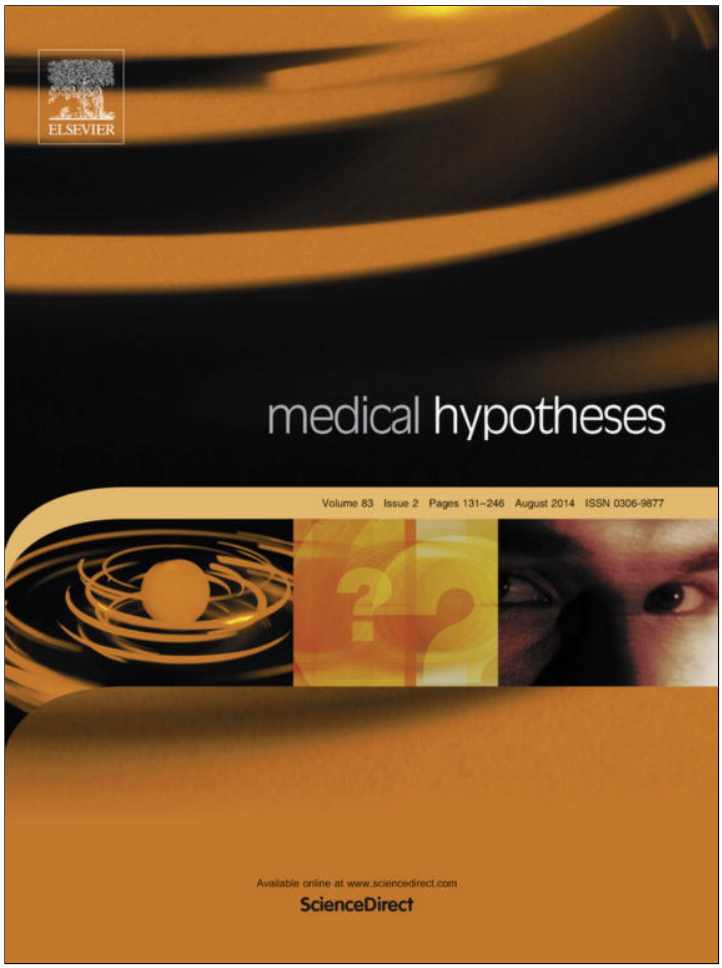

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Percutaneous excretion of iron and ferritin (through Al-hijamah) as a novel treatment for iron overload in beta-thalassemia major, hemochromatosis and sideroblastic anemia

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ABSTRACT

Iron overload is a big challenge when treating thalassemia (TM), hemochromatosis and sideroblastic anemia. It persists even after cure of TM with bone marrow transplantation. Iron overload results from increased iron absorption and repeated blood transfusions causing increased iron in plasma and interstitial fluids. Iron deposition in tissues e.g. heart, liver, endocrine glands and others leads to tissue damage and organ dysfunction. Iron chelation therapy and phlebotomy for iron overload have treatment difficulties, side effects and contraindications. As mean iron level in skin of TM patients increases by more than 200%, percutaneous iron excretion may be beneficial. Wet cupping therapy (WCT) is a simple, safe and economic treatment. WCT is a familiar treatment modality in some European countries and in Chinese hospitals in treating different diseases. WCT was reported to clear both blood plasma and interstitial spaces from causative pathological substances (CPS). Standard WCT method is Al-hijamah (cupping, puncturing and cupping, CPC) method of WCT that was reported to clear blood and interstitial fluids better than the traditional WCT (puncturing and cupping method, PC method of WCT). In other word, traditional WCT may be described as scarification and suction method (double S technique), while Al-hijamah may be described as suction, scarification and suction method (triple S technique). Al-hijamah is a more comprehensive treatment modality that includes all steps and therapeutic benefits of traditional dry cupping therapy and WCT altogether according to the evidence-based Taibah mechanism (Taibah theory). During the first cupping step of Al-hijamah, a fluid mixture is collected inside skin uplifting due to the effect of negative pressure inside sucking cups. This fluid mixture contains collected interstitial fluids with CPS (iron, ferritin and hemolyzed RBCs in thalassemia), filtered fluids (from blood capillaries) with iron and hemolyzed blood cells (hemolyzed RBCs, WBCs and platelets). That fluid mixture does not contain intact blood cells (having diameters in microns) that are too big to pass through pores of skin capillaries (6–12 nm in diameter) and cannot be filtered. Puncturing skin upliftings and applying second cupping step excrete collected fluids. Skin scarifications (shartat mihjam in Arabic) should be small, superficial (0.1 mm in depth), short (1–2 mm in length), multiple, evenly distributed and confined to skin upliftings. Sucking pressure inside cups (−150 to −420 mmHg) applied to skin is transmitted to around skin capillaries to be added to capillary hydrostatic pressure (−33 mmHg at arterial end of capillaries and −13 mmHg at venous end of capillaries) against capillary osmotic pressure (+20 mmHg). This creates a pressure gradient and a traction force across skin and capillaries and increases filtration at arterial end of capillaries at net pressure of −163 to −433 mmHg and at venous end of capillaries at net pressure of −143 to −413 mmHg resulting in clearance of blood from CPS (iron, ferritin and hemolyzed blood cells). Net filtration pressure at renal glomeruli is 10 mmHg i.e. Al-hijamah exerts a more pressure-

Abbreviations: CPS, causative pathological substances; CPC method, cupping puncturing and cupping method; DFO, deferasirox; DFP, deferiprone; DFX, deferoxamine; PC method, puncturing and cupping method; WCT, wet cupping therapy; TM, thalassemia.

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dependent filtration than renal glomeruli. Al-hijamah may benefit patients through inducing negative iron balance. Interestingly, Al-hijamah was reported to decrease serum ferritin significantly (by about 22%) in healthy subjects while excessive traditional WCT was reported to cause iron deficiency anemia. Al-hijamah is a highly recommended treatment in prophetic medicine. In conclusion, Al-hijamah may be a promising adjuvant treatment for iron overload in TM, hemochromatosis and sideroblastic anemia.

Introduction

Thalassemia (TM) is an inherited disorder of globin (of hemoglobin) synthesis resulting in chronic hemolytic anemia. Beta-thalassemia major is an inherited disorder of beta-globin synthesis resulting in chronic hemolytic anemia (hypochromic microcytic anemia) leading to accumulation of alpha chains inside RBCs causing hemolysis, which requires life-long transfusion therapy that may predispose to iron overload. The word "thalassemia" is derived from the Greek word "thalassa", which means sea. TM is distributed mainly in the countries surrounding the Mediterranean Sea. Now, the disease distribution expands to include Southeast Asia, Middle East, north India, the Indochina peninsula, Western European countries and even in USA and Canada due to immigrants, which caused a global distribution of the disease [1–3]. Hereditary hemochromatosis is an autosomal recessive genetic disease characterized by increased intestinal absorption of iron leading to accumulation of iron in tissues e.g. the liver causing liver deposits and cirrhosis. About 0.4% of people of northern European descent have the genetic mutation that increases the risk of developing hemochromatosis [4]. Sideroblastic anemias are anemias characterized by presence of ring sideroblasts in the bone marrow [5] and iron overload [6].

Manifestations of beta-thalassemia major and hemochromatosis

Manifestations of beta-TM are due to the triad of hemolysis, ineffective erythropoiesis and hemosiderosis (iron overload due to repeated blood transfusion and increased iron absorption). In severe TM, abnormal dietary iron absorption occurs due to ineffective erythropoiesis, increased body iron by 2–5 g per year and about double this amount with regular transfusions [7]. Thalassemic patients may present with hepatosplenomegally, mongoloid facies (prominent zygomatic bones, prominent maxilla, depressed nasal bridge and hypertelorism), hematological crises (hemolytic crisis precipitated by infection, hyperhemolytic crisis, aplastic crisis and megaloblastic crisis) [8]. However, iron overload and hemosiderosis are the most common complications due to increased intestinal iron absorption and repeated blood transfusion [8].

Regarding hemochromatosis, iron may be deposited in the pancreas, heart, gonads, pituitary gland and other organs. Early diagnosis followed by early and regular therapeutic phlebotomy can relieve iron overload and normalize patients' life expectancy. However, phlebotomy may result in anemia, which necessitates further future transfusions leading to iron overload again [9–11].

Early events in hemochromatosis are elevated serum ferritin, fatigue, arthralgia and skin pigmentation. Late manifestations and complications may include liver cirrhosis, hepatocellular carcinoma, skin pigmentation, arthritis, chondrocalcinosis, cardiomyopathy, heart failure, arrhythmia, endocrine disorders including diabetes (bronze diabetes), impotence and hypogonadism. Unless treatment is given for hemochromatosis, it progresses to iron overload causing organ damage and dysfunction [9–11].

In TM, iron overload may persist even after cure of TM with bone marrow transplantation, where iron-overloaded patients may require phlebotomy after transplantation to prevent the risks of residual iron excess causing hepatic fibrosis and other endocrine complications [12]. Moreover, growth failure, hypogonadism and infertility may develop secondary to iron excess or after the chemotherapeutic preparative conditioning regimens for bone marrow transplantation.

Serum ferritin

Ferritin serves to store iron in a non-toxic form, to deposit it in a safe form and to transport it to areas where it is required [13]. Free iron is toxic to cells as it acts as a catalyst in the formation of free radicals from reactive oxygen species (ROS) via the Fenton reaction resulting in the formation of the highly reactive hydroxyl free radical [14]. Serum ferritin was used to estimate iron overload in secondary haemochromatosis [15]. The myocardial iron can be examined with cardiac $T2^*$ magnetic resonance imaging. Serum ferritin levels correlated with cardiac $T2^*$ values in patients with abnormal myocardial iron loads [16].

Complications of iron overload

Iron overload disturbs the histological structure and function of body organs e.g. liver impairment is manifested by abdominal discomfort, lethargy and fatigue, while dyspnea with exertion and peripheral edema indicate cardiac impairment due to severe iron loading [17].

Liver abnormalities due to iron overload

Liver is the major site for iron deposition [18]. Hepatomegaly, fibrosis, disturbances in liver synthetic functions and micronodular cirrhosis occur [17,19]. Hepatic tenderness may occur. Hemosiderin aggregates and large quantities of ferritin can be visualized using electron microscopy resulting in hepatic damage secondary to excessive iron deposition. Hemochromatosis may also develop leading to hemosiderotic liver damage [17,20,21].

Heart abnormalities due to iron overload

Iron overload may cause premature atherosclerosis [22], congestive cardiomyopathy, heart failure, pericarditis, restrictive cardiomyopathy and angina (with no coronary artery disease) [23–26]. Conduction defects may result from iron deposition in the Bundle of His and the Purkinje system [27,28] leading to arrhythmias and sudden death. Iron is deposited in acidic compartments e.g. lysosomes as iron-loaded ferritin [29]. If the storage capacity of ferritin (about 2000 iron atoms/mol protein [30] is exceeded, the tissue's ability to safely store iron becomes disturbed, allowing release of partially degraded ferritin (hemosiderin) and redox-active low molecular weight (LMW) iron, which leads to generation of ROS capable of inducing oxidative damage to tissues [31,32]. LMW iron catalytically transforms [33] superoxide anion and hydrogen peroxide to the more aggressive prooxidant hydroxyl radical. LMW iron transforms lipid hydroperoxide to the more

pro-oxidant alkoxyl and peroxyl free radicals. Both collectively may initiate and propagate membrane lipid peroxidative injury. The presence of a preexisting iron-overload condition seems to amplify myocardial injury resulting from an imposed oxidative stress, such as ischemia/reperfusion [34].

Functional cardiac derangements may occur in thalassemic children receiving repeated blood transfusions [35,36] and not responding to medical intervention. Heart failure causes pulmonary congestion, peripheral edema and hepatic engorgement. This necessitates intensive iron removal [37]. Cardiac dysfunction may occur with little tissue iron deposition.

Therefore, cardiac damage is best prevented in patients with transfusional iron overload by maintaining a constant low level of chelator in the circulation.

Other abnormalities with iron overload

Iron overload may disturb the functions of endocrine glands as pancreas [38] causing diabetes mellitus [39]; pituitary gland causing dysfunctions [40] e.g. reduced gonadotropin levels and infertility [41]. Iron overload may disturb the functions of adrenal gland causing Addison's syndrome [42] and of parathyroid glands causing hypoparathyroidism and hypocalcemia [43].

Iron overload may cause skin hyperpigmentation (iron stimulates melanin production by melanocytes) and arthropathy [44] that affects the large joints [10] and is characterized by chondrocalcinosis (mostly present in hereditary hemochromatosis). Moreover, iron overload may cause severe muscle cramps (iron deposits in the myocytes), disabling myalgias and pulmonary hypertension [36,45,46].

Iron overload causes opportunistic Infections

The iron binding proteins transferrin and lactoferrin are bacteriostatic *in vitro* [47–49]. Iron overload may disturb the bacteriostatic functions of these proteins, which decreases their antimicrobial immunity leading to increased incidence of infections [47,50–52].

Treatment of iron overload

Several million patients worldwide have iron overload with the above-mentioned serious clinical implications. Iron overload is due to different genetic and environmental causes. Hereditary haemochromatosis and transfusional siderosis e.g. in TM and other refractory anemias are characterized by iron overload. Therapeutic options for iron overload are phlebotomy and iron chelation. Phlebotomy is the initial treatment of choice in haemochromatosis, while iron chelation is the current treatment for transfusional siderosis. Both were reported to treat TM. Principal iron chelators include deferoxamine, deferiprone and deferasirox. Combined subcutaneous DFX and oral DFP treatment seems to hold particular promise [53].

Deferoxamine (DFX)

DFX is isolated from *Streptomyces pilosus*. DFX is treated chemically to obtain the metal-free ligand to remove iron from hemosiderin, ferritin and, to a lesser extent, from transferrin. Iron atoms in hemoglobin or cytochromes are not removed by DFX [54]. Side effects of DFX include severe gastrointestinal upset, agranulocytosis, arthropathy, persistently raised liver enzymes, sepsis [55], hypotension, dysuria, abdominal discomfort, diarrhea, fever, leg cramps, tachycardia, cataract formation, neurotoxicity (during long-term use), visual and auditory changes [54,55]. Moreover, high-dose DFX therapy (10–25 mg/kg/h) resulted in pulmonary syndrome (tachypnea, hypoxemia, fever and eosinophilia). Contraindications for the use of DFX include renal insufficiency, anuria and pregnancy [54]. DFX is not recommended for hemochromatosis [54]. DFX was reported to be related to opportunistic infections with *Rhizopus orayzae*, causative of mucomycosis in patients with iron overload [56–58]. DFX-bound iron may be used by some pathogenic bacteria and fungi to promote their growth [59–61].

Deferiprone (DFP) and deferasirox (DFO)

DFP is available since 1987. It shows poor efficacy when used alone as compared to DFO [55]. Combination therapy using DFO and DFP for 6 months duration was statistically significant in chelating iron and lead to a progressive fall in the mean serum ferritin with significant improvement in the echocardiographic parameters of myocardial performance in TM patients [55]. DFP monotherapy (79.1 ± 4.3 mg/kg/day) reduced iron overload in transfusion-dependent TM for a 1-year clinical trial. However, drug-related side effects were gastrointestinal irritation, transaminitis and neutropenia. There was no mortality or agranulocytosis.

Zachariah et al. reported that there was no significant difference in mean serum ferritin level in TM patients receiving DFP versus DFO i.e. both DFP and DFO had comparable efficacy to each other as regard iron chelation (estimated by serial serum ferritin levels) [62].

Cappellini et al. investigated iron chelation with DFO in adult and pediatric patients with TM during a 5 years' follow-up period. DFO decreased serum ferritin significantly [63]. A proportion of patients (7.7%) discontinued treatment because of adverse events that included increased blood creatinine, abdominal pain, rash and gastrointestinal manifestations e.g. nausea. No adverse effects were observed regarding pediatric growth or adolescent sexual development. DFO was reported to induce renal failure fatalities, agranulocytosis and other toxicities [64].

Percutaneous route for excretion of iron overload

When there is iron overload, there is excess iron in interstitial fluid of skin and also intracellularlly [65,66]. Skin iron concentration is a reliable quantitative indicator of the body iron stores and is positively correlated with liver iron in patients with TM [66,67]. The mean iron levels in the skin of patients with beta-TM major and intermedia were elevated by greater than 200% and greater than 50%, respectively, compared with control values [68]. Wet cupping therapy (WCT) is a simple economic and evidence-based percutaneous excretory treatment [69] that we suggest for treating conditions of iron overload.

WCT as a treatment modality for clearing blood and interstitial fluids

Traditional WCT is a familiar line of treatment in Germany, Norway, Finland and other European countries [70]. Moreover, in Chinese hospitals and clinics, traditional WCT is a formally practiced line of treatment in treating different diseases [71]. In WCT, application of sucking cups to skin surface induces a pressure-dependent filtration and excretion of causative pathological substances (CPS) in interstitial fluid and blood at skin capillaries [69].

CPS in TM include high serum iron, high serum ferritin, high interstitial fluid iron, liberated hemoglobin (from hemolyzed RBCs) and fragments of hemolyzed and old RBCs [7,8]. Iron and ferritin CPS are found in blood plasma (fluid content of blood) and interstitial fluids but not attached to blood cells [65–67]. CPS of hemochromatosis and sideroblastic anemia are high serum iron and

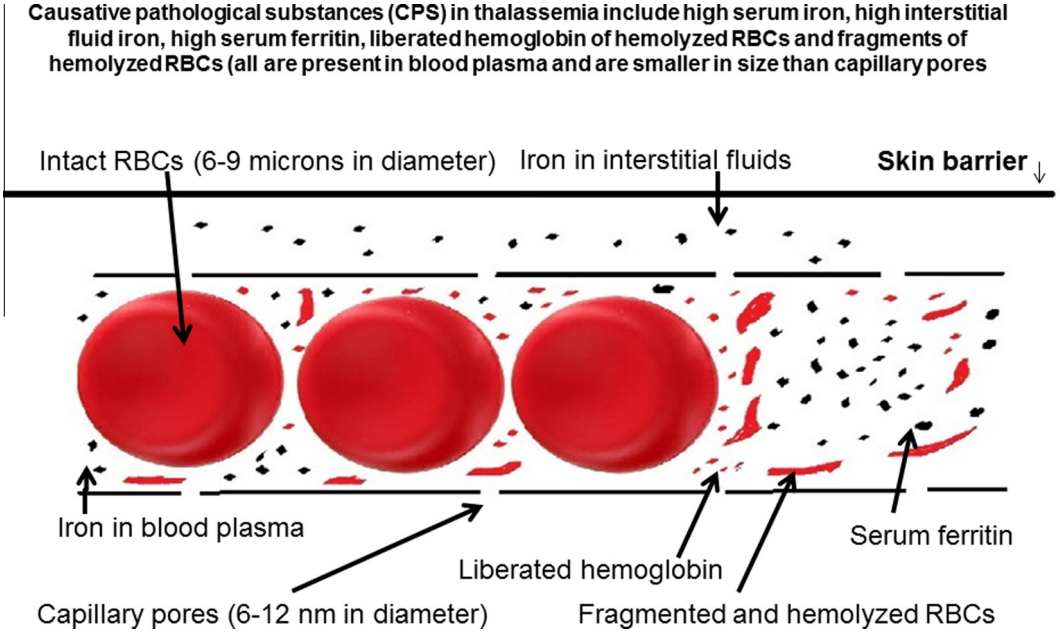

Fig. 1. Pathophysiology of iron overload conditions e.g. thalassemia. In iron overload conditions, serum and interstitial iron are high. There is high serum ferritin. In TM, liberated hemoglobin and hemolyzed RBCs may be present.

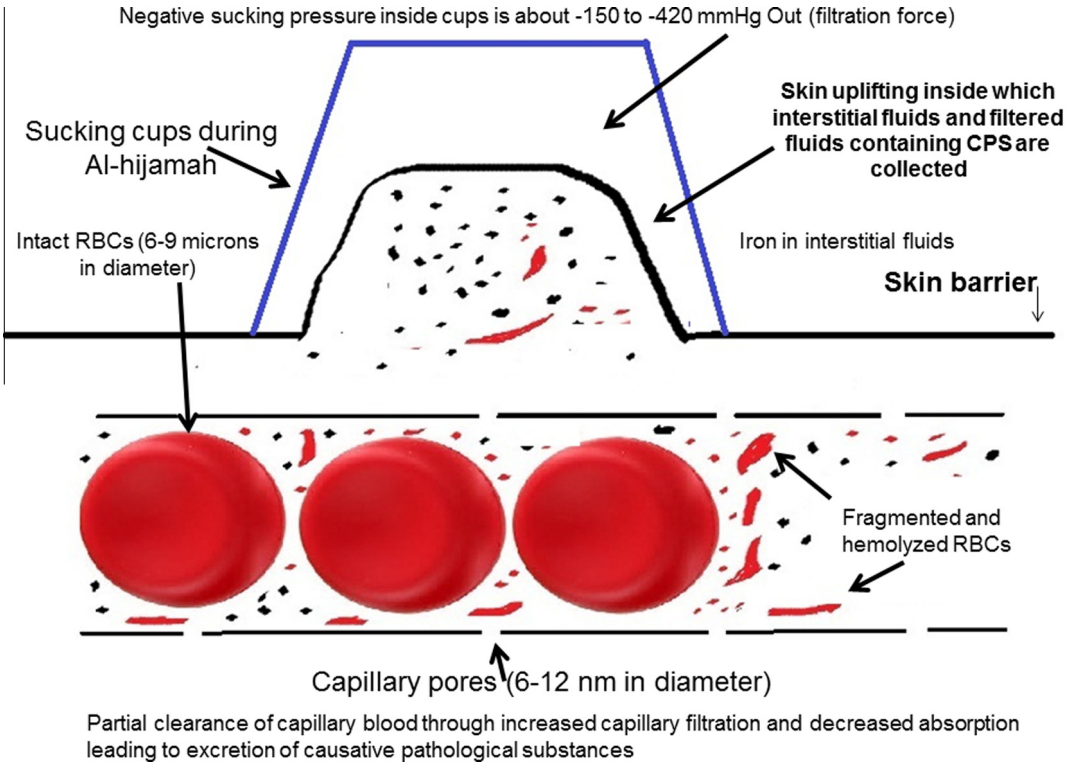

Fig. 2. Wet cupping therapy (Al-hijamah) for iron overload. Skin uplifting starts to form and progressively increases in size due to viscoelastic nature of the skin under effect of negative pressure suctioning. Boyle's law (pressure is inversely related to volume) is applied here. Collected fluids inside skin upliftings contain collected interstitial fluids with CPS (hemolyzed RBCs, high serum iron, liberated hemoglobin and high serum ferritin). No intact blood cells are found in filtered fluids as sizes of intact RBCs are much bigger than sizes of pores of skin capillaries.

high serum ferritin. All these CPS can be filtered through capillary pores (6–12 nm in diameter) of fenestrated skin capillaries [72].

Normally, tissue fluid is formed through filtration at arterial end of capillaries at net pressure of −13 mmHg and is absorbed at venous end of capillaries (Fig. 1) at net pressure of +7 mmHg [73].

Negative pressure (suction force) applied to skin surface using cups during WCT creates skin upliftings (gradually increasing in size due to viscoelastic nature of the skin). Local pressure around capillaries inside skin upliftings correspondingly decreases (Boyle's law) [74] causing increased capillary filtration with local collection

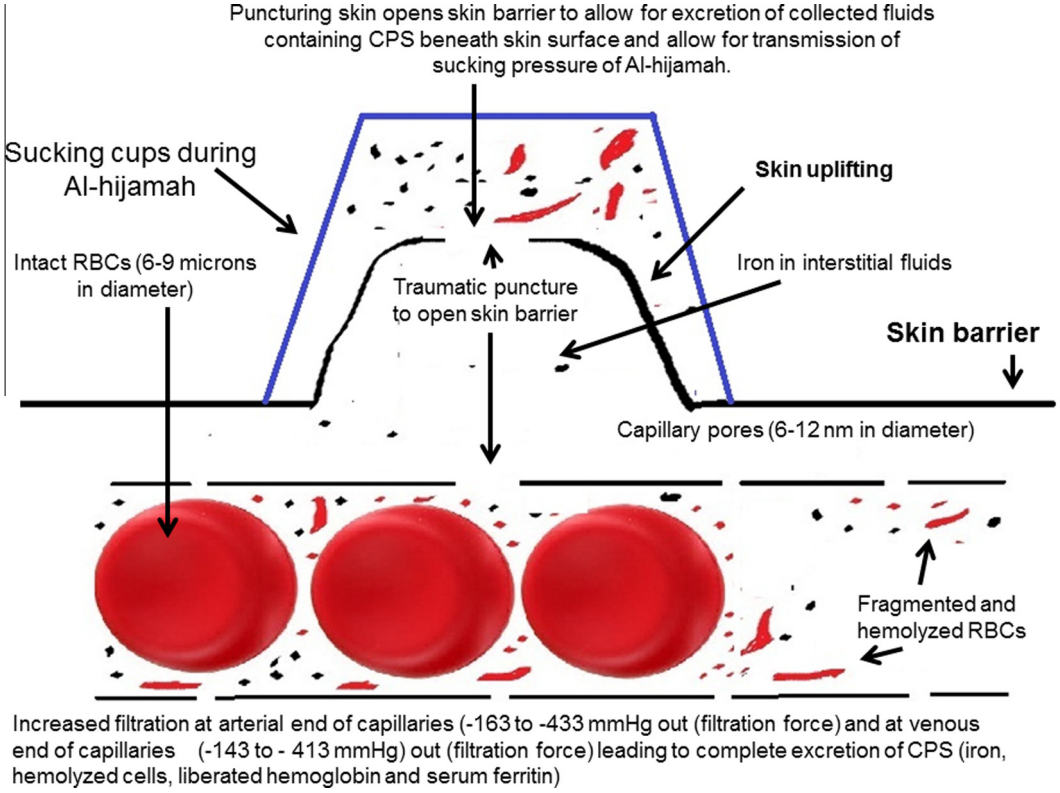

Fig. 3. Pressure-dependent excretion of CPS in iron overload conditions e.g. thalassemia during Al-hijamah.

of filtered fluids containing CPS and interstitial fluids containing CPS also (Fig. 2) which become retained inside skin upliftings [69].

Scarifying skin surface at skin upliftings opens skin barrier for evacuation of collected fluids with soluble CPS (Fig. 3). Applying sucking cups (for the 2nd time) creates a pressure gradient and a traction force across the skin leading to excretion of collected interstitial fluids with wastes (CPS) [69].

Applying sucking cups to skin surface also creates a pressure gradient and a traction force across the capillaries causing filtration of capillary fluids containing CPS and some bleeding at puncture sites. Old hemolyzed blood cellular fragments, molecules and particles smaller than capillary pore sizes selectively pass through capillary pores under suction pressure effect, while intact blood cells (having diameters in microns that are larger than pores of skin capillaries) do not (Fig. 3). Traumatized capillaries may bleed. Puncturing skin upliftings and applying second cupping step excrete collected fluids. Sucking pressure (from −200 to −560 hecta Pascal, equivalent to −150 to −420 mmHg) [75] is transmitted to around skin capillaries to be added to capillary hydrostatic pressure (−33 mmHg at arterial end of capillaries and −13 mmHg at venous end of capillaries [73]) against capillary osmotic pressure (+20 mmHg [73]). This creates a pressure gradient and a traction force across skin and capillaries (Fig. 3). By calculation of pressure differences, net pressure of −163 to −433 mmHg occurs at arterial ends of capillaries leading to increased filtration (exaggeration of normal condition). Net pressure of −143 to −413 mmHg occurs at venous end of capillaries leading to increased capillary filtration also (reversal of normal condition). This increase in filtration at both capillary ends results in clearance of blood and interstitial fluids (Fig. 4) from CPS (high iron, liberated hemoglobin, ferritin and hemolyzed blood cells) [69].

Al-hijamah versus traditional WCT

There are two different reported methods of WCT. First method is puncturing and cupping (PC, traditional WCT) method having five steps: skin demarcation, sterilization, puncturing, cupping and sterilization. Second method is cupping–puncturing–cupping (CPC, Al-hijamah) method having six steps: skin demarcation, sterilization, first cupping, puncturing, second cupping and sterilization [69]. CPC method of WCT (Al-hijamah) was reported to be better than PC method of WCT as regard blood and interstitial fluid clearance from CPS (with a lower degree of fresh blood loss) as Al-hijamah is a two-step filtration (cupping, purification) process while traditional WCT is a one-step filtration process [69]. CPC method is the cupping therapy practiced in Arabic countries, while PC method has a worldwide distribution [69].

Interestingly, excessive WCT (PC method) was reported to cause iron deficiency anemia [76–78]. The beauty of WCT comes from the fact that WCT is a simple, effective, repeatable and economic treatment. CPC method of WCT is called "Al-hijamah" in prophetic medicine [69], which is a recommended curative treatment by prophet Muhammad peace be upon him who said: "Cure is in three: in shartat mihjam, a gulp of honey and cauterization. I do not recommend my nation to cauterize" [79]. Cupping-bloodletting (traditional WCT but not Al-hijamah) has been already explored to treat disorders caused by iron overloading such as hemochromatosis [80].

WCT may have a priority and advantage when compared with similar currently used excretory procedures for treating TM and hemochromatosis e.g. phlebotomy. Phlebotomy is venesection to draw blood out to decrease concentration of an offending component [81] (CPS e.g. iron in TM and hemochromatosis). However, phlebotomy may increase anemic state in TM necessitating future transfusions, which increases again the iron overload from blood transfusions in TM. On the contrary, WCT does not cause anemia as blood cells are not filtered through capillary pores. The little amount of traumatic blood cells lost during skin scarifications of WCT step is too minimal to cause anemia (Table 1). However, excessive WCT (PC method) by unqualified practitioners was reported to cause iron-deficiency anemia [76–78].

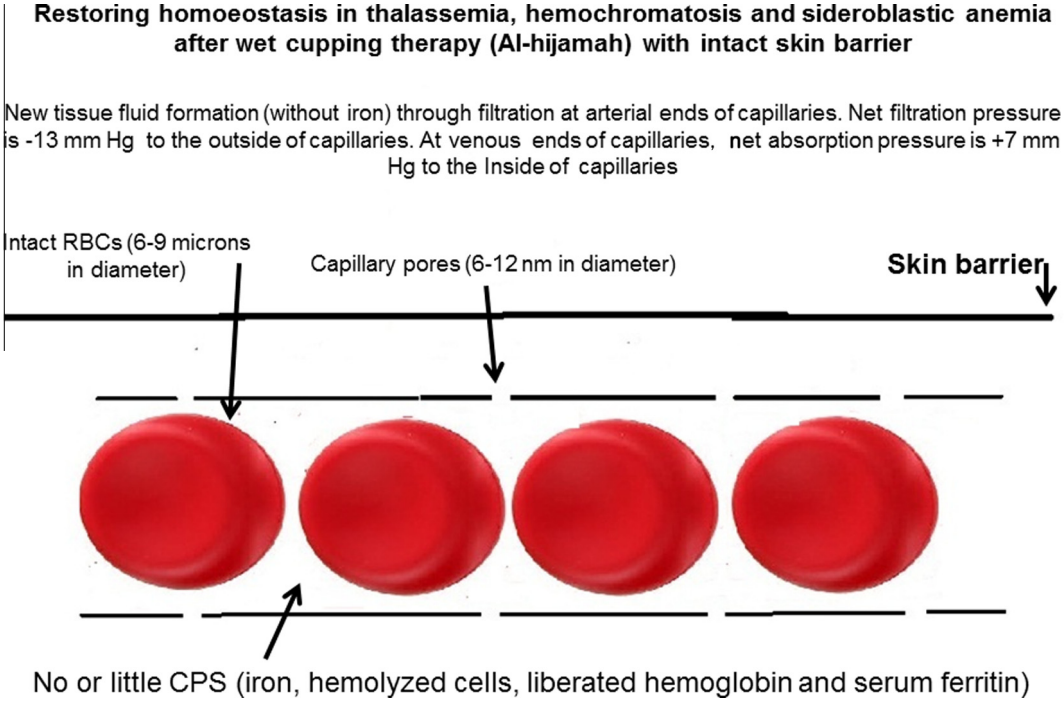

Fig. 4. Restoration of physiology and homeostasis after pressure-dependent excretion of CPS of iron overload conditions and thalassemia during Al-hijamah.

Table 1
Differences between Al-hijamah and phlebotomy.

	Phlebotomy	Wet cupping therapy (Al-hijamah)
Definition	Venesection, a procedure for cutting a vein to bleed to decrease a blood content or substances present in blood inside vessel wall	A minor surgical excretory procedure aiming at creating a pressure gradient across skin and blood capillaries to achieve a pressure-dependent clearance of blood and interstitial fluids from causative pathological substances (CPS)
Indication	To decrease a blood component or content e.g. red cell mass and hematocrit value in polycythermia and to decrease iron overload in TM	To clear (totally or partially) blood and interstitial spaces from excess fluids and or soluble CPS e.g. iron overload in TM and hereditary hemochromatosis (producing negative iron balance)
Effect on interstitial fluids	No effect	Clearance effect
Side effects	Anemia, bleeding, phlebitis	Reversible ecchymosis and iron-deficiency anemia with excessive cupping therapy done by unqualified therapists
Removal of	Whole blood	In the CPC method of WCT, there is removal of a fluid mixture containing collected interstitial CPS, hemolyzed blood cells (hemolyzed RBCs, WBCs and platelets) and filtered fluids (from blood capillaries) containing CPS (iron in TM and hemochromatosis) + a small amount of traumatic blood.
Types	One type	Two types of WCT 1. puncturing and cupping (PC) method of WCT 2. cupping, puncturing and cupping (CPC) method of WCT
Number of steps	One step	2 steps in the PC method (traditional WCT) 3 steps in the CPC method (Al-hijamah)
Other benefits	Removes a portion of blood including whole blood components and contents	Removes hemolyzed cells and liberated hemoglobin in hemolytic anemias
Requirement for subsequent transfusion	Increases due to phlebotomy-induced decrease in red cell mass	Does not increase
Effect of subsequent transfusion in thalassemic patients	Compensate for hemolysis and venesection-induced decrease in red cell mass, restores red cell mass and may increase iron overload again	Increases red cell mass
Analgesic effect	No analgesic effect	CPC method has a good analgesic effect (no need to administer an analgesic during the procedure)
Expected effect on thalassemic patients	Produces anemia and removes iron	• Removes hemolyzed blood cells and produces • Negative iron balance

Moreover, WCT clears fragmented RBCs, liberated hemoglobin (source of iron overload), high levels of ferritin and other hemolyzed cells. Clearance effect using WCT expands to include clearance of interstitial fluids, which were reported to be rich in iron [65,66]. Clearance of blood plasma will result in formation of a new clear interstitial fluid. This is expected to induce negative iron balance, where iron output may exceed iron intake. Combination of Al-hijamah with iron chelators may potentiate chelating effect of currently used iron chelators, where iron chelators mobilize iron from sites of tissue deposition to blood then WCT clears iron to outside. Table 2 lists differences between WCT and iron chelation therapy.

Table 2
Differences between CPC–WCT and iron chelation therapy.

	Iron chelation therapy	Wet cupping therapy (WCT)
Scientific principle	Form complexes with iron to enhance its urinary and fecal excretion	Exerts a pressure gradient and a traction force across the skin to create a pressure-dependent filtration of blood plasma through pores of cutaneous capillaries to get rid of CPS
Examples	Deferroxamine, deferiprone and deferasirox	Standard method is CPC method. Less effective is PC method of WCT
Cost	Expensive (being taken for life in treating TM)	Economic (few sessions are enough)
Effectiveness	Variable in efficacy with some limitations that may necessitate discontinuing treatment	Effective with almost no limitations
Side effects	*Deferroxamine causes:* gastrointestinal upset, agranulocytosis, arthropathy, persistently raised liver enzymes, sepsis, pulmonary syndrome. *Deferiprone causes:* gastrointestinal irritation, transaminitis and neutropenia *Deferasirox causes:* increased blood creatinine, abdominal pain, rash and, gastrointestinal symptoms e.g. nausea	Almost nothing when practiced properly in hospitals. Only reversible ecchymotic at sites of cup application.
Repetition	Every day or 5 days per week	Repeatable whenever indicated (once per 1–6 months may be satisfactory)
Target	Clear iron from tissues	Expected to induce negative iron balance and cause excretion of other CPS that increase in blood in TM patients e.g. high levels of serum iron, ferritin, liberated hemoglobin (source of iron) and fragmented blood cells.
Duration of treatment	For deferroxamine: 20–60 mg/kg/day (8–12 h per day, 5–7 days per week) For deferiprone: 25–100 mg daily orally For deferasirox: 20–40 oral daily	20–30 min (repeatable monthly)
Other benefits	No other benefits	– Clears interstitial spaces from CPS – Clears blood from high plasma solublecontents e.g. ferritin, liberated hemoglobin and fragments of hemolyzed cells.
Indications	To treat iron overload in TM	– Treats iron overload in TM and other disease conditions as hemochromatosis and sideroblastic anemia
Drug interactions	Deferiprone should be avoided with aluminum-containing antacids	WCT potentiates other pharmacological treatments (no chemical interaction)

Medical bases of Al-hijamah as a novel treatment for treating iron overload conditions e.g. hemochromatosis

Hemosiderosis is a condition of iron overload with an increased deposition of tissue iron without clinical signs while hemochromatosis is a clinically manifested iron overload characterized by organ dysfunction secondary to iron-induced injury, which may have genetic bases e.g. mutations in the HFE gene [82]. Excessive iron storage sometimes causes diabetes in patients with hemochromatosis [83]. Iron overload with hemosiderin accumulation occurs with an increased serum iron of 583 μg/dl (reference range: 77–253 μg/dl) with a total iron-binding capacity of 588 μg μg/dl (reference range: 275–443 μg/dl), an unbound iron-binding capacity of 5 μg/dl (reference range: 75–313 μg/dl), and an iron saturation of 99% (reference range: 20.5–72.5%) [84]. Iron increases in interstitial fluids also [83,85,86]. Serum iron and ferritin levels and dry-weight iron concentrations of liver, heart, and kidneys are markedly increased in hemochromatosis [84]. Serum level of saturated transferrin is also high [87]. Hemochromatosis is a progressive disease in which patients presumably begin absorbing excess iron at birth. Most patients with hemochromatosis have elevated serum ferritin and hemoglobin levels [88]. In addition, carriers of the hemochromatosis gene often have iron overload [88]. Serum concentrations of tissue inhibitor of metalloproteinase-1 (TIMP-1) and matrix metalloproteinase-3 (MMP-3) were reported to be significantly higher in hemochromatosis patients versus control subjects. Serum TIMP-1 correlates with both hepatic iron concentration and hepatic iron index [89].

Taibah mechanism for cupping therapy (Taibah theory) was recently introduced as an evidence-based mechanism for explaining the medical bases of all types of cupping therapy including Al-hijamah [90]. Al-hijamah includes all steps of traditional dry cupping therapy (DCT) and traditional WCT. For that, Al-hijamah is a more comprehensive modality of treatment that benefits patients with all the therapeutic benefits reported for both traditional DCT and WCT. Other health benefits of Al-hijamah include immunological benefits and pharmacological potentiation with conventional pharmacological therapies [91]. WCT practiced in Arabic countries (e.g. Saudi Arabia, Yemin, Egypt and others) is Al-hijamah, which is different from traditional WCT practiced elsewhere [92]. Al-hijamah is WCT of prophetic medicine [90].

During Al-hijamah, sucking cups are applied twice (double filtration) while in traditional WCT, cups are applied once (single filtration process). Al-hijamah induces a pressure-dependent and size-dependent non-specific clearance of blood and interstitial spaces from CPS, offending and noxious substances [90] e.g. excess inflammatory mediators in rheumatoid arthritis [91]. Traditional WCT was reported as a treatment for hemochromatosis [80]. Al-hijamah was not previously reported as a treatment for hemochromatosis.

Based on the above-mentioned literature reports, hemochromatosis is characterized by abnormal blood chemistry in the form of excess serum iron, excess serum ferritin and excess serum transferrin saturation, excess serum TIMP-1 and excess serum MMP-3. In addition, high iron is also present in interstitial fluids. Al-hijamah-induced clearance of blood and interstitial fluids may be a suggested treatment for conditions of iron overload and ferritin excess e.g. hemochromatosis. This can be supported by the report of Alshowafi (in Yemin) [93] who reported that serum ferritin decreased significantly in healthy subjects after blood cupping (termed Al-hijamah in Arabic countries) where serum ferritin decreased from 129.4 ± 59.2 to 100.6 ± 45.8 (ng/ml). The excretion value in this study is (ferritin level before Al-hijamah – ferritin level after Al-hijamah = 28.8 ng/ml) and the degree of blood clearance from ferritin (excretion value/ferritin level before Al-hijama) is about 22.25% i.e. blood was cleared from ferritin by 22%. The measurement was estimated 10 days after Al-hijamah, which gives the idea that the therapeutic effects of Al-hijamah is persistent for

a reasonable duration. Interestingly, in the same study, serum lipid profile improved dramatically giving the impression that Al-hijamah may treat more than one disease condition. Future research using Al-hijamah for treating patients with hemochromatosis and other iron overload conditions is strongly suggested and recommended where estimation of serum iron, ferritin and saturated transferrin should be done at different time intervals to confirm therapeutic benefits and their duration.

In conclusion, WCT may be promising to thalassemic patients in eliminating excess iron and hemolyzed blood cells and as an adjuvant or alternative treatment for iron overload conditions e.g. hemochromatosis and sideroblastic anemia.

Conflict of interest

The authors declare that there is no conflict of interest.

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References

[1] Kremastinos DT, Tsiapras DP, Kostopoulou AG, Hamodraka ES, Chaidaroglou AS, Kapsali ED. NT-proBNP levels and diastolic dysfunction in beta-thalassaemia major patients. Eur J Heart Fail 2007;9(5):531–6.
[2] Modell B, Khan M, Darlison M. Survival in beta-thalassaemia major in the UK: data from the UK Thalassaemia Register. Lancet 2000;355:2051–2.
[3] Olivieri NF, Nathan DG, MacMillan JH, Wayne AS, Liu PP, McGee A, et al. Survival in medically treated patients with homozygous beta-thalassemia. N Engl J Med 1994;331:574–8.
[4] Bokhoven MA, Deursen BM, Swinkels DW. Diagnosis and management of hereditary haemochromatosis. BMJ 2011;342.
[5] Cazzola M, Barosi G, Berzuini C, Dacco M, Orlandi E, Stefanelli M, et al. Quantitative evaluation of erythropoietic activity in dysmyelopoietic syndromes. Br J Haematol 1982;50(1):55–62.
[6] Camaschella C. Hereditary sideroblastic anemias: pathophysiology, diagnosis, and treatment. Semin Hematol 2009;46(4):371–7. http://dx.doi.org/10.1053/j.seminhematol.2009.07.001 [review].
[7] Mariani R, Trombini P, Pozzi M, Piperno A. Iron metabolism in thalassemia and sickle cell disease. Mediterr J Hematol Infect Dis 2009;1(1):e2009006. http://dx.doi.org/10.4084/MJHID.2009.006.
[8] Ashraf Magid, El-Din Mohamed Salah. Pediatric hematology & oncology. 2nd ed. The Scientific Book Center; 2003. p. 30.
[9] McCarthy GM, Crowe J, McCarthy CJ, Eustace S, Kenny D. Hereditary hemochromatosis: a common, often unrecognized, genetic disease. Cleve Clin J Med 2002;69(3):224–6. 229–230, 232–233 passim.
[10] Axford JS, Bomford A, Revell P, Watt I, Williams R, Hamilton EB. Hip arthropathy in genetic hemochromatosis. Radiographic and histologic features. Arthritis Rheum 1991;34(3):357–61.
[11] Bassett ML, Halliday JW, Powell LW. HLA typing in idiopathic hemochromatosis: distinction between homozygotes and heterozygotes with biochemical expression. Hepatology 1981;1(2):120–6.
[12] Angelucci E, Muretto P, Nicolucci A, et al. Effects of iron overload and hepatitis C virus positivity in determining progression of liver fibrosis in thalassemia following bone marrow transplantation. Blood 2002;100(1):17–21.
[13] Seckback J. Ferreting out the secrets of plant ferritin – a review. J Plant Nutr 1982;5(4–7):369–94. http://dx.doi.org/10.1080/01904168209362966.
[14] Orino K, Lehman L, Tsuji Y, Ayaki H, Torti SV, Torti FM. Ferritin and the response to oxidative stress. Biochem J 2001;357(Pt 1):241–7.
[15] Güngör T, Rohrbach E, Solem E, Kaltwasser JP, Kornhuber B. Logarithmic quantitation model using serum ferritin to estimate iron overload in secondary haemochromatosis. Arch Dis Child 1996;74(4):323–7.
[16] Lu MY, Peng SS, Chang HH, Yang YL, Chen CA, Jou ST, et al. Cardiac iron measurement and iron chelation therapy in patients with β thalassaemia major: experience from Taiwan. Transfus Med 2013. http://dx.doi.org/10.1111/tme.12014.
[17] Bassett ML, Halliday JW, Powell LW. Value of hepatic iron measurements in early hemochromatosis and determination of the critical iron level associated with fibrosis. Hepatology 1986;6(1):24–9.
[18] Bonkovsky HL. Iron and the liver. Am J Med Sci 1991;301(1):32–43.
[19] Conte D, Piperno A, Mandelli C, Fargion S, Cesana M, Brunelli L, et al. Clinical, biochemical and histological features of primary haemochromatosis: a report of 67 cases. Liver 1986;6(5):310–5.
[20] Hultcrantz R, Glaumann H. Studies on the rat liver following iron overload: biochemical studies after iron mobilization. Lab Invest 1982;46(4):383–92.
[21] Edwards CQ, Dadone MM, Skolnick MH, Kushner JP. Hereditary haemochromatosis. Clin Haematol 1982;11(2):411–35.
[22] Gursel O, Kurekci AE, Tascilar E, Ileri T, Altun D, Tapan S, et al. Premature atherosclerosis in children with β-thalassemia major. J Pediatr Hematol Oncol 2012;34(8):630–4.
[23] Schellhammer PF, Engle MA, Hagstrom JW. Histochemical studies of the myocardium and conduction system in acquired iron-storage disease. Circulation 1967;35(4):631–7.
[24] Fitchett DH, Coltart DJ, Littler WA, Leyland MJ, Trueman T, Gozzard DI, et al. Cardiac involvement in secondary haemochromatosis: a catheter biopsy study and analysis of myocardium. Cardiovasc Res 1980;14(12):719–24.
[25] Sanyal SK, Johnson W, Jayalakshmamma B, Green AA. Fatal "iron heart" in an adolescent: biochemical and ultrastructural aspects of the heart. Pediatrics 1975;55(3):336–41.
[26] Liu P, Olivieri N. Iron overload cardiomyopathies: new insights into an old disease. Cardiovasc Drugs Ther 1994;8(1):101–10.
[27] Buja LM, Roberts WC. Iron in the heart. Etiology and clinical significance. Am J Med 1971;51(2):209–21.
[28] Olson LJ, Edwards WD, McCall JT, Ilstrup DM, Gersh BJ. Cardiac iron deposition in idiopathic hemochromatosis: histologic and analytic assessment of 14 hearts from autopsy. J Am Coll Cardiol 1987;10(6):1239–43.
[29] Brun A, Brunk U. Histochemical indications for lysosomal localization of heavy metals in normal rat brain and liver. J Histochem Cytochem 1970;18:820–7.
[30] van der Schouw YT, van der Veeken PMWC, Kok FJ, Koster JF, Schouten EG, Hofman A. Iron status in the acute phase and six weeks after myocardial infarction. Free Rad Biol Med 1990;8:47–53.
[31] Giardina PJ, Grady RW. Chelation therapy in beta-thalassemia: the benefits and limitations of desferrioxamine. Semin Hematol 1995;32:304–12.
[32] Hershko C, Link G, Cabantchik I. Pathophysiology of iron overload. Ann N Y Acad Sci 1998;850:191–201.
[33] Aust SD, White BC. Iron chelation prevents tissue injury following ischemia. Free Rad Biol Med 1985;1:1–17.
[34] van der Kraaij AMM, Mostert L, van Eijk HG, Koster JF. Iron-load increases the susceptibility of rat hearts to oxygen reperfusion damage. Protection by the antioxidant (þ)-cyanidanol-3 and deferoxamine. Circ 1988;78:442–9.
[35] Wolfe L, Olivieri N, Sallan D, Colan S, Rose V, Propper R, et al. Prevention of cardiac disease by subcutaneous deferoxamine in patients with thalassemia major. N Engl J Med 1985;312(25):1600–3.
[36] Koren A, Garty I, Antonelli D, Katzuni E. Right ventricular cardiac dysfunction in beta-thalassemia major. Am J Dis Child 1987;141(1):93–6.
[37] Rahko PS, Salerni R, Uretsky BF. Successful reversal by chelation therapy of congestive cardiomyopathy due to iron overload. J Am Coll Cardiol 1986;8(2):436–40.
[38] Flynn DM, Fairney A, Jackson D, Clayton BE. Hormonal changes in thalassaemia major. Arch Dis Child 1976;51(11):828–36.
[39] Bomford A, Williams R. Long term results of venesection therapy in idiopathic haemochromatosis. Q J Med 1976;45(180):611–23.
[40] Costin G, Kogut MD, Hyman CB, Ortega JA. Endocrine abnormalities in thalassemia major. Am J Dis Child 1979;133(5):497–502.
[41] Schafer AI, Cheron RG, Dluhy R, Cooper B, Gleason RE, Soeldner JS, et al. Clinical consequences of acquired transfusional iron overload in adults. N Engl J Med 1981;304(6):319–24.
[42] Schafer AI, Rabinowe S, Le Boff MS, Bridges K, Cheron RG, Dluhy R. Long-term efficacy of deferoxamine iron chelation therapy in adults with acquired transfusional iron overload. Arch Intern Med 1985;145(7):1217–21.
[43] Gertner JM, Broadus AE, Anast CS, Grey M, Pearson H, Genel M. Impaired parathyroid response to induced hypocalcemia in thalassemia major. J Pediatr 1979;95(2):210–3.
[44] Mathews JL, Williams HJ. Arthritis in hereditary hemochromatosis. Arthritis Rheum 1987;30(10):1137–41.
[45] Aessopos A, Stamatelos G, Skoumas V, Vassilopoulos G, Mantzourani M, Loukopoulos D. Pulmonary hypertension and right heart failure in patients with beta-thalassemia intermedia. Chest 1995;107(1):50–3.
[46] Grisaru D, Rachmilewitz EA, Mosseri M, Gotsman M, Lafair JS, Okon E, et al. Cardiopulmonary assessment in beta-thalassemia major. Chest 1990;98(5):1138–42.
[47] Bullen JJ, Spalding PB, Ward CG, Gutteridge JM. Hemochromatosis, iron and septicemia caused by *Vibrio vulnificus*. Arch Intern Med 1991;151(8):1606–9.
[48] Reiter B, Brock JH, Steel ED. Inhibition of *Escherichia coli* by bovine colostrum and post-colostral milk. II. The bacteriostatic effect of lactoferrin on a serum susceptible and serum resistant strain of *E. coli*. Immunology 1975;28(1):83–95.
[49] Lawrence 3rd TH, Biggers CJ, Simonton PR. Bacteriostatic inhibition of *Klebsiella pneumoniae* by three human transferrins. Ann Hum Biol 1977;4(3):281–4.
[50] Abbott M, Galloway A, Cunningham JL. Haemochromatosis presenting with a double Yersinia infection. J Infect 1986;13(2):143–5.
[51] Capron JP, Capron-Chivrac D, Tossou H, Delamarre J, Eb F. Spontaneous *Yersinia enterocolitica* peritonitis in idiopathic hemochromatosis. Gastroenterology 1984;87(6):1372–5.
[52] Brennan RO, Crain BJ, Proctor AM, Durack DT. Cunninghamella: a newly recognized cause of rhinocerebral mucormycosis. Am J Clin Pathol 1983;80(1):98–102.
[53] Flaten TP, Aaseth J, Andersen O, Kontoghiorghes GJ. Iron mobilization using chelation and phlebotomy. J Trace Elem Med Biol 2012;26(2–3):127–30. http://dx.doi.org/10.1016/j.jtemb.2012.03.009.

[54] Brunton LL, Parker KL. In: Goodman & Gilman's. Manual of pharmacology and therapeutics. The McGraw-Hill Companies; 2008. p. 1142.
[55] Daar S, Pathare AV. Combined therapy with desferrioxamine and deferiprone in beta thalassemia major patients with transfusional iron overload. Ann Hematol 2006;85(5):315–9.
[56] Boelaert JR, van Roost GF, Vergauwe PL, Verbanck JJ, de Vroey C, Segaert MF. The role of desferrioxamine in dialysis-associated mucormycosis: report of three cases and review of the literature. Clin Nephrol 1988;29(5):261–6.
[57] Rex JH, Ginsberg AM, Fries LF, Pass HI, Kwon-Chung KJ. *Cunninghamella bertholletiae* infection associated with deferoxamine therapy. Rev Infect Dis 1988;10(6):1187–94.
[58] Daly AL, Velazquez LA, Bradley SF, Kauffman CA. Mucormycosis: association with deferoxamine therapy. Am J Med 1989;87(4):468–71.
[59] Prpic JK, Robins-Browne RM, Davey RB. In vitro assessment of virulence in *Yersinia enterocolitica* and related species. J Clin Microbiol 1985;22(1):105–10.
[60] Robins-Browne RM, Tzipori S, Gonis G, Hayes J, Withers M, Prpic JK. The pathogenesis of *Yersinia enterocolitica* infection in gnotobiotic piglets. J Med Microbiol 1985;19(3):297–308.
[61] Robins-Browne RM, Prpic JK. Effects of iron and desferrioxamine on infections with *Yersinia enterocolitica*. Infect Immun 1985;47(3):774–9.
[62] Zachariah M, Tony S, Bashir W, Al Rawas A, Wali Y, Pathare A. Comparative assessment of deferiprone and deferasirox in thalassemia major patients in the first two decades-single centre experience. Pediatr Hematol Oncol 2013;30(2):104–12.
[63] Cappellini MD, Bejaoui M, Agaoglu L, Canatan D, Capra M, Cohen A, et al. Iron chelation with deferasirox in adult and pediatric patients with thalassemia major: efficacy and safety during 5 years' follow-up. Blood 2011 Jul 28;118(4):884–93.
[64] Kontoghiorghes GJ. Deferasirox: uncertain future following renal failure fatalities, agranulocytosis and other toxicities. Expert Opin Drug Saf 2007;6(3):235–9.
[65] Cavill I, Staddon G, Jacobs A. Iron kinetics in the skin of patients with iron overload. J Invest Dermatol 1972;58(2):96–8.
[66] Youssry I, Mohsen NA, Shaker OG, El-Hennawy A, Fawzy R, Abu-Zeid NM, et al. Skin iron concentration: a simple, highly sensitive method for iron stores evaluation in thalassemia patients. Hemoglobin 2007;31(3):357–65.
[67] Farquharson MJ, Bagshaw AP, Porter JB, Abeysinghe RD. The use of skin Fe levels as a surrogate marker for organ Fe levels, to monitor treatment in cases of iron overload. Phys Med Biol 2000;45(5):1387–96.
[68] Gorodetsky R, Goldfarb A, Dagan I, Rachmilewitz EA. Noninvasive analysis of skin iron and zinc levels in beta-thalassemia major and intermedia. J Lab Clin Med 1985;105(1):44–51.
[69] El Sayed SM, Mahmoud HS, Nabo MMH. Methods of wet cupping therapy (Al-Hijamah). In light of modern medicine and prophetic medicine. Altern Integ Med 2013;2(3):1–16.
[70] Salomonsen LJ, Skovgaard L, la Cour S, Nyborg L, Launsø L, Fønnebø V. Use of complementary and alternative medicine at Norwegian and Danish hospitals. BMC Complement Altern Med 2011;18(11):4. http://dx.doi.org/10.1186/1472-6882-11-4.
[71] Cao H, Li X, Liu J. An updated review of the efficacy of cupping therapy. PLoS ONE 2012;7(2):e31793. http://dx.doi.org/10.1371/journal.pone.0031793.
[72] Sarin H. Physiologic upper limits of pore size of different blood capillary types and another perspective on the dual pore theory of microvascular permeability. J Angiogenes Res 2010;11(2):14. http://dx.doi.org/10.1186/2040-2384-2-14.
[73] Saladin KS. Anatomy & physiology: the unity of form and function. In: The circulatory system, blood vessels and circulation. The McGraw-Hill Companies; 2008. p. 761.
[74] West JB. The original presentation of Boyle's law. J Appl Physiol 1999;87:1543–5.
[75] Huber R, Emerich M, Braeunig M. Cupping – is it reproducible? experiments about factors determining the vacuum. Complement Ther Med 2011;19:78–83.
[76] Kim KH, Kim TH, Hwangbo M, Yang GY. Anaemia and skin pigmentation after excessive cupping therapy by an unqualified therapist in Korea: a case report. Acupunct Med 2012;30(3):227–8.
[77] Yun GW, Yang YJ, Song IC, Park KU, Baek SW, Yun HJ, et al. A prospective evaluation of adult men with iron-deficiency anemia in Korea. Intern Med 2011;50(13):1371–5.
[78] Lee HJ, Park NH, Yun HJ, Kim S, Jo DY. Cupping therapy-induced iron deficiency anemia in a healthy man. Am J Med 2008;121(8):e5–6.
[79] Al-Bukhari MI. Chapter of cure is in three. In: The English translation of Sahih Al Bukhari. Book of medicine, Hadeeth numbers 5680–5681, Assryia library, Sayda, Lebanon; 2002.
[80] McMullin MF, Bareford D, Campbell P, Green AR, Harrison C, Hunt B, et al. Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. Br J Haematol 2005;130(2):174–95.
[81] Greenstone Gerry. The history of bloodletting. BCMJ 2010;52(1):12–4.
[82] Fairbanks VF, Brandhagen DJ. Disorders of iron storage and transport. In: Beutler E, Lichtman SM, Coller BS, Kipps TJ, Seligsohn U, editors. Williams hematology. New York, NY: McGraw-Hill; 2001. p. 489–502.
[83] Kishimoto M, Endo H, Hagiwara S, Miwa A, Noda M. Immunohistochemical findings in the pancreatic islets of a patient with transfusional iron overload and diabetes: case report. J Med Invest 2010;57(3–4):345–9.
[84] Sprague WS, Hackett TB, Johnson JS, Swardson-Olver CJ. Hemochromatosis secondary to repeated blood transfusions in a dog. Vet Pathol 2003;40(3):334–7.
[85] Schumacher Jr HR. Ultrastructural characteristics of the synovial membrane in idiopathic haemochromatosis. Ann Rheum Dis 1972;31(6):465–73.
[86] Costello DJ, Walsh SL, Harrington HJ, Walsh CH. Concurrent hereditary haemochromatosis and idiopathic Parkinson's disease: a case report series. J Neurol Neurosurg Psychiatry 2004;75(4):631–3.
[87] Brandhagen DJ, Fairbanks VF, Baldus W. Recognition and management of hereditary hemochromatosis. Am Fam Physician 2002;65(5):853–60.
[88] Beaton MD, Adams PC. The myths and realities of hemochromatosis. Can J Gastroenterol 2007;21(2):101–4.
[89] George DK, Ramm GA, Powell LW, Fletcher LM, Walker NI, Cowley LL, et al. Evidence for altered hepatic matrix degradation in genetic haemochromatosis. Gut 1998;42(5):715–20.
[90] El Sayed SM, Mahmoud HS, Nabo MMH. Medical and scientific bases of wet cupping therapy (Al-hijamah): in light of modern medicine and prophetic medicine (A review article). Altern Integ Med 2013;2(5):1–16.
[91] Ahmed SM, Madbouly NH, Maklad SS, Abu-Shady EA. Immunomodulatory effects of bloodletting cupping therapy in patients with rheumatoid arthritis. Egypt J Immunol 2005;12(2):39–51.
[92] Huang YL. Cupping-bloodletting therapy of Saudi Arabia and its clinical application. Zhongguo Zhen Jiu 2008;28(5):375–7.
[93] Alshowafi FK. Effect of blood cupping on some biochemical parameter med. J Cairo Univ 2010;78(1):311–5.