Lack of Correlation Between Serum Ferritin Levels and Patient Outcome in Israeli Adults with Hepatitis A Infection

David Hakimian MD, Elliot Turvall MSc, Sarah Israel MD and Zvi Ackerman MD AGAF

Department of Medicine, Hadassah–Hebrew University Medical Center, Mount Scopus Campus, Jerusalem, Israel

ABSTRACT: **Background:** In developed countries, hepatitis A virus (HAV) infection occurs mainly in adults. It is usually symptomatic and may cause acute liver failure (ALF). In patients with chronic liver disease, serum ferritin levels (SFL) can predict short-term prognosis.

Objectives: To determine whether admission SFL can serve as a prognostic marker in patients with HAV infection.

Methods: A retrospective analysis of 33 adults with HAV infection was conducted. Because none of our patients presented with ALF, the parameter "length of hospital stay," was used as a surrogate marker of disease severity.

Results: The mean (± SD) at admission SFL was 2529 ± 4336 ng/ml. SFL correlated with the levels of international normalized ratio (INR), liver enzymes, and degree of hemolysis that occurred during the disease course. SFL did not correlate with the levels of either albumin or bilirubin or with the length of the hospital stay. The mean length of hospital stay was 5.1 ± 2.0 days, which correlated with the levels of INR, albumin, and bilirubin as well as the degree of hemolysis. However, in multivariate analysis only albumin and bilirubin predicted the length of the hospital stay. Follow-up SFL, which were available only in eight patients, decreased during the hospital stay.

Conclusions: In adults with acute HAV infection, SFL may be increased. SFL correlated with the degree of liver injury and hemolysis that occur during the disease. However, in our cohort of HAV patients, who had a relatively benign disease course, SFL were of no prognostic value.

IMAJ 2019; 21: 676–680

KEY WORDS: length of hospital stay, hepatitis A virus (HAV) infection, hemolysis, prognostic marker,serum ferritin levels (SFL)

Hepatitis A viral (HAV) infection is the most common cause of acute viral hepatitis worldwide [1]. In Israel, a mandatory childhood vaccination program against HAV was introduced in 1999 [2]. Since the implementation of the vaccination program, in addition to improvements in the living and sanitation conditions, a substantial decline in the incidence of HAV infection was observed in all age groups of the Jewish and the non-Jewish (Arab-Palestinian) population in Israel [3]. However, despite the dramatic decrease of the HAV infection among the pediatric population, outbreaks of HAV infection still occur, mainly among non-vaccinated adolescents and adults [3,4]. While HAV infection in children is almost asymptomatic or mild, HAV infection in adults may manifest with severe hepatitis with intrahepatic and extra-hepatic complications and even with acute liver failure (ALF) [5,6]. Therefore, a marker is required that will enable early detection of adults with HAV infection who have a worse prognosis [6].

In patients with decompensated cirrhosis, high serum ferritin levels (SFL) may have prognostic value, which is correlated with the severity of hepatic decompensation and associated with early liver related death [7]. High SFL were also reported among a subset of patients with decompensated cirrhosis with acute on chronic liver failure and multi-organ failure [8,9]. It was suggested that in these patients, the occurrence of the acute on chronic liver failure with multi-organ failure is a consequence of the evolution of a condition of systemic inflammation and macrophage activation [9,10]. High SFL were also reported in patients with acute liver injury from various etiologies (including HAV infection) [11-13].

The aims of our study were to report admission SFL among a cohort of adult patients with HAV infection, to examine the validity of admission SFL as a marker for disease severity in HAV patients, and to compare the validity of SFL as a marker of disease severity with the prothrombin time (measured as International Normalized Ratio [INR]). INR is a reliable marker for the presence of severe liver injury, in patients with acute liver disease of any etiology [14].

Because none of the patients from our cohort presented with fulminant liver failure, the length of hospital stay was used as a surrogate marker of disease severity. Length of hospital stay was recently reported to be a reliable marker of disease severity in both acute and chronic diseases that affect the liver [15].

PATIENTS AND METHODS

This retrospective observational study was conducted in the two Jerusalem hospitals of the Hadassah–Hebrew University Medical

Center located in both East and West Jerusalem, Israel. The participating hospitals serve as primary, secondary, and tertiary medical care facilities for the Jewish and Arab-Palestinian population of Jerusalem. This study included adult patients who were admitted to one of the medical center campuses because of symptomatic acute HAV infection between April 2004 and July 2016.

Clinical, biochemical, and serological data of the patients included in the study were collected retrospectively from their electronic medical records. Acute HAV infection was identified by a combination of the appropriate clinical scenario, acute elevation of hepatic aminotransferase levels (to at least three times the upper limit of normal values), the presence of positive anti-HAV immunoglobulin M serology (Abbott Diagnostics, USA) and the absence of other etiologies for acute liver injury.

Additional laboratory parameters like, liver enzyme activity (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT], lactate dehydrogenase [LDH]) and serum/plasma levels of bilirubin, creatinine, urea, albumin, INR, and hematological parameters (i.e., hemoglobin levels, red blood cell [RBC], white blood cell [WBC], and platelets counts) were measured using standard automated procedures. During the study period, laboratory tests were performed by the same on-site laboratory facilities, using identical procedures and kits.

SFL were measured using Architect Ferritin assay (Abbott Ireland Diagnostic Division Lisnamuck, Longford Co., Longford, Ireland). The Architect Ferritin assay is a two-step immunoassay to determine the presence of ferritin in human serum and plasma using chemiluminescent micro particle immunoassay technology. The mean analytical sensitivity of the Architect Ferritin assay was calculated to be < 1 ng/ml, with the assay range from 0–2,000 ng/ml.

Statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). Descriptive statistics (count, mean and standard deviation, minimum and maximum) for the study variables are presented in the results section and in Table 1. The study variables were compared between genders using *t*-tests. The Pearson correlation coefficient and its significance were calculated between SFL, peak INR level, and the length of hospital stay on one hand and the other study variables on the other. The significant variables according to Pearson correlation (univariate analysis) were entered as independent variables into a linear regression (multivariate analyses), where the significant variables were left in the model.

The study was approved by the institutional ethics committee at the medical center in agreement with the Helsinki Declaration Helsinki Committee.

RESULTS

During the study period, 73 adult patients with acute HAV infection were admitted to our medical center. Patients with concomitant infection by chronic hepatitis C, chronic hepatitis B, acute Epstein-Barr virus infection (5 patients), non-alcoholic fatty liver disease (2 patients), or chronic biliary tract disease (1 patient) were excluded. Among the remaining 65 patients, only 33 patients underwent SFL determination during their hospital stay. The decision to perform SFL determination was made by the physicians assigned to the patients within the departments of medicine in both campuses of Hadassah Medical Center. At that time, no research was envisioned.

Table 1. Laboratory tests observed during the hospital course (n=33)

Laboratory parameter	Normal range	Type	Mean value ± SD	Observed range
Serum ferritin level (ng/ml)	10–120	Admission	2529 ± 4336	89–19,590
INR	1.4–1.0	Peak	1.6 ± 0.7	1.0–4.7
Serum albumin level (g/L)	35.0–50.0	Nadir	31.9 ± 4.2	21.0–40.0
Serum TB level (μmol/L)	0.0–17.0	Peak	161.2 ± 130.6	29.0–720.0
ALT level (U/L)	0–40	Peak	3016 ± 1520	361–8032
AST level (U/L)	0–35	Peak	2356 ± 1740	129–6711
ALP level (U/L)	40–130	Peak	222 ± 117	82–638
GGT level (U/L)	5–61	Peak	284 ± 236	59–1283
LDH level (U/L)	240–480	Peak	3671 ± 4357	352–15,827
Hemoglobin level (g/dl)	12.0–18.0	Peak	14.1 ± 2.1	9.0–16.8
Hemoglobin level (g/dl)	12.0–18.0	Nadir	12.6 ± 2.1	7.3–16.0
Hemoglobin difference (g/dl)	NA	NA	1.54 ± 0.86	0.4–4.0
WBC count (10^3 cells/μL)	4.0–10.0	Peak	7.02 ± 2.4	3.22–15.60
WBC count (10^3 cells/μL)	4.0–10.0	Nadir	4.77 ± 1.5	1.97–8.00
Platelet count (10^9/liter)	140–400	Nadir	194 ± 90	90–538

ALP = alkaline phosphatase, ALT = alanine aminotranspherase, AST = aspartate aminotranspherase, GGT = gamma-glutamyl transferase, INR = international normalized ratio, LDH = lactate dehydrogenase, NA = not applicable, TB = total bilirubin, WBC = white blood cell

The mean age ± standard deviation (SD) of the patients was 27.7 ± 12.9 years (range 17–69). Eighteen of the patients (54.6%) were male. Twenty-seven of the patients were of Arab-Palestinian origin and six patients were Jewish. The results of the SFL, synthetic liver function tests, liver enzymes, and the hematological parameters of the patients are presented in Table 1. None of the patients presented with acute liver failure.

During the hospital stay, a drop in the hemoglobin level of 1.54 ± 0.86 gram/dl (range 0.4–4.0) was noted among the HAV patients. Assuming that this drop in hemoglobin resulted mainly from the RBC hemolysis, we considered the value of hemoglobin difference as a marker of RBC hemolysis [Table 1] [16,17].

During the disease course, the values of the laboratory parameters detected among the male and female patients were not similar and were higher among the male patients: admission SFL (4141 ± 5402 vs. 595 ± 440, $P = 0.013$), nadir albumin levels (33.3 ± 4.1 vs. 30.1 ± 3.8, $P = 0.03$), peak hemoglobin

(15.3 ± 1.1 vs. 12.7 ± 2.0, $P = 0.0002$), and nadir hemoglobin levels (13.8 ± 1.2 vs. 11.2 ± 2.2, $P = 0.0005$).

The mean admission SFL was 2529 ± 4336 ng/ml (range 89–19,590). SFL significantly correlated with the admission levels of the following parameters: INR ($P = 0.0014$), ALT ($P < 0.0001$), AST ($P = 0.0002$), LDH ($P = 0.01$), peak hemoglobin level ($P = 0.046$), and to the degree of hemolysis that occurred during the hospital stay ($P = 0.014$). SFL did not correlate with the following parameters: the length of hospital stay, serum levels of albumin and bilirubin, peak and nadir WBC counts, and the age of the patients [Table 2].

The mean peak INR level was 1.6 ± 0.7 (range 1.0–4.7). The INR levels significantly correlated with the following parameters: SFL ($P = 0.0014$), serum albumin ($P = 0.008$), ALT ($P < 0.0001$), AST ($P = 0.0011$), and the degree of hemolysis that occurred during the hospital stay ($P = 0.0004$). Peak INR levels also correlated with the length of hospital stay ($P = 0.01$). The INR levels did not correlate with the following parameters: serum bilirubin, liver enzymes (ALP, GGT, and LDH), peak and nadir hemoglobin levels, platelet and WBC counts, and the age of the patients [Table 3]. Multivariate analysis (linear regression) disclose that only serum albumin ($t = -4.33$, $P = 0.0002$) with ALT ($t = 6.10$, $P < 0.0001$) were predictors of the INR level.

The mean length of hospital stay of our patients was 5.1 ± 2.0 days (range 2–11). The length of hospital stay significantly correlated with the levels of the following parameters that were measured during the stay in the hospital: peak INR ($P = 0.01$), serum albumin ($P = 0.01$), total serum bilirubin ($P = 0.01$), and the degree of hemolysis that occurred during the hospital course ($P = 0.007$). The length of hospital stay did not correlate with either the SFL or the levels of all liver enzymes (hepatocellular and cholestatic) or the peak and nadir hemoglobin levels [Table 4]. Multivariate analysis (linear regression) disclose that only serum albumin ($t = -2.59$, $P = 0.015$), with total serum bilirubin ($t = 2.49$, $P = 0.019$) were predictors of the length of hospital stay.

Follow-up SFL were available for only eight patients. The mean SFL obtained toward their hospital discharge was 503 ± 254 ng/ml (range 148–891).

DISCUSSION

In the present study, results of admission SFL in a selected group of Israeli adults with HAV infection were available for assessment. The admission SFL that were detected in the study patients ranged from normal values to values more than 70 times the upper limit of normal. Since phenotypic hereditary hemochromatosis is not a frequent finding among residents of the Middle East [18,19], and since, in a smaller subgroup of patients, follow-up SFL decreased during the hospital course, we assumed that the increased SFL levels that were detected at admission, were a consequence of HAV infection.

Table 2. Univariate associations between admission serum ferritin levels and study variables

Variable	R value	*P* value
Length of hospital stay (days)	0.085	0.64
INR level (peak)	0.540	**0.0014**
Serum albumin level (nadir)	0.030	0.87
Serum TB level (peak)	0.227	0.20
ALT level (peak)	0.671	**< 0.0001**
AST level (peak)	0.608	**0.0002**
ALP level (peak)	-0.201	0.26
GGT level (peak)	0.231	0.20
LDH level (peak)	0.464	**0.01**
Hemoglobin level (peak)	0.356	**0.046**
Hemoglobin level (nadir)	0.168	0.36
Hemoglobin difference	0.431	**0.014**
WBC count (peak)	0.064	0.73
WBC count (nadir)	-0.07	0.70
Platelet count (nadir)	-0.275	0.13
Age (years)	-0.122	0.50

Bold indicates significance

ALP = alkaline phosphatase, ALT = alanine aminotranspherase, AST = aspartate aminotranspherase, GGT = gamma-glutamyl transferase, INR = international normalized ratio, LDH = lactate dehydrogenase, TB = total bilirubin, WBC = white blood cell

Table 3. Univariate associations between peak International Normalized Ratio and study variables

Variable	R value	*P* value
Serum ferritin level (admission)	0.540	**0.0014**
Length of hospital stay (days)	0.439	**0.01**
Serum albumin level (nadir)	-0.463	**0.008**
Serum TB level (peak)	0.212	0.24
ALT level (peak)	0.658	**< 0.0001**
AST level (peak)	0.551	**0.0011**
ALP level (peak)	-0.337	0.06
GGT level (peak)	-0.217	0.23
LDH level (peak)	0.084	0.67
Hemoglobin level (peak)	0.058	0.75
Hemoglobin level (nadir)	-0.181	0.32
Hemoglobin difference	0.590	**0.0004**
WBC count (peak)	0.217	0.23
WBC count (nadir)	0.0308	0.86
Platelet count (nadir)	-0.038	0.84
Age (years)	0.040	0.83

Bold indicates significance

ALP = alkaline phosphatase, ALT = alanine aminotranspherase, AST = aspartate aminotranspherase, GGT = gamma-glutamyl transferase, INR = international normalized ratio, LDH = lactate dehydrogenase, TB = total bilirubin, WBC = white blood cell

Table 4. Univariate associations between the length of hospital stay and study variables

Variable	R value	*P* value
Serum ferritin level (admission)	0.085	0.64
INR level (peak)	0.439	**0.01**
Serum albumin level (nadir)	-0.443	**0.01**
Serum TB level (peak)	0.430	**0.01**
ALT level (peak)	0.185	0.30
AST level (peak)	0.095	0.60
ALP level (peak)	0.118	0.51
GGT level (peak)	-0.027	0.88
LDH level (peak)	-0.084	0.66
Hemoglobin level (peak)	-0.146	0.43
Hemoglobin level (nadir)	-0.328	0.07
Hemoglobin difference	0.468	**0.007**
WBC count (peak)	0.086	0.64
WBC count (nadir)	-0.227	0.21
Platelet count (nadir)	-0.249	0.17
Age (years)	0.133	0.46

Bold indicates significance

ALP = alkaline phosphatase, ALT = alanine aminotranspherase, AST = aspartate aminotranspherase, GGT = gamma-glutamyl transferase, INR = international normalized ratio, LDH = lactate dehydrogenase, TB = total bilirubin, WBC = white blood cell

High SFL among patients with acute liver injury from various etiologies was previously reported [11-13]. Bhagat and colleagues [11] suggested that leakages of ferritin from the necrotic hepatocytes cytosol may be the cause for the high SFL observed in such patients.

Kotoh and co-authors [12] observed high admission SFL in 100 patients with acute liver injury (including 9 patients with HAV, 31 with hepatitis B, and 3 with hepatitis C). Patients who developed ALF had higher SFL than those without ALF. By using multivariate logistic regression analysis, the authors revealed that the log of SFL, in addition to serum albumin concentrations and platelet counts, were independent predictive factors for ALF in patients with acute viral hepatitis of any etiology [12]. Ozawa et al. [13] reported the presence of high SFL in 54 patients with acute viral hepatitis (including 16 patients with HAV). Patients with the most severe forms of hepatitis and ALF had the highest SFL.

The SFL that were observed in the Japanese patients with ALF from these studies [12,13] were very high, but were within the range that is usually seen in patients with hyperferritinemic syndrome (also known as macrophage-activating syndrome) [20]. Based on outcomes of these findings, the authors of both studies hypothesized that over-activation of macrophages probably occurs in patients with acute viral hepatitis and that over activation of macrophages is probably an essential step for the development of ALF in these patients [12,13]. Findings from the study conducted by Møller et al. [21] corroborate above hypothesis. These authors reported that excessive production of another macrophage activation marker like sCD163, might predict mortality in the patients with ALF [21].

In the present study, SFL correlated with markers of hepatic cell necrosis and inflammation (e.g., peak serum levels of the liver enzymes and INR), but did not correlate with other liver dysfunction markers, like serum albumin and total bilirubin. Moreover, while serum albumin and total bilirubin had some value in the prediction of the disease course, SFL had no such value.

Another interesting finding in our study is that SFL correlated with the value of the hemoglobin difference. As mentioned earlier, we considered the parameter hemoglobin difference as a marker of RBC hemolysis, which probably occurred in our HAV patients. RBC hemolysis during HAV infection is a frequent finding that is assumed to occur because of various RBC enzymopathies like glucose-6-phosphate dehydrogenase (G6PD) deficiency [22]. While G6PD deficiency is rare in Japan, it is very prevalent in Israel among the Jewish and Arab-Palestinian subjects [23,24]. In 200 patients with HAV who were admitted to our institution from 1980 to 1999, 18 patients (9%) were found to have G6PD deficiency. RBC hemolysis was found to be present in 8 of them (44.4%) [22].

LIMITATIONS

Our study has several limitations. First, it is retrospective, and as such subjected to selection bias. Second, the number of patients included in this study is relatively small. The small number of patients precluded separate correlation analysis for males and female patients. It includes only hospitalized patients and does not include adults with HAV infection that were treated in an outpatient setting. None of our patients presented with fulminant ALF. The results of this study could have been different if patients with fulminant ALF had been included. Last, measuring SFL was not part of the standard laboratory evaluation of HAV patients. The decision whether to perform SFL on the specific patient was likely to be affected by the clinical approach of the different attending physicians and by the disease course. Patients who appeared to be sicker, were therefore more likely to be included in this cohort. Moreover, in the majority of the patients included in this cohort, follow-up SFL were not performed.

CONCLUSIONS

In adults with HAV infection, admission SFL can increase to more than 10 times the upper limit of normal. High SFL during the early stages of HAV infection are a temporary finding. In contrast to other disease states, the hyperferritinemia observed in adult Israeli HAV patients, probably played no role in the disease progression or regression of the acute liver injury that is associated with HAV infection [20]. In these patients, the high SFL probably originated from the existence of several

pathogenic factors, like leakage of ferritin from the damaged and inflamed hepatocytes and RBC hemolysis [25]. The disease course in most adult Israeli patients is relatively benign and thus SFL are probably of no value in the prediction of the disease course and prognosis.

Correspondence
Dr. Z. Ackerman
Dept. of Medicine, Hadassah–Hebrew University Medical Center, Mount Scopus Campus, Jerusalem 91240, Israel
Phone: (972-2) 584-4111
Fax: (972-2) 582-3515
email: zackerman@hadassah.org.il

References

1. Lavanchy D. Viral hepatitis: global goals for vaccination. *J Clin Virol* 2012; 55: 296-302.
2. Manor Y, Lewis M, Ram D, et al. Evidence for Hepatitis A virus endemic circulation in Israel despite universal toddlers' vaccination since 1999 and low clinical incidence in all age groups. *J Infect Dis* 2017; 215: 574-80.
3. Stein-Zamir C, Shoob H, Nubani N, Zentner G. Hepatitis A in Jerusalem–the exception that proves the rule? *Vaccine* 2008; 26: 5241-3.
4. Ly KN, Klevens RM. Trends in disease and complications of hepatitis A virus infection in the United States, 1999-2011: a new concern for adults. *J Infect Dis* 2015; 212: 176-82.
5. Mackinney-Novelo I, Barahona-Garrido J, Castillo-Albarran F, et al. Clinical course and management of acute hepatitis A infection in adults. *Ann Hepatol* 2012; 11: 652-7.
6. Israel S, Fruchtman H, Hakimian D, Ackerman Z. Ascites and gallbladder abnormalities are frequent findings in adults with hepatitis A virus infection. *IMAJ* 2019; 21: 24-8.
7. Maiwall R, Kumar S, Chaudhary AK, et al. Serum ferritin predicts early mortality in patients with decompensated cirrhosis. *J Hepatol* 2014; 61: 43-50.
8. Wu J, Chen L, Chen Y, Yang J, Wu D. Serum ferritin concentration predicts mortality in patients with hepatitis B virus-related acute on chronic liver failure. *Arch Med Res* 2014; 45: 251-6.
9. Bruns T, Nuraldeen R, Mai M, et al. Low serum transferrin correlates with acute-on-chronic organ failure and indicates short-term mortality in decompensated cirrhosis. *Liver Int* 2017; 37: 232-41.
10. Maras JS, Maiwall R, Harsha HC, et al. Dysregulated iron homeostasis is strongly associated with multiorgan failure and early mortality in acute-on-chronic liver failure. *Hepatology* 2015; 61:1306-20.
11. Bhagat CI, Fletcher S, Joseph J, Beilby JP. Plasma ferritin in acute hepatocellular damage. *Clin Chem* 2000; 46: 885-6.
12. Kotoh K, Ueda A, Tanaka M, et al. A high prevalence of extreme hyperferritinemia in acute hepatitis patients. *Hepat Med* 2009; 1: 1-8.
13. Ozawa E, Abiru S, Nagaoka S, et al. Ferritin/alanine aminotransferase ratio as a possible marker for predicting the prognosis of acute liver injury. *J Gastroenterol Hepatol* 2011; 26: 1326-32.
14. Koch DG, Speiser JL, Durkalski V, et al. The natural history of severe acute liver injury. *Am J Gastroenterol* 2017; 112: 1389-96.
15. Cholankeril G, Perumpail RB, Hu M, Skowron G, Younossi ZM, Ahmed A. Chronic hepatitis B is associated with higher inpatient resource utilization and mortality versus chronic hepatitis C. *Dig Dis Sci* 2016; 61: 2505-15.
16. Barcellini W, Fattizzo B. Clinical applications of hemolytic markers in the differential diagnosis and management of hemolytic anemia. *Dis Markers* 2015; 2015: 635670.
17. Ackerman Z, Pappo O, Ben-Dov IZ. The prognostic value of changes in serum ferritin levels during therapy for hepatitis C virus infection. *J Med Virol* 2011; 83: 1262-8.
18. Reish O, Shefer-Kaufmann N, Shimshoni DC, et al. Frequencies of C282Y and H63D alleles in the HFE gene among various Jewish ethnic groups in Israel: a change of concept required. *Genet Med* 2010; 12: 122-5.
19. Alkhateeb A, Uzrail A, Bodoor K. Frequency of the hemochromatosis gene (HFE) variants in a Jordanian Arab population and in diabetics from the same region. *Dis Markers* 2009; 27: 17-22.
20. Rosário C, Shoenfeld Y. The hyperferritinemic syndrome. *IMAJ* 2014; 16: 664-5.
21. Møller HJ, Grønbaek H, Schiødt FV, et al. U.S. Acute Liver Failure Study Group. Soluble CD163 from activated macrophages predicts mortality in acute liver failure. *J Hepatol* 2007; 47: 671-6.
22. Gotsman I, Muszkat M. Glucose-6-phosphate dehydrogenase deficiency is associated with increased initial clinical severity of acute viral hepatitis A. *J Gastroenterol Hepatol* 2001; 16: 1239-43.
23. Nkhoma ET, Poole C, Vannappagari V, Hall SA, Beutler E. The global prevalence of glucose-6-phosphate dehydrogenase deficiency: a systematic review and meta-analysis. *Blood Cells Mol Dis* 2009; 42: 267-78.
24. Abu Omar R, Algur N, Megged O, Hammerman C, Kaplan M. Glucose-6-phosphate dehydrogenase screening in Israel-Arab and Palestinian-Arab Neonates. *J Pediatr* 2015; 167: 169-72.
25. Kell DB, Pretorius E. Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. *Metallomics* 2014; 6: 748-73.

Capsule

Multiscale reverse engineering of the human ocular surface

Seo et al. presented a miniaturized analog of a blinking human eye to reverse engineer the complexity of the interface between the ocular system and the external environment. This model comprises human cells and provides unique capabilities to replicate multiscale structural organization, biological phenotypes and dynamically regulated environmental homeostasis of the human ocular surface. Using this biomimetic system, the authors discovered new biological effects of blink-induced mechanical forces. Furthermore, they developed a specialized in vitro model of evaporative dry-eye disease for high-content drug screening. This work advances the ability to emulate how human physiological systems interface with the external world, and may contribute to the future development of novel screening platforms for biopharmaceutical and environmental applications.

Nature Medicine 2019; 25: 1310
Eitan Israeli

"Circumstances do not make the man, they reveal him"

James Allen (1864–1912), British philosophifarmer writer known for his inspirational books and poetry and as a pioneer of the self-help movement