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Interplay Between Iron Overload, Thyroid Dysfunction, and Biochemical Disturbances in Thalassemia Intermedia (BTI): A Cross-Sectional Study

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Abstract

Thalassemia Intermediate (BTI) is one of the inherited disorders with diminished or lacking chains of beta-globin production. Abnormal enzymes and hormones are commonly associated with thalassemia patients. The current study investigates variations in levels of thyroid hormones, hepatic, renal enzymes, and serum ferritin. Additionally, detection the distribution of blood groups with participants. Levels of thyroid hormones, including biochemical and hormones parameters were measured in patients and compared across sex groups. The result revealed that O+ RH was a high percentage (32%) associated with patients more than other blood groups. Also, a slight increase in the serum of TSH and T4 levels in males' patients compared to females. Total serum bilirubin (TSB) concentrations were also higher in males compared to females, with a positive correlation of 0.88 and forward to TSB and AlP according to radar plot analysis. In conclusion, levels of ferritin, TSB, and alkaline phosphatase (ALP) were significantly elevated in the males compared to females. The observed correlations between these parameters and disease status underscore the importance of regular monitoring and timely transfusion to mitigate biochemical disturbances and potential organ dysfunction.

Keywords: Beta Thalassemia Intermedia, Thyroid hormones, Hepatic enzyme, and Ferritin levels.

1. Introduction

Thalassemia is a hereditary disorder marked by either the total lack or decreased synthesis of beta-globin chains, which constitute one of the two subunits of adult hemoglobin (HbA) [1].

It is an inherited blood illness that changes the molecular structure and function of hemoglobin, which is the main metalloprotein in red blood cells that carries oxygen. Thalassemia happens when the body doesn't make enough of either the alpha or beta chains of hemoglobin. Beta-thalassemia is a result of mutations or deletions in the beta-globin gene situated on chromosome 11. These mutations make it harder for beta-globin chains to be made, which means that normal hemoglobin (HbA) is made less often [2-4].

Beta thalassemia arises from a deficiency or structural defect in the beta-globin chains of hemoglobin. The condition is classified into several forms. Thalassemia minor, which results from a defect in a single beta-globin chain and is typically asymptomatic, though mild anemia may be detected during routine laboratory evaluations. Thalassemia intermedia, representing an intermediate phenotype between the minor and major forms, in which patients often lead a normal life but may require occasional blood transfusions during periods of illness or pregnancy [5-8].

Thalassemia intermedia presents a heterogeneous array of clinical manifestations, including chronic anemia, splenomegaly, extramedullary masses, iron overload, jaundice, and growth abnormalities [9-11]. Among the most common complications in thalassemia patients due to iron overload are endocrine disorders, particularly thyroid disorders. One of the fundamental tests for thalassemia patients is the ferritin test. People with thalassemia, particularly those who require blood transfusions frequently, have iron buildup, which can harm important organs like the liver and heart.

Raise levels of total serum bilirubin (TSB), liver enzymes (GOT and GPT), and urea are common symptoms of kidney and liver dysfunction, which is more common in patients with this disease. Frequent blood transfusions or the disease's underlying pathology might be the cause of these abnormalities [12-16]. There is a significant correlation between thalassemia and nephropathy, as chronic hemolysis, iron overload, and chelation therapy in thalassemia patients contribute to oxidative stress and renal tubular damage, leading to impaired kidney function [17].

The study aims to evaluate the biochemical and hormonal alterations associated with β-thalassemia intermedia by investigating the correlations between iron overload (serum ferritin) and thyroid function (TSH, T3, T4). Liver function (TSB, GPT, GOT, ALP), renal function (Blood Urea, S.Creatinine), as well as nutritional and metabolic indicators (albumin, serum calcium). Also, identify the distributions of blood groups with participants.

2. Methodology

2.1 Study Design

A cross-sectional study involving 120 patients (49 females and 71 males) diagnosed with beta thalassemia intermedia (βTI) was conducted. Samples were randomly selected from the Thalassemia Center at Al-Kut Hospital for Obstetrics, Gynecology, and Pediatrics in Kut City, between May and August 2025. Participants were inquired regarding their name, gender, age, and any relevant medical history. Patients of both genders, aged 5 to 60 years, who meet the criteria for beta thalassemia in Iraq.

The diagnosis of beta thalassemia was established using standard clinical and hematological criteria. This observational study followed the strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. All Equipment were calibrated before use. Independent verification of data entry and analysis was conducted by two researchers. Furthermore, all experiments were performed in triplicate to ensure reproducibility.

2.2 Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Committee of Scientific Research Ethics at the College of Basic Education, Wasit University. Approval No:2022/AI, on 24th of March 2025. The written informed consent was obtained from all participants prior to sample collection. All procedures involving human participants were performed following the ethical standards of the institution and relevant guidelines.

2.3 Types of Samples

In this study, approximately 5 ml blood was collected from a peripheral vein from each patient as shown in figure 1. A purposive sampling strategy was employed to select participants who met the inclusion criteria for this study. Eligible participants were identified by Wasit Hospital and invited to participate by phone numbers. This approach was chosen to ensure that the sample included individuals with the relevant characteristics necessary for the research objectives. All participants who agreed to take part provided written informed consent prior to sample collection.

2. 4 Inclusion Criteria

Patients with confirmed β-thalassemia intermedia of both sexes, receiving intermittent blood transfusions, with available thyroid hormone, biochemical, and ferritin data, were included.

2.5 Exclusion Criteria

Patients with other hematological disorders, recent infections or surgery, heart congestion, liver failure, and positive viral hepatitis were excluded from the study.

2.6 Patient Consent Statement

Information consent was obtained from all participants or their legal guardians prior to enrollment in the study. The consent process included a thorough explanation of the study's purpose, procedures, potential risks, and benefits. Participants were assured that their participation was voluntary, that they could withdraw at any time without consequences, and that all personal information would be kept strictly confidential in accordance with institutional guidelines and applicable laws.

2.7 Measurement of thyroid hormone concentration in the serum of patients and controls

Thyroid hormones and ferritin were measured in the serum of patients using depended on the fully-auto chemiluminescence immunoassay (CLIA) system MAGLUMIX3in the diagnosis. Numbers of kits used 242240221, 243240231, 241240531, and 263240311.

2. 8 Estimation of Biochemical parameters concentration in the serum of patients and controls.

Serum levels of TSB, ALT, AST, ALP, ALB, FBS, Bl, Urea, S. Creatinine, and Ca. Analyses were performed using an Abbott Architect c4000 analyzer. Furthermore, the procedure depended on the kit of Alinity company. All experiments were performed in triplicate to ensure reproducibility.

2. 9 Statistical Analysis

Data was executed by Python package v3.12 statsmodels. Data following normal distribution. The comparisons across groups were carried out by T-test. Results were illustrated in Mean ± Standard error (SE), counts (%) with p-values <0.001 and VS-MPR. Effect sizes were determined using Cohen's d and Glass's delta to assess group differences. Effect sizes ranged from moderate to large (0.6–1.0), indicating notable differences in biomarker levels between groups.

3. Results

A total of 120 participants were included in the analysis (49 females and 71 males). The distribution of ABO blood groups in both genders according to sex is summarized in (table 1). Among males, the most frequent groups were B+ (32.4%) and O+ (28.2%), while in females, the most frequent groups were O+ (24.5%) and B (22.4%). On the other hand, less frequent groups included A-. O-, B-, and AB- were rare in both genders.

Table1: Disruption of ABO blood groups in different sexes.

ABO groups	Female n (%)	Male n (%)	Total n (%)
O+	12 (24.5)	20 (28.2)	32 (26.7)
B+	11 (22.4)	23 (32.4)	34 (28.3)
A−	3 (6.1)	0 (0.0)	3 (2.5)
AB+	9 (18.4)	4 (5.6)	13 (10.8)
O−	3 (6.1)	2 (2.8)	5 (4.2)
A+	8 (16.4)	18 (25.4)	26 (21.7)
B−	3 (6.1)	2 (2.8)	5 (4.2)
AB−	0 (0.0)	2 (2.8)	2 (1.7)
Total	49 (100)	71 (100)	120 (100)

A Chi-square test of independence was performed to determine whether ABO blood group distribution differed significantly between males and females. The test showed a statistically significant association between sex and ABO group (X2 = 13.836, p = 0.044). Males tended to have slightly higher concentration of T3 and T4 2.1 ± 0.9 ng/ml, 110.8 ± 2.6 ng/ml. respectively compared with females 1.6 ± 0.8 ng/ml and 88.9 ± 2.6 ng/ml with statistically significant of PT3 = 0.032, PT40.041 as shown in (figure 1).

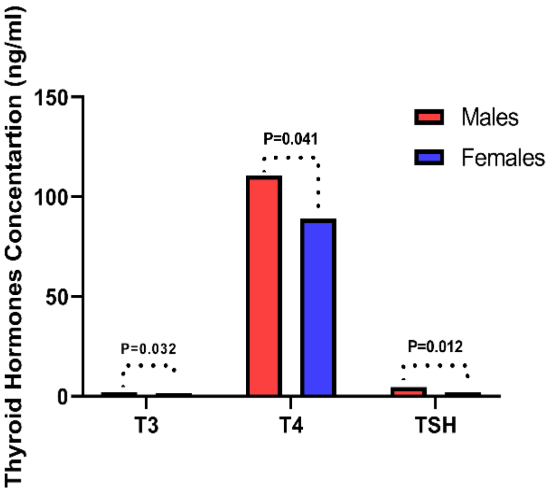

Figure 1: Demonstration T3, T4, and TSH thyroid hormones in different relative sex groups.

In contrast, females demonstrated lower level of TSH (1.8 ± 0.9 ± ng/ml) compared to male (4.5 ± 0.7 ng/ml) with a high significant different of (P = 0.012). Finally, all three hormones, there was considerable overlap between groups. The distribution of ferritin levels showed a marked difference between sexes, as illustrated in the (figure 2).

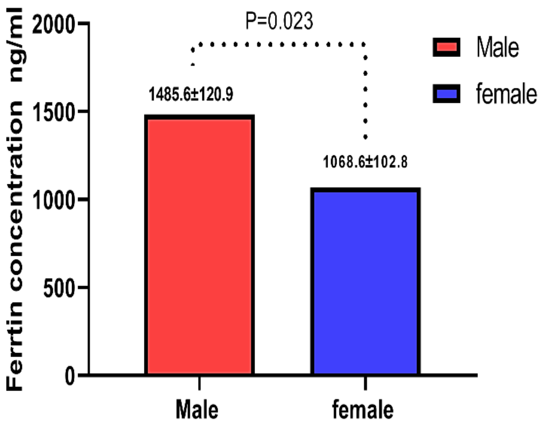

Figure 2: Comparison between concentration of ferritin in females and male in the intermediate thalassemia patients.

Males exhibited significantly higher (P=0.023) ferritin concentration (1484.5 ± 120.5 ng/ml) compared to females (1068.6 ± 102.3 ng/ml). These findings revealed a sex-based disparity in iron storage biomarkers, which may have implication for clinical interpretation and public health screening strategies. In the study, positive correlation between blood transfusion timer (T-Timer) and serum levels of both TSH and Ferritin was observed in patients with thalassemia intermedia, as illustrated in (figure 3).

The correlation coefficient (r) for ferritin and T-Timer was 0.88 with high significantly different statistical (P =0.001). Likewise, the correlation between TSH levels and T-Timer was positive, with an r of 0.89 and statistical significance (P = 0.021).

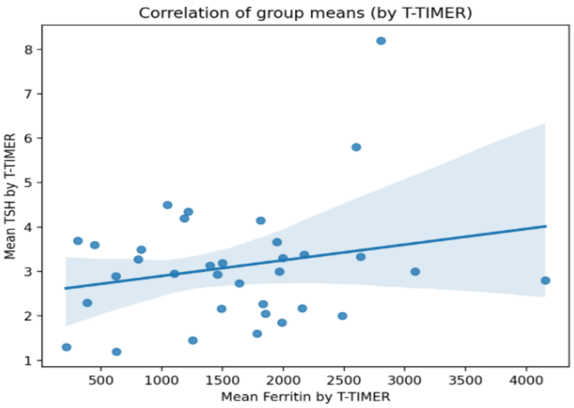

Figure 3: Correlation coefficient between serum levels of ferritin and TSH with fluctuation of blood transfusion timer.

Moreover, no significant difference was observed in most parameters in (table 2) except for serum calcium, which showed a statistically significant difference (P = 0.002, VS-MPR = 1.7). Regarding descriptive statistic, serum level of TSB was slightly higher in male (2.78 ± 0.29 ng/ ml) compared with females (2.12 ± 0.17 ng /ml).

Furthermore, serum level of AST was comparable between male (35.59 ± 2.6 ng/ml) and females (37.4 ± 4.6 ng /ml). Similarly, no significant variation was found in serum creatinine, albumin, fasting blood sugar, blood urea, ALP, and ALT between the two groups.

Table 2: Comparison between males and females in serum levels of biochemical parameters with Thalassemia intermediate.

Variable	Male	Female	P-Value	VS-MPR
	Mean ± SE	Mean ± SE		
TSB	2.7 ± 0.28	2.1 ± 0.17	0.314^{ns}	1.012
AST	35.5 ± 2.0	37.4 ± 4.6	0.245^{ns}	1.067
ALP	131.2 ± 7.1	125.3 ± 8.7	0.309^{ns}	1.014
ALT	24.9 ± 2.7	29.7 ± 4.5	0.785^{ns}	1.000
ALB	48.9 ± 0.4	52.9 ± 1.7	0.852^{ns}	1.000
FBS	108.4 ±2.5	109.0 ± 4.3	0.555^{ns}	1.000
BL.Urea	27.4 ± 0.9	25.5 ± 0.8	0.659^{ns}	1.000
S.Creatitin	0.4 ± 0.02	0.3 ± 0.04	0.440^{ns}	1.000
Ca	8.7 ± 0.1	10.2 ± 0.07	0.002^{**}	1.700

*(P≤0.05), ** (P≤0.01), NS: Non-Significant.

However, females demonstrated a slightly higher mean ALT level (29.7 ± 4.5 ng/ml) compared with males (24.9 ± 2.7 ng/ml). The result of Radar plot presented in figure 4 revealed that some time points, such as T-Timer 5 and 8, exhibited higher normalized values across multiple parameters, particularly GOT and GPT, suggesting transient elevations in liver enzymes.

Conversely, other time points showed lower overall normalized values, indicating reduced biochemical activity. The overlapping polygons indicated patterns of similarity among certain time points, while the spread illustrated variability in the biochemical responses over time.

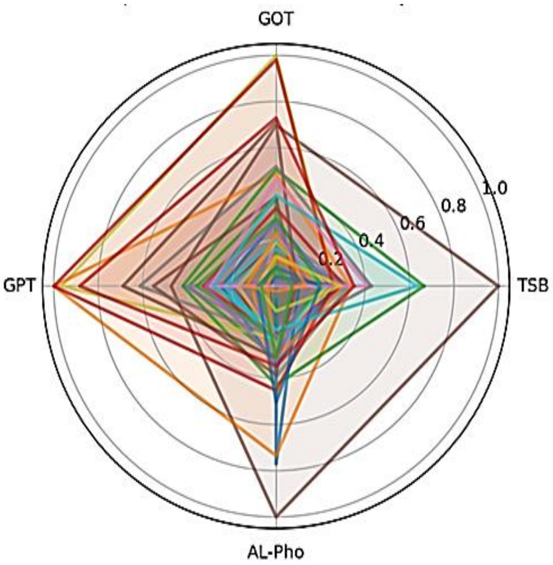

Figure 4: A radar plot of normalized mean values for biochemical parameters (TSB, ALT, AST, and ALP) across different T-Timer points.

The correlation matrix of group mean for five key biochemical parameters is shown in figure 5. Notably, ALT, and AST exhibited a high positive correlation (r = 0.88), suggesting a shared hepatic or inflammatory pathway. Conversely, ALB demonstrated consistent negative correlation with AST (r = -0.32), ALT (r = -0.27), and ALP (r = 0.20), potentially reflecting the inverse relationship with hepatic stress or synthetic capacity. TSB showed moderate correlations with both AST and ALP (r = 0.37), indicating possible cholestasis or hepatocellular involvement.

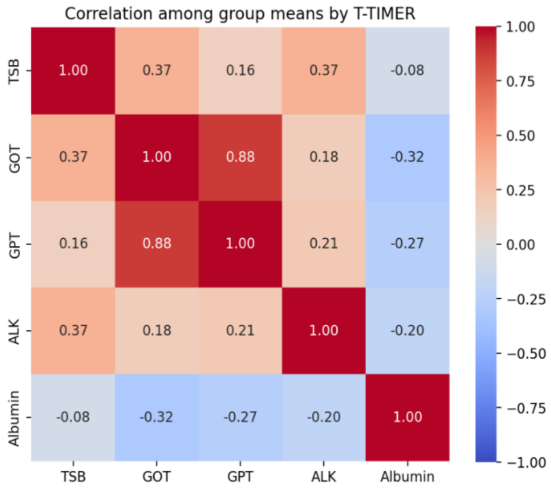

Figure 5: Heatmap correlation coefficient among biomarkers, generated using T-Timer. Color intensity reflects strength and direction of correlation.

4. Discussion

Thalassemia is a critical world health challenge due to the associated complexes in pathochemicalgenicity. The current study reveals that the prevalence of thalassemia is significantly higher among males than it is among women, and that the prevalent blood type differs between the sexes as demonstrated in table 1. The percentage of people with blood group B+ was high in males, while the percentage of people with blood group O+ was high in females.

Following this, the percentages of the various blood groups were different from one another. On the other hand, patients with blood groups AB (-ve) (1.7%) and A (-ve) (2.5%) are less than patients with other blood groups. This provides some insight into the sorts of blood groups that are more likely to contain the β-thalassemia gene [17].

According to findings that indicated a higher prevalence of thalassemia in males compared to females. Our finding was agreed with several studies demonstrated that among male and female patients, the proportion of ABO blood types and Rh-positive status corresponded to the following hierarchy O > B > A > AB [18-20]. Furthermore, there was not a significant difference in the distribution of ABO blood groups between sexes. Despite this, it was demonstrated that within the female population, the prevalence of Rh-negative blood types was significantly higher ($P < 0.05$) compared to females [18-22].

Furthermore, patients who were diagnosed with this disease had a higher prevalence of blood type O+, followed by blood type B+, and a lower prevalence of blood type AB-. On the other hand, the study did not reveal any statistically significant differences in the distribution of ABO blood types between male and female patients [23-26]. The result agrees with findings of another study where the group with the lowest percentage was AB (negative), which had 0%, while the group with the highest percentage was A (negative), reached 1.9%

[26]. In addition, Rh (-) phenotype among patients with β-thalassemia, as a percentage, when compared to the Rh (+) phenotype. This suggests that the Rh (-) phenotype is resistant to thalassemia [26]. The current study also revealed a significant disparity between sexes, with males exhibiting somewhat higher than average levels of T3 and T4 than females.

There are no significant gender-related differences in thyroid hormone levels or the prevalence of thyroid dysfunction in individuals with beta-thalassemia, according to research that was conducted in the past. Age shown to be the key factor connected to endocrine issues, including hypothyroidism, according to a cross-sectional study that included 114 patients [27, 28]. The investigation found that sex did not have a significant association with thyroid malfunction. According to a study that included sixty patients with beta-thalassemia (46 males and 44 females). Both genders had raised levels of TSH and T4 in comparison to the control group, with the females exhibiting a more substantial rise (above the control group).

On the other hand, levels of T3 and T4 in males did not distinguish themselves significantly from those in the control group. Although levels of TSH were found to be raised in both males and females [29, 30]. No significant variations detected in the distribution of thyroid and hypothyroid status between males and females, in a study that involved 84 youngsters of both sexes [31]. Figure 3 indicated a significant gender difference, with males exhibiting higher ferritin concentrations than females. A cross-sectional study involving 97 transfusion-dependent beta-thalassemia patients found that males had significantly elevated serum ferritin levels compared to females.

A negative correlation was identified between ferritin levels and sex hormones in males, indicating that iron overload may have a more significant effect on endocrine complications in this population [21]. A study involving 108 patients (54 males and 54 females) indicated that 17-year-old females had the highest mean ferritin concentration (13.1 ± 1.6 ng/mL), in contrast to 12-year-old males (8.2 ± 0.2 ng/mL).

Both sexes exhibited significantly elevated ferritin levels, suggesting insufficient chelation therapy rather than a consistent pattern related to sex (30). In beta-thalassemia carriers, iron deficiency is more common in females of reproductive age, while males typically exhibit normal iron stores, indicating sex-related differences in iron metabolism within this group [31]. The present study revealed a positive correlation between the blood transfusion timer (T-Timer) and serum concentrations of TSH and ferritin. According to results of figure 4, increased transfusion requirements during pregnancy in patients with thalassemia intermedia have been linked to significant elevations in serum ferritin, thereby reinforcing the relationship between transfusion frequency and iron status [27].

However, no significant correlation was observed between transfusion frequency and TSH levels in thalassemia intermedia. Research indicates that the prevalence of hypothyroidism is similar in patients with regular transfusions compared to those (22% vs. 21%), (P = 1.0), and TSH concentrations do not significantly vary according to transfusion status [19-22]. Further research corroborates these findings, demonstrating that TSH levels and thyroid dysfunction in thalassemia intermedia cannot be accurately predicted by transfusion frequency or iron overload alone [20, 21].

In conclusion, transfusion frequency is significantly linked to increased ferritin levels and iron overload in thalassemia intermedia. However, it does not seem to directly affect TSH concentrations or the occurrence of thyroid dysfunction. Consistent monitoring of ferritin and thyroid parameters is essential, despite TSH abnormalities not being directly influenced by the timing or frequency of transfusions.

The current investigation indicated no substantial sex-based differences in most of the assessed parameters, except for calcium, which exhibited a statistically significant variation. Descriptive statistics revealed that males possessed marginally elevated TSB levels, whereas females demonstrated slightly higher mean values for blood glucose, urea, ALP, and ALT. as listed in table 2. A study involving 57 individuals with thalassemia intermedia revealed a correlation between bone mineral density and hemoglobin levels, but other biochemical indicators, such as calcium, showed no sex-related differences [22].

A cross-sectional study involving 40 children with thalassemia intermedia (ages 5-17 years, both genders) revealed no significant variations in total serum bilirubin (TSB) levels between boys and females, as assessed by measures of TSB, ferritin, and liver enzymes. The demographic distribution (62.2% male and 37.8% female) indicated that TSB was assessed in both sexes with no statistically significant sex-based differences were observed [21-23]. Data indicate that sex does not substantially affect TSB levels in thalassemia intermedia, as fluctuations in TSB are more closely associated with disease severity and iron overload than with sex. Most metabolic abnormalities are ascribed to iron excess and pancreas dysfunction rather than to sexual dimorphism.

Thorough biochemical evaluations in thalassemia patients reveal that blood urea levels typically remain within acceptable ranges, with no notable differences based on sex detected. Moreover, research assessing ALP and ALT levels in patients with thalassemia intermedia has indicated values that diverge from those of healthy controls, where significant variations between males and females were seen [24-27]. Research indicates that sex does not substantially influence blood sugar, urea, ALP, or ALT levels in thalassemia intermedia. Variations in these parameters are predominantly linked to disease severity and iron overload [28-30].

Nevertheless, these investigations have not examined or quantified a definitive association between the transfusion timer (T-Timer) or the frequency and spacing of transfusions and serum GOT or GPT levels. Although frequent transfusions are recognized to heighten the risk of iron overload, hence increasing liver enzyme levels, the direct correlation between transfusion time and these hepatic indicators remains inadequately elucidated in the existing literature [30].

5. Conclusion

This study demonstrates notable sex related difference and transfusion associated biochemical and hormonal changes in patients with beta thalassemia intermedia. A significant association was observed between sex and ABO blood group distribution. Thyroid hormone analysis revealed higher T3 and T4 levels in males, whereas females showed lower TSH concentrations, indicating sex depended endocrine variation. Although, serum ferritin and TSH exhibited strong positive correlations with blood transfusion timing, highlighting the influence of transfusion intervals on iron overload and endocrine dysfunction.

The serum calcium, which was significantly elevated in females. Statistical analysis revealed transients' elevations in liver enzyme at specific transfusion time points and strong positive association between AST and AlT, suggesting hepatic involvement. Overall, these findings underscore the importance of individualized transfusion schedules and continuous biochemical and hormonal monitoring to minimize iron related complications and optimize clinical management in thalassemia intermediate.

6. References

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