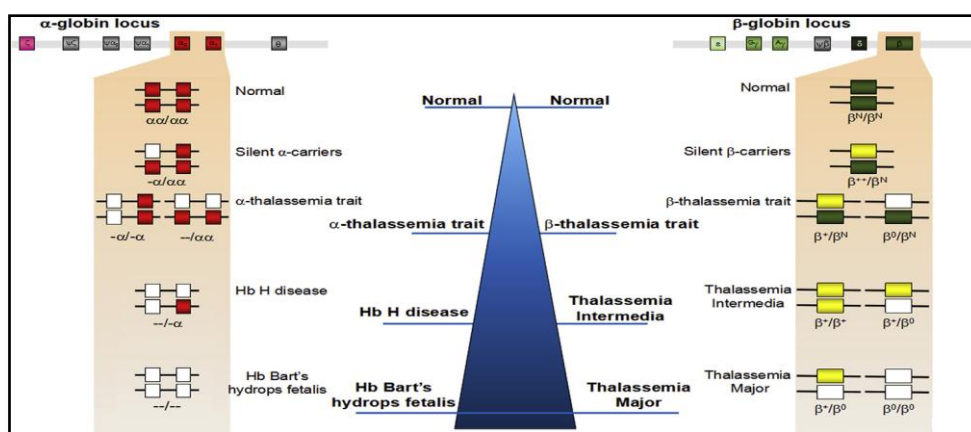
The strategy used to search the literature was designed to capture published theoretical and empirical articles related to disease knowledge and treatment adherence among patients with thalassemia, particularly adult patients. The review of the literature was conducted using the following databases: Current Index to Nursing and Allied Health Literature (CINAHL), Google Scholar, PubMed, and EBSCO. A manual search of the references list of each article was also performed to identify related articles. The search was limited to articles published in English from 2009 to 2018 in order to focus on the most current literature. The following keywords were used: "disease knowledge," "treatment adherence," "thalassemia," and "patients with thalassemia". Unpublished studies, editorials, documents, and descriptive reports discussing experiences and ideas about disease knowledge and treatment adherence in patients with thalassemia, and studies published in other languages were excluded.

Thalassemia is the most common genetic blood disorder worldwide. The word thalassemia derives from Greek roots meaning sea "Thalassa" and blood "Hema" (Wong, Fuller, Gillespie, & Milat, 2016). The normal human hemoglobin of adults (HbA) contains two sets of globin chains — two alpha ( $\alpha$ ) and two beta ( $\beta$ ) — the synthesis of which is normally closely coordinated to make sure about equal production (Ribeil, Arlet, Dussiot, Moura, Courtois, & Hermine, 2013). Thalassemia is a hereditary hemoglobinopathic disease, which is due to the absence of, or a lower synthesis rate of either the  $\beta$  or the  $\alpha$  globin chain. Depending on which globin chain is involved, thalassemia is classified as  $\beta$ -thalassemia or  $\alpha$ -thalassemia (Saxena, Sharif, Siddiqui, & Singh, 2017).

The most common type of thalassemia is  $\beta$ -thalassemia, which is divided into three distinct subtypes:  $\beta$ -thalassemia major,  $\beta$ -thalassemia intermedia, and  $\beta$ -thalassemia minor, based on clinical severity (Inatiet al., 2015; Saxena et al., 2017). The other type of thalassemia ( $\alpha$ -thalassemia) has two different types of genes that are associated with disease severity; the more severe form is called the Hb Barts Hydrops Fetalis and the milder form is called Hemoglobin H (HbH) disease (Taher, Weatherall, & Cappellini, 2018). The complete absence of  $\alpha$ -globin leads to hydropic births and intrauterine failure, while a fetus that lack the three  $\alpha$ -genes or has three dysfunctional  $\alpha$ -genes (HbH disease) will survive gestation (Rachmilewitz & Giardina, 2018). Figure 2.1 shows the types of thalassemia.

Patients with thalassemia suffer from anemia, which results from the shortened survival time of red blood cells (RBC) caused by hemolysis, and the early death of erythroid precursors in bone marrow and ineffective erythropoiesis (IE) (Ribeil et al., 2013). A lack of, or a reduction in globin synthesis causes anemia, IE, and poor oxygen supply (Jaing, 2017). Ineffective erythropoiesis is related to bone expansion and extramedullary hematopoiesis in the spleen, liver, and other organs (Jaing, 2017). Patients affected with  $\beta$ -thalassemia may also present with retarded growth, failure to thrive, or other more specific signs and symptoms, such as symptoms of anemia, encompassing fatigue, headache, dizziness, exercise intolerance, and lethargy even with hemoglobin levels that overlap within normal ranges (Galanello & Origa, 2010; Di Mauro, et al., 2016; Wong et al., 2016). However, the signs and symptoms of patients with  $\alpha$ -thalassemia vary depending on the

amount and type of hemoglobin synthesized (Galanello, 2012). The  $\alpha$ -abnormalities impact the fetuses and are distinguishable at birth. The severity of disease symptoms depends on the number of genes involved (Tari et al., 2018). Single  $\alpha$ -globin gene deletions results in mild thalassemia-trait phenotypes (possibly borderline anemia and microcytosis), whereas one or two deleted or defective  $\alpha$ -globin genes can, in combination, results in three or more than three gene deletions with far more severe clinical complications. Moderate to severe destruction of RBCs (HbH disease) will occur in people without three  $\alpha$ -globin genes, and the lacking of all four genes is serious in uterus (Ferguson, 2018).



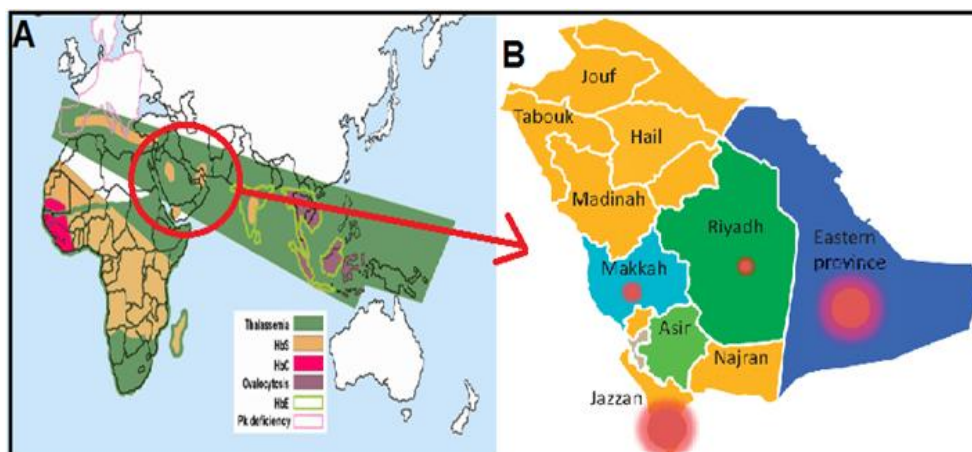
**Fig 2.1** Clinical classification and genotype phenotype correlation of  $\alpha$ - (left) and  $\beta$ -thalassemia (right).

Patients with thalassemia may suffer from complications directly due to the disease, which include skeletal deformities, chronic hemolytic anemia, pulmonary hypertension, and thromboembolic disorders, such as deep vein thrombosis (DVT) and splenomegaly (Ribeil et al., 2013). There are also complications due to treatment for thalassemia, such as infections related to blood transfusions (Inati, et al., 2015). Iron overload, which results from continuous blood transfusions, can cause cardiomyopathy, liver fibrosis or cirrhosis, endocrinopathies, delayed growth, diabetes mellitus, delayed puberty, hypogonadism, and hypothyroidism (Cappellini, Porter, Viprakasit, & Taher, 2018). Skeletal deformities are a complication of thalassemia that are the consequence of bone marrow hyperplasia that causes weakening of the cortical structures (Di Mauro et al., 2016; Bouguila et al., 2015). Another complication occurs in the facial bones, which lead to severe deformity, frequently referred to as rodent face (Di Mauro et al., 2016). The expansion of marrow in the facial skeletons causes overgrowth of the maxillae and the forward displacement of the maxillary incisors producing malocclusion, which leads to difficulties in speech, swallowing, and eating (Di Mauro et al., 2016; Ribeil et al., 2013). The patients typically have anterior teeth spacing, protrusion, and class II malocclusion resulting in speech, swallowing, and eating difficulties (Bouguila et al., 2015).

### **Incidence and Prevalence**

The highest prevalence of thalassemia is found in about 60 countries in the southern Far East, and Southeast Asia, the Middle East, parts of North and West Africa, the Indian subcontinent and Mediterranean region (Kourorian, Azarkeivan, Hajibeigi, Oshidari, & Shirkavnd, 2014). The percent for  $\beta$ -thalassemia carriers in these regions ranged from one percent to 20% (Kourorian et al., 2014). The prevalence of mild  $\alpha$ -thalassemia is greatly higher, fluctuating from 10% to 20% in sub-Saharan Africa areas, and more than 40% in some Indian and Middle Eastern people (De Sanctis et al., 2018). The previously mentioned countries together with Asia compose the so-called "thalassemia belt" (Figure 2.2).

Generally, it is projected that 270 million people are thalassemia patients and carriers (80 million are  $\beta$ -thalassemia carriers). Between 300 and 400 thousand children are born with severe hemoglobin disorders each year (23,000 with  $\beta$ -thalassemia major) and around 90% of these childbirths happen in the developing countries (De Sanctis et al., 2018). Both  $\alpha$ - and  $\beta$ -thalassemia are highly prevalent in Asian populations. The prevalence of the thalassemia trait in the world population is 1.7% (Warghade et al., 2018). The regions with a high prevalence of the  $\beta$ -thalassemia are Iran (4-10%), Greece (5-15%), Sicily (10%), and Sardinia (11-34%) (Kourorian et al., 2014). On the other hand,  $\alpha$ -thalassemia is the most public hemoglobin disorder worldwide, which is more prevalent in the Middle East, Southeast Asia, and parts of Africa (Taher et al., 2018).

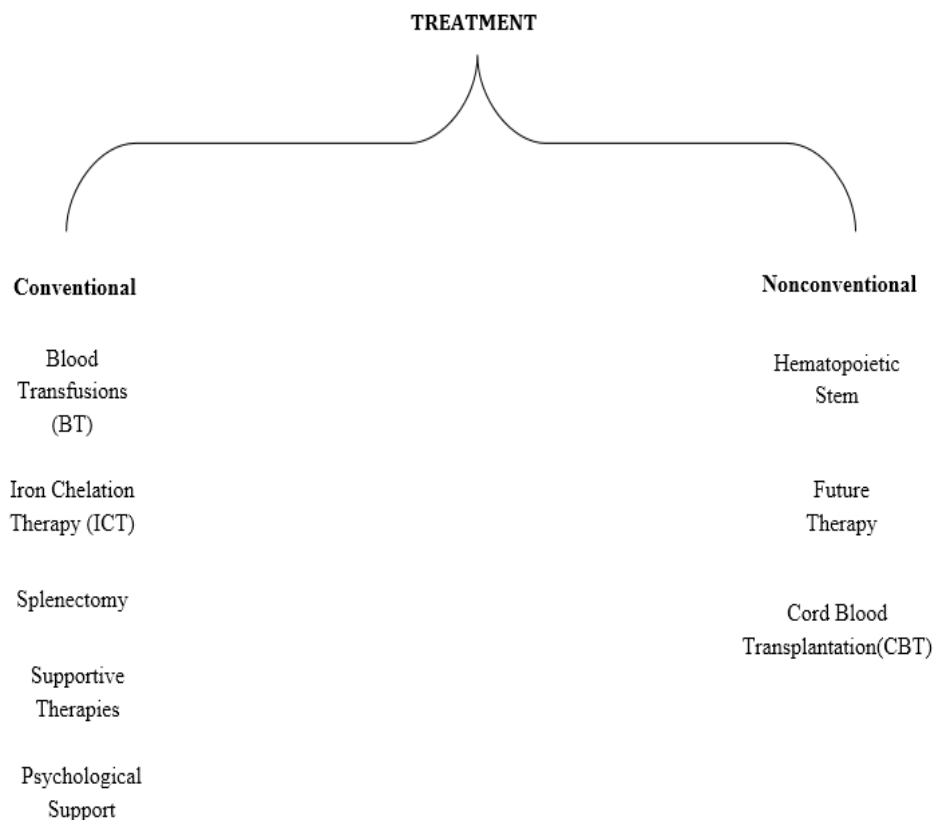


**Figure 2** Geographic distribution of thalassemia. A- In the world,  $\beta$ -thalassemia major is common in the Mediterranean basin and equatorial regions of Asia and Africa (Armando Moreno Vranich, 2010). B- Demographic representation of beta thalassemia prevalence in different regions of Saudi Arabia. The larger the red circle, the greater the prevalence.

Among the Arab countries, the KSA covers more than two million km<sup>2</sup>, making it the biggest country by region in the Middle East (WHO, 2016). It is mostly affected by  $\beta$ -thalassemia and its prevalence is considered high compared to neighboring nations in the Middle East (0.1%, and 4.5%, in the KSA) (Alsaeed et al., 2017; Alaithan et al., 2018). The prevalence of  $\beta$ -thalassemia carriers is distributed in all regions of the KSA (Alaithan et al., 2018), with the Eastern Province of the KSA having a 5.9% prevalence rate of  $\beta$ -thalassemia (Borgio et al., 2016). Both  $\alpha$ - and  $\beta$ -thalassemia are highly prevalent in the residents of the Al-Ahsa and Al-Qatif areas in the Eastern Region of the KSA, while its prevalence rate is 0.4% in the Northern region (Al-Amodi, Ghanem, Aldakeel et al., 2018). Jazan, which is located in South of the KSA has the second highest prevalence of  $\beta$ -thalassemia (Akhtar, Qaw, Borgio, Albuali et al., 2013). The high prevalence of  $\beta$ -thalassemia in the KSA is due to certain cultural factors that are resistant to change, including large family size, high rates of consanguineous marriages (exceeding 55%), and high paternal and maternal ages (Memish et al., 2011). Many other factors could be accountable for this problem, for examples: screening at a late stage of the marriage process (screening test is regularly carried out after the official engagement), failure to find alternatives that is a socially appropriate, couple commitment, or inability of healthcare professionals to provide sufficient information to partners that might influence their decisions to marry (Memish et al., 2011). There could well be another aspect, which is the potential psychosocial stigma associated with acknowledging incompatibility to the public (Alenazi et al., 2015).

### **Medical Management of Thalassemia**

The treatment of thalassemia should be tailored and individualized to the patient's clinical situation. There are two main types of treatments; the first type is conventional treatment, which consists of blood transfusions, iron chelation therapy, supportive therapies, splenectomy, and psychological support (Inati et al., 2015). The second type is nonconventional treatment; this includes hematopoietic stem cell transplantation (HSCT), which is the only beneficial treatment, gene therapy, and fetal hemoglobin modulation (Inati et al., 2015).



**Figure 2** Medical Management of Thalassemia

The goals of blood transfusion, which is the primary treatment for thalassemia, are to correct anemia, inhibit gastrointestinal iron absorption, and suppress erythropoiesis (Origa, 2017). The Thalassemia International Federation (TIF) suggests that frequent blood transfusions, generally ordered every two or five weeks, to sustain the hemoglobin levels of patients with thalassemia within or above 9–10.5 g/dl (Viprakasit, Lee-Lee, Chong, Lin, & Khuhapinant, 2009). Transfusion therapy works by suppressing ineffective erythropoiesis and supplying normal erythrocytes, controlling all essentially downstream pathophysiological mechanisms in thalassemia (Taher et al., 2017). Frequent RBCs transfusion is not essential in non-transfusion dependent thalassemia (NTDT), but may be rarely required during times of high levels of physiological stress, such as surgery, pregnancy, and severe infections (Taher et al., 2017).

Unfortunately, hyper-transfusion therapy is not without complications. Frequent blood transfusion can cause worsening iron overload and infections (Sleiman et al., 2018). Iron overload is one of the major causes of mortality and morbidity in thalassemia patients (Aydinok et al., 2014; Trachtenberg, 2012). It is an unavoidable consequence of regular blood transfusions, which is due to the human body's inability to excrete excess iron (Origa, 2017). The standard therapy is consistent blood transfusions and well monitored Iron chelation medications (Origa, 2017). Iron chelation medications prevent iron accumulation, treat iron-induced end-organ complications and iron overload, and can reach a typical form of complication-free survival and better quality of life in patients with thalassemia (Aycicek, Koc, Bayram, & Abuhandan, 2016).

Iron chelation therapy traditionally has been recommended for patients with thalassemia to take it after 10–20 blood transfusions or once Serum Ferritin level goes above 1000 lg/l (Origa, 2017). There are three iron chelators currently available (Origa, 2017). Since the 1980s, deferoxamine (DFO) has been the only iron chelation medication that is administered as a subcutaneous infusion (Aydinok, Kattamis, & Viprakasit, 2014). Precautions are contained in most up-to-date recommendations that put in considerations specifically to the use of DFO (Musallam et al., 2013). The major disadvantage of this method of treatment is its route of administration. Deferoxamine is taken subcutaneously in a dosage of 30–50 mg/kg with a special syringe for eight to 12 hours every day for a minimum of five days a week, leading to a significant load on the psychological and social life of patients with thalassemia and their families (Musallam et al., 2013). A new treatment is deferiprone (DFP), the first iron chelation medication taking orally was approved to use in 1995 in India, and granted a European license in 2000 under restricted precautions (Aydinok et al., 2014). Recently, the USA approved another line of treatment for patients with thalassemia who have poor responses to, or have contraindications for DFO or DFP. Deferiprone was approved by the Ministry of Health in the KSA in 2005,



with a recommended dosage of 75–80 mg/kg/day, divided into three doses (Al Hawsawi, Sairafy, Tarawah, Zolaly, & Al Hegaily, 2010; Aydinok et al., 2014). Deferasirox (DFX) is an oral chelator administered once daily at a dosage of 20–40mg/kg/day confirmed its effect in decreasing Serum Ferritin levels and liver damage over a year in patients with different transfusion-dependent anemia (Aycicek et al., 2016).

The surgical treatment splenectomy is traditionally performed as an adjunct or alternate to blood transfusion. It should be considered in a few, select circumstances because it has an increased risk of pulmonary hypertension and venous thrombosis, beside potentially serious post-operative infections (Origa, 2017). Splenectomy helps to maintain higher concentrations of hemoglobin, and improves growth and quality of life (Taher et al., 2018), but it can lead to risk of severe infections, particularly life-threatening postoperative sepsis (Taher et al., 2018). Therefore, patients who plan to undergo splenectomy must receive immunizations, such as Pneumococcal 23-valent polysaccharide, Hemophilus influenza, and the Meningococcal polysaccharide vaccines at least two weeks before performing the surgery (Sleiman et al., 2018). The spleen works as an artificial tank for toxic iron scavengers in the human body and thus removing the spleen can inhibit the scavengers' effectiveness, thereby putting a patient at a greater risk of end-organ damages (Taher et al., 2018). The recent guidelines for splenectomy are limited to patients who are unable to receive iron-chelation medications or blood transfusion, as well as patients with clinically hypersplenism or symptomatic splenomegaly (Taher et al., 2018).

General therapeutic measures to optimize bone health in adult patients with thalassemia entail a complex approach; vitamin D, calcium, and zinc supplements, regular exercise, and healthy nutrition are currently the key treatment and prevention measures for bone disease (De Sanctis et al., 2018). Hydroxyurea medication is also recover the  $\alpha/\beta$  globin-chain imbalance and consequently enhancing effective erythropoiesis (Sleiman et al., 2018).

Alternate types of available treatments are nonconventional, such as HSCT or BMT from an HLA-identical sibling. Transplantation is applied broadly as another modality of treatment to traditional blood transfusion and iron chelation medications, which is the best curative choice available for patients with thalassemia major. However, an adult patient with advanced stage of thalassemia has a more possibility of transplant-related toxicity, and with current treatment protocols, the cure rate is approximately 65% (Origa, 2017). Hematopoietic stem cell transplantation (HSCT) to change mutant cells is still the most curative therapy for all types of thalassemia, with success rates of 80% among HLA-matched sibling-donor transplants. Gene therapy is one of the promising treatment modalities in thalassemia management (Sleiman et al., 2018). There are several therapies under investigation, for example, the stimulation of fetal Hb synthesis, which can decrease the severity of thalassemia by correcting the difference between  $\beta$ -globin and non- $\alpha$ -globin chains (Origa, 2017). Numerous pharmacological compounds, including decytabine, butyrate derivatives, and 5-azacytidine have had hopeful results in clinical trial studies. These medications stimulate HbF by varied mechanisms of actions that are not yet well described by medical researchers. Their positive effects in the management of thalassemia is being studied (Origa, 2017). The cornerstone of the management of thalassemia patients is adherence to the treatment plan.

### **Disease Knowledge among Adult Patients with Thalassemia**

Research has shown there is a relationship between level of awareness about the disease and treatment adherence among adult patients with thalassemia, in which patients with greater knowledge exhibit greater compliance with treatment than patients with inadequate knowledge (Mohamed, 2017). Related research has also found that inadequate knowledge about the disease can result in irregular and incorrect adherence to treatment (Kourorian et al., 2014).

Brunner and Suddarth (2013) indicated that one of human beings' basic needs is the need for training, learning, and gaining of knowledge. Phipps et al. (2008) showed that teaching people in accordance with their health needs is a crucial element of their education. Kourorian et al. (2014) concluded that increasing patients' awareness and knowledge about their disease and treatment had a good effect on patients' quality of life. This, in turn, improved patients' ability to handle their lifelong illness and challenges during treatment.

Research indicates that a higher level of knowledge and awareness of thalassemia among family members improve patient adherence to DFO infusion and follow-up visits (Lee et al., 2009). A cross-sectional study conducted in Taiwan investigated disease knowledge and adherence to treatment in a purposive sample of 32 patients with thalassemia major. The results showed a strong correlation between knowledge about the disease and adherence with follow-up visits. It also found a significant correlation between disease knowledge and adherence to DFO infusion. The researchers concluded that the positive relationship between knowledge and adherence to treatment and the factors associated with individuals' knowledge point out the essential for an efficient education for patients with thalassemia and their families. However, reports indicate that thalassemia patients and their families are educated about their disease (Ghazanfari et al., 2010).

Researchers have pointed out the importance of knowledge level and the educational needs of patients with thalassemia in a study that was conducted in Kerman, Iran. The study, which had a sample of 300 adult patients, reported that the mean scores were between 2.79 and 2.96 (out of a maximum score of 4) on 20 knowledge items. Parents' knowledge was less than 50% on all the items and their mean total score was 37% correct. There was a positive correlation between parents' level of knowledge and their educational needs ( $p < .05$ ) (Ghazanfari et al., 2010). Researchers have concluded that patients with thalassemia and their parents do not have adequate information about the disease and they need more education about it (Haywood, 2009; Ryan, 2014).

Studies indicate that patients' adherence with treatment is affected by a variety of factors, including their knowledge, beliefs, attitudes, behavioral skills, perceived support from family members, friends, and religion (Kourorian et al., 2014). Although treatment adherence can be influenced by many factors, patients' knowledge of their disease seems to be a fundamental factor (Kourorian et al., 2014). Abu Shosha (2016) found that patients' knowledge about their disease and treatment was positively correlated with treatment adherence, and other studies have found that patients with greater knowledge are more compliant with treatment than patients with insufficient knowledge (Abu Shosha, 2016). Therefore, it is necessary to investigate the knowledge and educational needs of adult patients with thalassemia in order to take a positive step towards improving efforts to support their health in the KSA. The evidence shows that adult patients with thalassemia who are treated at an optimal level can lead a long and productive life and contribute to society (Antoniadou, Angastiniotis, & Xceriou, 2018). Rashid and Karimi (2011) concluded that knowledge awareness about ICT and its

### **Treatment Adherence among Adult Patients with Thalassemia**

Adherence to the treatment plan is a cornerstone in the management of patients with chronic diseases, such as thalassemia (Shaker, 2015). The key to the successful management of patients with thalassemia is the initiation of early treatment, supportive methods, and adherence to treatment, which lead to a higher patient survival rate (Jassim, Yousef, & Azab, 2017; Kourorian et al., 2014). Patient adherence to treatment is reported to be one of the greatest challenges for patients with thalassemia for surviving and improving their quality of life (Antoniadou et al., 2018). Prior research has found that adherence to the treatment routine is very challenging, especially for patients with chronic illnesses, such as thalassemia (Al-Kloub, Al Khawaldeh, Al Tawarah, & Froelicher, 2014).

Some research has reported that the average life expectancy of patients with thalassemia is 32 years, and it is much shorter if the disease is not treated (Koren, Profeta, Zalman, Palmor et al., 2014). In contrast, other research indicates that patients treated with regular blood transfusions with chelation therapy have a median survival exceeding 50 years old (Koren et al., 2014). Therefore, it appears that poor treatment adherence leads to increased morbidity, medical complications, and frequent hospitalization, and reduces quality of life (e.g., fatigue), and overuse of the health care system such as unnecessary medical consults and testing (Shaker, 2015). The treatment routine of patients with thalassemia is very exhausting, with studies showing that the average rate of adherence to thalassemia treatment is only 58% among patients in developed countries (Al-Kloub et al., 2014).

Additionally, the strict requirements for receiving the treatment and the undesirable adverse effects of iron chelation medications may have a negative effect on well-being and daily activities, and this in turn, may affect adherence to treatment (Rofail, 2010). Other factors that affect adherence to treatment include inappropriate use of medication materials, the quality of information provided to the patient, and complex treatment regimens, as well as patients' reluctance to be exposed to the potential harm caused by the treatment (Ryan, 2014).

Many patients with thalassemia report that adherence to iron chelation medications, particularly by subcutaneous infusion, to be exhausting, consequently they abandon treatment altogether (Al-Kloub et al., 2014). The research indicates that patients receiving chelation therapy often experience unpleasant swelling or bruises and pain at the needle site, which can lead to poor adherence and reduced quality of life. Adherence to such invasive procedures is very difficult (Vosper et al., 2018). Furthermore, the side effects of DFO, which includes skin reactions at the injection site, pain, retinal toxicity, and loss of hearing, can contribute to poor adherence (Fisher 2013). The other iron chelator, Deferasirox (Exjad), which is an oral treatment, is convenient because its once-daily dosing combined, and it has an acceptable safety profile. However, the price of this treatment is unaffordable for most patients.

### **Disease Knowledge and Treatment Adherence and Sociodemographic Characteristics**

Research has shown that the main reason for non-adherence is the high cost of treatment for thalassemia, which makes it unaffordable in most developing countries. In addition, transfusion reactions, and all immunization can lead to poor adherence by patients receiving combined transfusion and chelation therapy

(Mohamed,2017).Several factors have a particular impact on adults' adherence, such as their developmental stage, emotional issues, and family environment (Al-Kloub et al., 2014). Other reasons for non-adherence are related to problems with medications (e.g., their side effects), and disagreement about the need for treatment or other patient-specific factors (Kattamis, Aydinok, &Taher, 2018).Other factors known to complicate adherence among adult patients with thalassemia are lacking of knowledge about the disease, family issues (education, income, number of children, having diseased siblings), and demographic and clinical factors, such as age, gender, and severity of disease (Al-Kloub et al., 2014).

Psychosocial factors have frequently been shown to be associated with treatment adherence (Vosper et al., 2018). Problems that have been linked to poor adherence include an increase in psychological symptoms and distress consistent with negative emotional impact (e.g. anxiety and depression), as well as the unpleasant burdens of a subcutaneous method. Age and gender also affect adherence, with older patients tending to have poorer adherence while female patients tend to have better adherence (Shaker, 2015). Moreover, there is a variety of factors, such as clinical factors (e.g. duration of chelation therapy and frequent hospitalizations), healthcare system factors (e.g., coverage of incorporated care), and psychosocial factors (e.g. knowledge about disease, mood, educational level, perceived satisfaction with care provided and problems of non-adherence) that have been presented to be associated with adherence to treatment

### **Gaps in Current Literature**

As mentioned previously, thalassemia is common in the KSA, especially  $\beta$ -thalassemia, and is found in various regions of the KSA. Many international studies have investigated different aspects of thalassemia, such as treatments, complications, and disease knowledge in relation to treatment adherence; however, such research appears to be very limited in the KSA. Most studies conducted on thalassemia in the KSA have examined premarital testing and the availability of genetic counseling. Therefore, this study was conducted to investigate the disease knowledge and treatment adherence among adult patients with thalassemia receiving their treatment in KAUH, Jeddah City, KSA, in order to establish the viability of clinics and to develop educational programs for patients and their families about their disease management and treatment adherence.

### **Summary**

This literature review presented findings of studies on the disease knowledge and treatment adherence that affects the quality of life of adult patients with thalassemia. The researcher discussed evidence from various studies on the levels of knowledge and adherence to treatment, and possible factors leading to non-adherence among this population.

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