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Haematological Changes in Predialyzed and Hemodialyzed Chronic Kidney Disease patients in Libya

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Abstract: *Chronic kidney disease (CKD) is an emerging public health problem worldwide, with increasing cost of healthcare particularly in third world nations like Libya. Hematological parameters are generally influenced in CKD and the effect increases with the stage of CKD. Hematological profiles are rarely investigated in CKD subjects in our population. This study was conducted to determine the hematologic profile in Libyan CKD subjects and to compare it in both hemodialyzed and pre-dialyzed patients. The study included 55 hemodialyzed CKD patients, 50 pre-dialyzed CKD patients, and 48 healthy controls.*

Blood Samples were analyzed for urea, creatinine, and complete blood counts including hemoglobin concentration, red blood cells (RBCs), white blood cells (WBCs) and platelets count. The data were statistically analyzed using SPSS. Our results revealed that hypertension was the most common cause of CKD among the studied group. A significantly lower ($p< 0.05$) RBCs count, hemoglobin levels (Hb), and hematocrit in CKD patients than healthy controls. Platelet count was lower ($p< 0.05$) in hemodialyzed CKD patients than pre-dialyzed CKD subjects. WBC count showed no significant change in CKD patients compared to control. The prevalence of anemia among hemodialyzed-CKD was markedly high (96% and 100% for males and females respectively) and double that of the predialyzed CKD patients (53% and 52% for males and females respectively).

Estimated glomerular filtration rate showed a significant positive correlation with hemoglobin (Hb) concentration but non-significant correlations with other hematological parameters. These hematological abnormalities expose CKD patients to higher risk of anemia-related complications and bleeding disorders, and the risk increase with the stage of CKD, which may have a role in increasing the rate of patient mortality and morbidity. Moreover, hypertension as the most common cause of CKD in our study, this may indicate the lack management programs for blood pressure in hypertensive patients.

I. Introduction

Chronic kidney disease (CKD), also called Kidney or renal failure can be a temporary (often acute) condition or become a chronic condition resulting in the inability of the kidneys to filter waste from the blood. CKD is considered as a serious health problem throughout the globe (1). It has a global public health problem. The high cost of care for CKD patients represents a substantial burden in third world nations.

The three most important risk factors for CKD in Arabian countries are diabetes, hypertension, and obesity and the prevalence of them is greater than in other nations (2). The real prevalence rate of CKD in Libya is unknown. The end stage kidney disease (ESKD) in Libya is a major health problem where the incidence rate is one of the highest in the globe. The total number of adult cases was 2417. The prevalence rate of ESKD undergoing dialysis was 624 per million population (3). CKD diagnosed as glomerular filtration rate (GFR) < 60ml/min per $1.73m^2$, which is mostly accompanied by symptoms of uremia and need a maintenance dialysis therapy or even a kidney transplant (4). On the other hand, anemia is also found in diabetics even with a GFR of > 60 ml/min (5).

Anemia is defined as a hemoglobin (Hb) level lower than 13 g/dL in men and post-menopausal females, and lower than 12 g/dL in pre-menopausal females according to WHO (6). Generally, the prevalence of CKD-associated anemia is reaching 50%. Although anemia may be found at different CKD stages, a strong correlation exists between the incidence of anemia and the degree of CKD severity (7).

It is well known that hematological parameters are reduced in CKD. The most affected ones are erythrocyte indices. This is because majority of erythropoietin is synthesized in the juxta glomerular apparatus except 10% in liver and other organs. Apart from decreased erythropoietin, changes in red blood cells (RBCs) indices may be caused by vitamin B12, iron and folic acid deficiencies, which are consequences of dietary insufficiency or blood loss (8), or by decreased erythrocytes' life span (9). Other causes of anemia in CKD may include gastrointestinal bleeding; severe hyperparathyroidism and systemic inflammation (10). The CKD-

associated anemia is treated by recombinant human erythropoietin. This way of treatment has replaced transfusions and led to major improvement of the survival rates of CKD-associated anemic patients (11).

Other affected hematological parameters in CKD include total leukocytes and its differential counts, platelet count, bleeding time and prothrombin time. White blood cells (WBCs) count, platelet count and bleeding time were within normal ranges in CKD subjects (12). Other findings reported include eosinophilia and prolonged bleeding time (13). Thrombocytopenia is regarded as a consequence of hemodialysis. However, its occurrence is rare in patients undergoing hemodialysis using biocompatible membranes (14). Platelet count tends to be decreased in both predialysis and hemodialysis patients (15).To our knowledge, the present study is the first of its kind in Libya, and It is conducted to determine the hematologic profile of CKD patients and compare the hemodialyzed and pre-dialyzed patients with normal healthy controls.

II. Subjects And Methods

2.1. Subjects:

The present cross sectional study was performed during a period from August to November 2016, and included 105 CKD patients (55 hemodialyzed patients undergoing conventional maintenance hemodialysis and 50 pre-dialyzed patients) selected from Center of Kidney Diseases Services – Benghazi and 48 age and sex-matched healthy subjects recruited from Alkeesh Polyclinic to serve as controls. Informed consent was obtained from all participants before the study. The selection of patients was based on previous diagnosis with chronic kidney disease, and that diagnosis dependent on KDIGO guidelines (CKD is defined as either kidney damage marked by albuminuria and GFR less than 60 mL/min per 1.73 m^2 for ≤ 3 months) (16).

Clinical information and medical history were obtained through the review of patient medical files and patients' interviews. Face-to-face interview was based on a questionnaire, that included variables such as age, sex, date of the diagnosis, cause of the disease, blood pressure, weight, height, duration of hemodialysis with exclusion of patients undergoing hemodialysis for less than 6 months, times of hemodialysis/ week, CKD treatments and any health problems or prescriptions.

Patients suffering from any disease other than CKD that could affect their metabolic status and the parameters studied such as malignancy, inherited or acquired blood diseases, hepatitis or other liver diseases, infection, acute or chronic inflammation, connective tissues diseases, dehydration, or recent hemorrhagic episode were excluded from the study. Pregnant and lactating women were excluded, and patients with a history of recent surgery, smoking or alcohol intake were also excluded. The history of medication was recorded and patients taking any drugs that could affect the parameters studied such as aspirin, non-steroidal anti-inflammatory drugs, or antihistamines were excluded. The control group consisted of healthy subjects with no history of inherited or acquired kidney or blood diseases. They were not suffering from infection or inflammation.

III. Methods

Venous blood samples were drawn from all participants, and collected in EDTA and plain tubes. Plain tube was centrifuged and serum was separated and stored at 2- 8 C^0 until it was analyzed within a week. Whole blood obtained by EDTA containing tube immediately analyzed for complete blood counts (WBCs, RBCs count, hemoglobin concentrations, hematocrit levels and platelets count) using a fully automated KX 21 hematology analyzer (Sysmex, Japan), While serum was used for estimation of creatinine and urea using a fully automated Cobas Integra 400 Plus (Roche, Germany).

Kinetic test with urease and glutamate dehydrogenase was used in the estimation of urea. Urea is hydrolyzed by urease to form ammonium and carbonate. In the second reaction, 2-oxoglutarate reacts with ammonium in the presence of glutamate dehydrogenase (GLDH) and the coenzyme NADH to produce L-glutamate. In this reaction two moles of NADH are oxidized to NAD for each mole of urea hydrolyzed. The rate of decrease in the NADH concentration is directly proportional to the urea concentration in the specimen. It is determined by measuring the absorbance at 340 nm (17).

Creatinine estimation is based upon a modification of the original picrate reaction (Jaffe) (18). Creatinine under alkaline conditions reacts with picrate ions forming a reddish complex. The formation rate of the complex measured through the increase of absorbance in a prefixed interval of time is proportional to the concentration of creatinine in the sample (19). The glomerular filtration rate was estimated by using Cockcroft-Gault formula (20):

$$\text{Men: } \frac{(140 - \text{age in years}) \, (\text{weight in Kg})}{72 \times serumCreatinine}$$

$$\text{Women: } \frac{(140 - \text{age in years}) \, (\text{weight in Kg})}{72 \times serumCrreatinine} \times 0.8$$

Statistical analysis:

The data were analyzed using the statistical package for the social sciences (SPSS version 17). Descriptive characteristics of the study participants were calculated as mean ± standard deviation (SD). Analysis of variance (ANOVA) was used to determine the differences in subject characteristics. Pearson's correlation coefficient determination was done to evaluate the degree of association between hematological changes and clinical and biochemical parameters. *P* value < 0.05 was considered as statistically significant.

IV. Results

The mean age and standard deviation (SD) of the hemodialyzed CKD patients selected for this study was 42.5 ± 12.3, and the male: female ratio was 7:4. The age range was 21- 70 years with duration of disease ranged from 1- 40 years, and duration of hemodialysis ranged from 1- 34 years. The mean age and SD of the pre-dialyzed CKD patients included in the study was 57.6 ± 14.8, and the male: female ratio was 3:5. The age range was 25- 90 years with duration of disease ranged from 1- 30 years. The mean age and SD of the healthy control subjects was 47.4 ± 12.4, and the male: female ratio was 1:2. The age range was 19- 67 years.

The most frequent cause of CKD among the studied group was hypertension, followed by diabetes mellitus; then glomerular nephritis, and cardiovascular diseases (Figure 1).

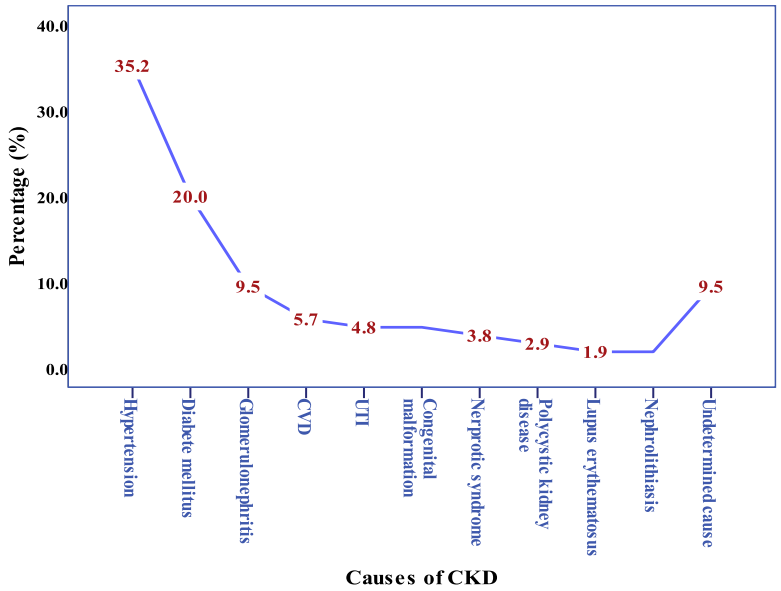

Figure 1. The Causes of chronic kidney disease among the study group.

Mean RBCs count, hemoglobin concentration and hematocrit levels were significantly lower in both groups of CKD patients than normal healthy controls ($p < 0.05$). On the other hand, WBCs count and platelets counts were significantly higher in pre-dialyzed CKD patients compared to hemodialyzed CKD patients ($p < 0.05$). No significant difference in platelet count was seen between pre-dialyzed CKD patients and normal healthy controls ($p= 0.74$). There was a non-significant difference in WBCs count of pre-dialyzed CKD patients or hemodialyzed-CKD patients when compared with control group ($p= 0.052$; $p= 0.09$, respectively). Similarly, platelet counts were significantly unchanged in both CKD groups compared with the control. Table 1 shows the comparison of the haematological parameters of both CKD groups with that of the healthy controls.

Table 1. Haematological profiles (mean ± SD) of pre-dialyzed-CKD, hemodialyzed -CKD patients and healthy control subjects.

Parameters	PreHD-CKD	HD-CKD	PreHD vs HD *P* value	Controls	CKD vs Control *P* value
WBC ($\times 10^9$/L)	7.61 ± 2.16	6.24 ± 1.76	*P* < 0.05	6.97 ± 1.75	NS
RBC ($\times 10^{12}$/L)	4.17 ± 0.8	3.35 ± 0.99	NS	4.59 ± 0.43	*P* < 0.05
Hgb (g/dl)	12.4 ± 2.19	9.77 ± 1.68	NS	13.79 ± 1.2	*P* < 0.05
Hct (%)	33.27 ± 9.58	28.5 ± 10.6	NS	39.75 ± 3.46	*P* < 0.05
Platelets ($\times 10^9$/L)	259.8 ± 55.7	213.5 ± 68.7	*P* < 0.05	264.3 ± 72.5	NS

Where; HD-CKD patients: Chronic Kidney Disease patients with at least 6 months duration of Hemodialysis treatment and Pre-HD-CKD patients: Chronic kidney Disease patients didn't undergo Hemodialysis treatment.

In the present study, subjects were considered as anaemic on the basis of WHO criteria of Hb less than 13 g/dL for male and less than 12 g/dL for female (21). Applying this criterion indicated that the percentage of anemia in hemodialyzed-CKD was about twice that in pre-dialyzed CKD patients. On the other hand, control subjects showed absence of anemia as shown in table 2.

Table 2. Prevelenceof anemia among CKD patients and control subjects

Subjects	Gender	Number	Percentage of anemia
Hemodialyzed CKD	Male	35	96.4%
Hemodialyzed CKD	Female	20	100%
Pre-dialyzed CKD	Male	20	53.3%
Pre-dialyzed CKD	Female	30	52.2%
Control subjects	Male	17	Zero%
Control subjects	Female	31	Zero%

Correlations of hematological changes with other parameters:

There were non-significant correlations between haematological profiles (WBCs count, RBC count, hemoglobin, hematocrit, and platelet count) and duration of disease, or duration of hemodialysis in CKD patients.

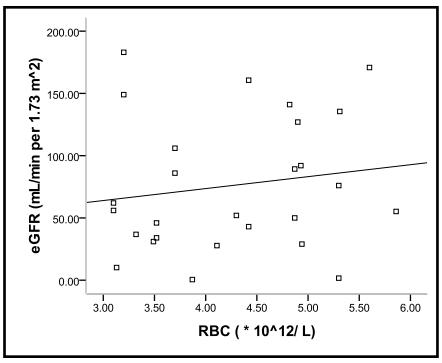

Figure 2. Correlation between eGFR and RBCs count.

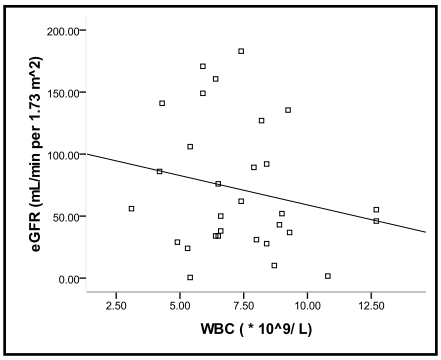

Figure 3. Correlation between eGFR and WBCs count.

In pre-dialyzed CKD patients, eGFR showed non-significant correlations with RBC count(r= 0.156 ,*p*= 0.43) (Figure 2), WBC count (r= - 0.206 , *p*= 0.27) (Figure 3), and platelet count (r= - 0.099 , *p*= 0.6) (Figure 4), but showed a significant positive correlation with hemoglobin (r= 0.371, *p*= 0.048) (Figure 5).

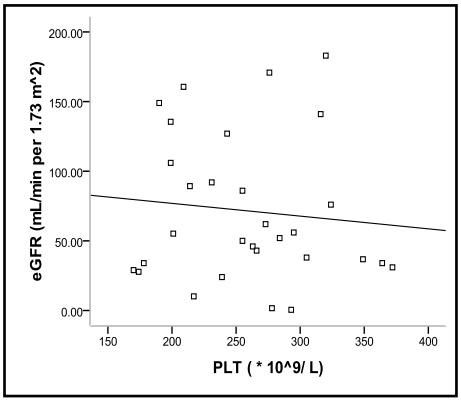

Figure 4. Correlation between eGFR and Platelets count.

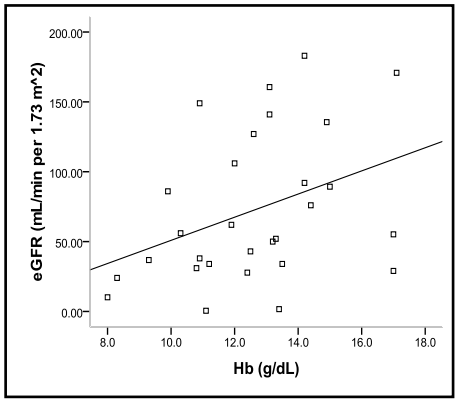

Figure 5. Correlation between eGFR and Hb concentrations.

V. Discussion

The present study was conducted on 105 CKD patients and 48 healthy controls, and revealed significantly lower RBC count, hemoglobin concentration, and hematocrit levels in CKD patients when compared to healthy subjects and the difference was more profound in hemodialyzed CKD patients than predialyzed CKD patients. These findings were consistent with Almahdi and colleagues (2016) who found significant decrease in hemoglobin levels in Libyan CKD patients compared to control group (22). Another recent work was consistent with our results and found that hemoglobin concentration and RBCs count were significantly different from that of the control at the severe CKD patients in Nigeria (Shittu and colleagues, 2013). Similarly, our results were in agreement with many other studies (23, 28).

Primary cause of decreased RBCs count in chronic renal failure is impaired erythropoietin production and other factors which suppress marrow erythropoiesis and shortened red cell survival. Erythropoietin is the hormone which is the major humoral regulator of red cell production and helps to maintain the viability of RBC by retarding the cleavage of DNA that occurs normally in CFU-Es. In the absence of EPO, DNA cleavage is rapid and leads to cell death. RBC survival is decreased in uremic patients in proportion to the blood urea nitrogen concentration, and it improves significantly after intensive hemodialysis. Uremic plasma increases the expression of phosphatidyl serine on the outer cell surface in red blood cells. This enhances the recognition of damaged red blood cells by macrophage, leading to their subsequent destruction and decreased survival (29).

The hemolytic factor implicated in decreased red blood cells survival is presumed to be a toxic substance normally excreted or metabolized by the kidneys, one such substance is guanidine and its derivatives which appear to be a subset of the many retained metabolites, adversely affect erythrocyte survival (30). The hemoglobin concentration and hematocrit generally provide an accurate reflection of the extent to which the circulating red cell mass is reduced. In chronic renal disease because of impaired erythropoietin secretion, increased destruction of red blood cells, leads to a fall in red blood cell count, which reduces the hemoglobin concentration and hematocrit (31). In progressive renal insufficiency, the degree of anemia is in general, proportional to the severity of azotemia (32). The lower GFR or EPO production, greater loss of hematopoietic nutrient elements and inflammation due to dialysis membrane can lead to lower mean hemoglobin and hematocrit levels in hemodialysis patients (33).

In our study, we found a significant positive correlation between creatinine clearance and hemoglobin concentration in pre-dialyzed patients, this finding confirms the previous evidence and consistent with a recent studies which found that Hb levels correlated significantly ($p < 0.05$) with eGFR ($r = + 0.43$) and showed that Hb values in diabetic-CKD patients gradually decreased along with decreasing GFR (34) and also in agreement with Afshar, R. and colleagues, (2010). Another study did not find such correlation (28). Our work showed insignificant correlation between hematocrit levels and RBC count with GFR. These findings were in accordance with Afshar and colleagues in 2010. On the contrary, others showed a significant positive correlation between GFR and hemoglobin level, hematocrit, and RBC count (24).

The duration of hemodialysis didn't affect hemoglobin, hematocrit or RBC count, and this finding is in accordance with that of Afshar, R., et al and Suega, K., et al, (23, 28). Our results also observed an insignificant association between duration of disease and hemoglobin, hematocrit, and RBC count, and this observation contrasts with findings of other studies that revealed a significant negative correlation between duration of disease and hemoglobin concentration and RBC count (27). It has been observed that, the platelet count is significantly decreased in hemodialyzed CKD patients, and insignificantly decreased in pre-dialyzed patients. Many studies found a statistically significant decrease in platelet count of CKD patients (25, 27, 35, 36). A study of George and colleagues conducted on 50 end stage renal disease patients undergoing hemodialysis or peritoneal dialysis, revealed an increase in platelet count (26). Erythropoietin potentites the effect of megakaryocyte colony stimulating factors, acetylhydrolase (PAF-AH) and paraoxonase (PON1). In chronic renal disease, impaired erythropoietin secretion leads to a decrease in platelet count (37). The detection of receptors for erythropoietin in megakaryocytes is understandable, because erythropoietin levels can affect platelet level and because of extensive homology between erythropoietin and thrombopoietin, erythropoietin act as the major humoral regulator of platelet mass.

In patients with chronic renal disease treated with erythropoietin, a minor increase in platelet count has been noted (38). The decrease in platelet count in patients with chronic renal disease leads to prolonged bleeding time and altered hemostasis. Platelets have been known to interact with dialysis membranes since the 1970. Dialysis membranes have been shown to cause platelet adhesion, aggregation, and activation (39). Platelet activation has been demonstrated by elevated levels of platelet factor 4 , as well as thromboxane following hemodialysis (40, 41). Hakim and Schafer suggested that thrombocytopenic episodes occurring with hemodialysis were associated with complement activation, specifically C3a, in addition to activation of platelets themselves (42). Complement activation occurred specifically in the setting of cuprophane membranes, and thrombocytopenia was only observed in the presence of complement activation (43). The present study found a non-significant correlation between platelet count and the time period the patients have been on dialysis, and this finding is in consistency with results of Ali and his colleagues in 2008 (44). In contrast to our finding, Alghythan, et al., found a significant negative relationship between platelet count and duration of hemodialysis, and they explained their observation by the finding that megakaryocytopoiesis decreases with years on HD; possibly contributing to their annual decreases in platelet counts (35, 46). The present study also indicated that there was a non-significant correlation between platelet count and GFR. This observation consistent with findings of some studies (47, 48), but inconsistent with others which showed presence of negative correlation between platelet count and serum creatinine (25).The findings of our study revealed a non-significant change of WBC count in predialyzed and hemodialyzed patients compared to control, and this observation is in agreement with that of other studies (26, 49). A study of Alghythan, et al. (35), revealed an insignificant difference in

WBC count between hemodialyzed CKD patients and control group. On the other hand, WBCs count was lower in hemodialyzed patients than in pre-dialyzed CKD patients. This finding is in contrast with Shittu and colleagues (2013) who found that WBC count was significantly increased with progression of the disease (49).

The possible mechanism by which chronic renal disease leads to a slight decrease in total leukocyte count may be explained by complement activation in vivo due to exposure of blood to artificial membranes in dialyser in patients undergoing dialysis. The complement is typically C3a or C5a, produced by the classic complement activation pathway. Complement activation stimulate neutrophil aggregation and adherence to endothelial surface which result in decreased leukocyte count. In patients undergoing hemodialysis the incidence of this affect may be as high as 20% (50). In the present work, we observed that WBC count is insignificantly correlated to the period of dialysis. Similarly, and in support to our study Mohamed et al., reported that the time period the patients have been on dialysis did not affect the leukocyte count (44).

According to WHO criteria; patients categorized as anemic if male H b< 13 g/dL or female Hb < 12 g/dL. Applying this criterion to our Hb results revealed that majority of hemodialyzed-CKD patients are categorized anemic (96% and 100% for males and females respectively) which were double that of the predialyzed CKD patients 53% and 52% for males and females respectively). This finding is in agreement with recent study by Abdu and colleagues (2009) who showed that, prevalence of anaemia was about 94% in CKD patients. Another recent study found that about 36% of type2 diabetic-CKD patients were anemic (22). Anemia is highly prevalent in CKD patients and the incidence increases with the progression of the disease. Therefore, anemia should be assessed and continuously monitored even to those without overt renal dysfunction. Furthermore, it was observed that hypertension (35%) followed by diabetes mellitus (20%) are most common causes for CKD in the studied group, and this finding highlights the alarming lack of blood pressure control, and promotes the primary healthcare providers to take into account the development of suitable measures to control blood pressure and prevent its secondary complications.

The major limitation of the present study was less sample size. Also, we have not studied male and female comparison, and the variations between different studies may be attributable to variations in study design, analytical techniques, statistical methods, or dialysis membranes used. In our future studies, we plan a multi-centered study with higher sample size to confirm the results and also to observe male and female differences. From the present study it can be concluded that patients with chronic kidney disease show abnormal haematological parameters, precisely reduced levels of RBC count, hemoglobin, hematocrit, and platelet count. In addition hemodialysis patients are more anemic and thrombocytopenic than predialysis patients. These findings expose CKD patients to higher risk of anemia-related complications and bleeding disorders, which may have a role in increasing the rate of patient mortality and morbidity. Moreover, hypertension is the most common cause of CKD , and this is may be indicator of lack of blood pressure control in hypertensive patients.

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