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Iron Homeostasis and Diabetes Risk

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Abstract

Iron binds to protein in the form of heme and functions as co-factor of enzymes that mediate redox reactions for energy production and intermediate of metabolism. Individual iron status is reflected as the combination of nutritional and pathological diseases. Iron overload (IO) and iron deficiency anemia (IDA) are the risk factor for diabetes. The association of iron and diabetes was investigated in β -thalassemia patients, in high dietary iron levels, and in iron deficiency anemia were also associated with diabetes risk. IO and IDA play the major role of oxidative stress and inflammation, mediated insulin resistance and β -cell dysfunction to causal diabetes. The underlying mechanisms mediated of these effects still waiting for searching.

Keywords: Iron overload; Iron deficiency anemia; Oxidative stress; Diabetes mellitus

Abbreviations: DMT-1: Divalent Metal Transporter 1; Hmox: Hemeoxygenase; DCTB: Duodenal Cytochrome b; HEPH: Hephaestin; FPN: Ferroportin; Tf: Transferrin; TfR1: Transferrin Receptor 1; TfR2: Transferrin Receptor 2; HJV: Hemojuvelin; BMP: Bone Morphogenic Protein; SMAD: Human Homolog of *Drosophila Mad*

Introduction

Iron is one of the major functional compo¬nents in many proteins, involved in the wide range of vital biochemical functions. Iron is also functions as co-factor of enzymes that mediate redox reactions for energy production and intermediate of metabolisms. The major iron metabolism is on the traditional areas of erythropoiesis and nutrition. Iron is also represent as a major role in oncology, neurological, cardiology, infectious diseases and many pathology diseases. Individual iron status is reflected as the combination of pathological diseases, nutritional, environmental and genetic factors. Iron may directly bind to protein (or as the iron containing) in the form of heme or iron–sulfur clusters. Normal iron levels ensure ready availability for optimal metabolic activity to maintain the normal physiological function and immune system. For understanding the degree of the changing of normal iron status can predispose to the wide variety of disorders. Transition heavy metals including ferrous iron (Fe^{2+}) and copper (Cu^{+}) can increase oxidative stress, especially in Fe^{2+} may cause autooxidation to generate superoxide ($O^{2\bullet-}$) and/or to generate hydroxyl radical (OH•) by interaction with hydrogen peroxide(H_2O_2) via the Fenton and Harber Weiss reactions [1]. Major cellular oxidative stress came from mitochondrial respiration. Heart, brain, kidney, liver and skeletal muscle are the major effective organs for oxygen consumption. These organs converted oxygen to $O_2^{\bullet-}$ [2]. Electron transport chain in mitochondrial has also been sourced to $O_2^{\bullet-}$ [3].

Many research studies demonstrated the association of increased oxidative stress with insulin resistance, insulin signals dysfunction and adipocytokines dysregulation [4,5]. Type 2 diabetes mellitus is a common and well described in terms of insulin resistance and β -cell dysfunction. Recent studies have been demonstrated the abnormalities of insulin signaling and insulin secretion caused from the activation of stress pathways, mitochondrial dysfunction, hepatic fuel homeostasis, and central nervous system dysregulation [6-9]. Obesity is the well accepted predictor for the disease. Therefore, it is well accepted that the most reliable predictor for the disease is obesity. The attention has also been paid to the nutrients and the nutrient-sensing pathways in the conditions of chronic caloric excess. Most of the interest role of nutrients in diabetes risk is attended on macronutrients while a micronutrient is iron closely associated with diabetes risk. Body iron store elevation has been linked to factors of the metabolic syndrome, obesity, dyslipidemia, hypertension, hyperglycemia and diabetes [10-14]. The association between iron and diabetes were demonstrated that the mean (±SD) concentration of ferritin was significantly higher than controls [109 (±105) vs 71.5 (±68.7)ng/mL; P<0.001] and the mean (±SD) ratio of transferrin receptors to ferritin

was significantly lower [102 (±205) vs 141 (±340); P=0.01], respectively for developing diabetes [15]. Iron deficiency is also associated with obesity, diabetes risk and also with diabetes risk for anemia. In this review will briefly summarize the homeostasis of iron, iron and oxidative stress, the association of excess iron with increased diabetes risk, the effects of iron on insulin resistance, iron deficiency and diabetes risk, and anemia in diabetes patients.

Iron and oxidative stress

In eukaryotic cells, reactive oxygen species (ROS) was produced as the normal aerobic physiological metabolism [16]. ROS levels were counter-balanced with the antioxidants in the normal physiological conditions. ROS was defined as any chemicals those have reactive activities to accommodate or donate electrons (e-) to the biological molecules. ROS also include instability radicals arise from an unpaired e- [17].

$O_2 + e + H+ \rightarrow HO_2\bullet$ (hydroperoxyl radical)

$HO_2\bullet \rightarrow H+ + O_2\bullet-$ (superoxide radical)

$O_2\bullet- + 2H^+ + e \rightarrow H_2O_2$ (hydrogen peroxide)

$H_2O_2 + e \rightarrow OH^- + OH\bullet$ (hydroxyl radical)

However, at the normal physiological state in the living systems, oxygen consumption always produce oxygen-derived free radicals including $O_2^{\bullet-}$, OH•, alkoxylradical (RO•), peroxylradical ($RO_2\bullet$), peroxynitrite (ONOO-) and oxygen derived non-radicals such as H_2O_2, hypochlorous acid (HOCl) and hypobromous acid (HOBr). These reactive molecules (both in free radicals and non-radicals) were also played an adverse role in the physiological systems as oxidative stress mediated cellular damages [18]. In normal condition, neutralization of ROS productions by cellular antioxidant defense mechanisms was determined as the physiological condition and do not causes any oxidative damage [19]. In the imbalance condition, over ROS production and reduction of the antioxidant defense mechanisms in the living systems can caused cellular dysfunction and damage [20]. ROS may also be derived from the physiological and biochemical reactions to generate ROS as by-products or end products. In mitochondrial, electron transport chain, peroxisomes and cytochrome P450 system are the major sources of ROS production (involves in $O_2^{\bullet-}$ production) [21]. Moreover, various enzymes in physiological condition can be accelerated ROS production including cyclooxygenases [22,23], xanthine oxidase [24], uncoupled nitric oxide synthases (NOS) [25-27] and NADPH oxidases [28]. Heavy metals (Fe, Cd, Pb, Hg) as the toxic substances [29-32], acrolein, chloroform, carbon tetrachloride [33], tertiary butyl hydroperoxide [34-37], environmental pollutants (oxides of nitrogen, SO_2, CO_2), xenobiotics, UV irradiation and the other factors induce ROS overproduction. The transition heavy metals, iron (Fe^{2+}) and copper (Cu^+) can be produced reactive radicals (oxidative stress), especially in Fe^{2+} may cause autooxidation to cause $O_2^{\bullet-}$ generation and/or interaction with H_2O_2 can generate OH• via the Fenton and Harber Weiss reactions [1]. Fenton reaction may also be causes lipid peroxides generation and propagation [38].

Auto oxidation of Fe^{2+}: $Fe^{2+} + O_2 \rightarrow Fe^{3+} + O_2\bullet$

Fenton reaction: $H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + OH- + OH\bullet$

Fe

Haber-Weiss reaction: $H_2O_2 + O_2^{\bullet-} \rightarrow O_2 + OH- + OH\bullet$

Iron demonstrated the reversibly oxidized and reduced property, it plays the importance role in the pathophysiology of disease because of the generation of powerful oxidant species via the Fenton and Harber Weiss reactions [39]. Because iron participates in the ROS formation then organisms take great care of iron handling. Indeed, iron sequestration in transport and storage proteins may contribute to antioxidant defenses mechanism.

Iron homeostasis

Iron is a major cofactor for energy generation of oxidation and electron transport reactions. Iron also cause increased oxidative damage when it dys-regulated, sequestered or excess. Thus, extensive mechanisms are importance for control the iron homeostasis in the body. Iron and physiological metabolism connections are well established, even in lower organisms. Iron in mammalian organisms is recycled in about rate of 20-25mg/day through the major site, the erythroid pool as macrophages endocytose of the senescent erythrocytes. Approximately 5%-10% of iron amount per day was taken up through the intestine. In mammals, do not have mechanisms for the excess iron excretion to regulate iron balance. In equilibrium, losses may via the death of the intestinal epithelium and other cells death, and the biliary excretion may balance with the intestinal uptake. When exceeds uptake to cause excessive iron sequestered intracellular. Because the disposal of excess iron in humans was the slow process, but the iron uptake from the intestine was highly regulated.

At duodenumenterocytes, enzyme ferrireductase duodenal cytochrome b (DCTB) reduces ferric iron (Fe^{3+}) from transferrin to ferrous iron (Fe^{2+}). Fe^{2+} ions enter to the cytosol through the divalent metal-ion transporter 1 (DMT1 or SLC11A2). Zip14, a non-transferrin-bound iron transportercan also enter the cytosol through DMT1 [40,41]. Fe^{2+}-DMT1pass through the circulation via iron export channel, ferroportin (FPN or SLC40A1). The Fe^{2+} is oxidized to Fe^{3+} by hephaestin (HEPH) and then, binds to transferrin in the circulation. This transferrin can be taken into cells via transferrin receptors (TfRs), TfR1 was found and mediated iron uptake in most cells. The soluble-transferrin receptor, a soluble form of the transferrin receptor bound with transferrin, it level is a sensitive indicator for functional iron deficiency [42]. Transferrin saturation is the mechanisms

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to play a major role of iron overload conditions. Most of irons were used for heme and iron-sulfur cluster synthesis in mitochondria. Iron levels in cytosol were autoregulated via the binding with iron regulatory proteins (IRPs). IRPs were released from the iron-responsive element (IRE) of the TfR1 messenger RNA (mRNA) at the 30 untranslated region (UTR) and at the 50UTR of the ferritin mRNA and at the UTRs of mRNAs of the other iron-regulated proteins when excess iron were occurred. Resulting in decreased TfR mRNA stability, further decreased iron uptake, increased ferritin translation and sequestering iron inside the cell. Then, increased ferritin level is translated to the largely free iron as a marker of tissue iron stores. Transferrin-bound iron can also interacts with the hepatocyte TfR2 and HFE protein on the surface of hepatocytes [43] via the signaling process including with hemojuvelin (HJV), bone morphogenic protein 6 (BMP6) [44,45] and the SMAD (human homolog of *Drosophila mad*) pathway [46] for the stimulation of the hepcidin production. TfR2, HJV, HFE, and hepcidin were involved in human iron homeostasis demonstration in iron overload by human mutations of these proteins.

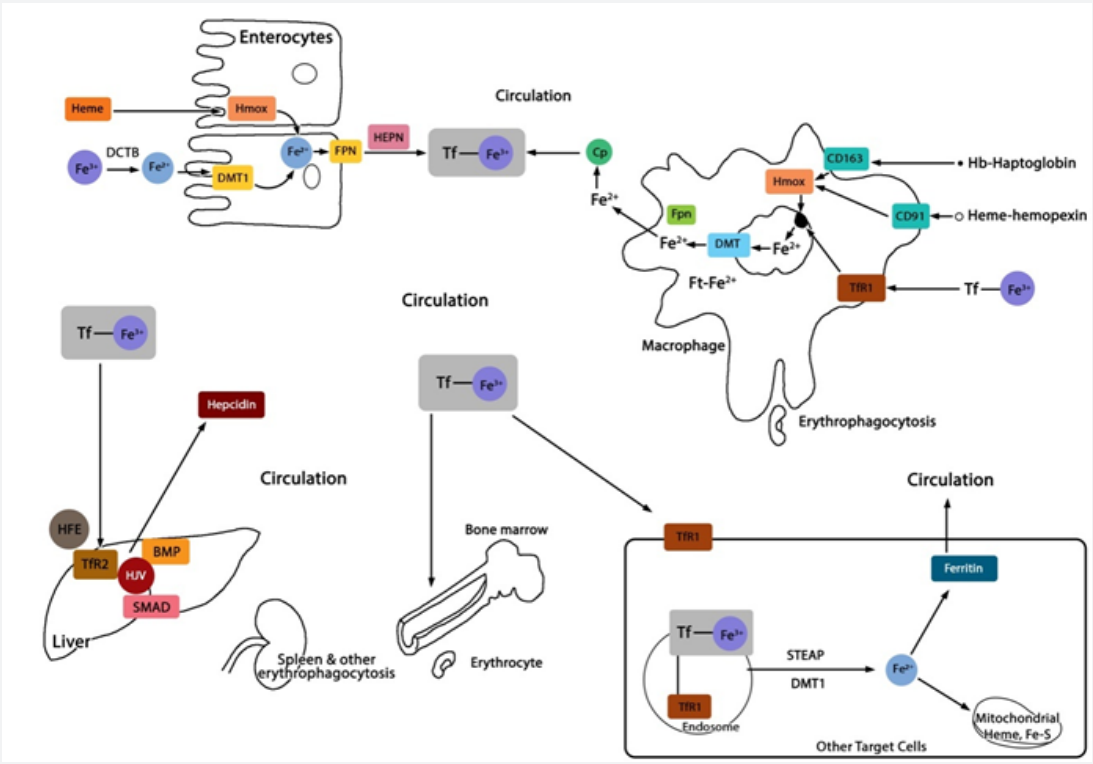

Figure 1: Schematic of iron handling: At duodenum enterocytes, ferric (Fe^{3+}) iron is reduced to Fe^{2+} by DCTB and enters the cell through the divalent metal-ion transporter 1 (DMT1).

Hepcidin, a 25 amino acid peptide, an acute-phase reactant protein, which is secreted by hepatocytes and acts as a negative feedback regulator of iron absorption, it induces internalization and degradation of intestinal epithelial ferroportin in circulation [47]. Hepcidin also regulates efflux of iron from macrophages, express the high ferroportin levels. The releasing of iron from the enterocyte is the major control point for iron entry into the body. DMT1 is regulated by iron levels, hepcidin-dependent mechanisms and hypoxia-inducible transcription factor (HIF)-2a [48,49]. Dietary heme is directly absorbed through the enterocyte pathways and using hemeoxygenase (Hmox) iron releasing from heme [50], these were summarized in Figure 1. While dietary heme is absorbed and iron is released by hemeoxygenase (Hmox). Iron exits the enterocyte through the iron export channel ferroportin (FPN) and oxidized by hephaestin (HEPH) to Fe^{3+} and binds with transferrin (Tf) in circulation. Thereafter, Tf-Fe^{3+} transported to bone marrow to produce heme for erythrocyte production. In the spleen, most of the iron was taken up by macrophages via the phagocytosis of senescent erythrocytes and also reabsorbed iron by systemic macrophages with their specific receptors. CD163 binds hemoglobin-haptoglobin complexes, CD91 binds heme-hemopexin complexes, and TfR1 binds Tf-Fe^{3+}. Once bound with their receptor, iron is endocytosed and pH changed induces iron reduction and release into the cytoplasm. Iron is released from cells via Fpn1 and bound with Tf. This Tf-Fe^{3+} can bind to transferrin receptors 1 and 2 (TfR1 and TfR2) on the surface of target cells. In most cells, after Tf-Fe^{3+} bound to TfR1 and acidification in endosome, iron was released and reduced by STEAP and bind to DMT1 enters the cytosol, where it is used for heme or Fe-S cluster synthesis in the mitochondrion. In excess, were sequestered by the form of ferritin into the circulation. Ferritin level serves as a marker for tissue iron stores. In the liver, Tf-Fe^{3+} binds TfR2 and the protein HFE, GPI anchored protein

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hemojuvelin (HJV), bone morphogenic proteins (BMP) and the SMAD play the concert signal transduction pathway of hepcidin production. Hepcidin induces internalization and degradation of FPN, thus completing a negative feedback regulatory loop.

For the evaluation of the effects of iron on metabolism, the important consideration is the wide normal range of serum ferritin in humans, 30-300ng/ml in men and 15-200ng/ml in women [51,52]. These serum ferritin levels in humans have a 10-fold of normal variation, these may not be an ideal normal value. Because of the extensive regulation of iron uptake, the dietary iron excess can achieve tissue iron levels higher than the necessary levels to maintain physiological erythropoiesis and metabolic function. For example, in general commercial rodent chows, there are the large variations in iron content a factor greater than ten times. The bioavailability of iron is considered more important than the absolute levels, many chows deliver higher iron contents that are consumed by mice living in the wild necessary to maintain normal breeding and blood hemoglobin concentrations. The same results of the many humans diets. Then, within the boundaries of tissue iron levels defined by overt iron deficiency and pathological of overload, the broad range of normal iron levels may include the levels that confer health risks which unaware.

In circulation, there are three main iron forms: Fe^{3+} bound to transferrin (Tf), hemoglobin bound to haptoglobin and heme bound to hemopexin. In bone-marrow erythroblasts, iron is used for hemoglobin formation in the nascent erythrocytes. Senescent erythrocytes are phagocytosed by splenic macrophages. The iron is recycled back for the erythroblasts formation, the recycled iron by macrophages is a 10-fold higher than the absorbed iron from duodenum [53]. Macrophages are responsible for cycling iron in many tissues such as spleen, bone marrow, liver and lung [54-56]. Macrophages also express the three types of iron receptors also present in serum including(i) transferrin receptor (TfR1) binds to Fe^{3+}-Tf, (ii) cluster of differentiation 91 (CD91) binds to heme–hemopexin, and (iii) CD163 binds to haptoglobin-hemoglobin (Hp-Hb). These were also demonstrated in.

Iron homeostatic pathways are tightly linked to inflammation. This inflammation causes from a significant hepcidinupregulation, via interleukin-6 (IL-6), and also results in increases serum ferritin levels [57]. Inflammation can cause the suppression of intestinal iron uptake, it has been hypothesized to be related with the beneficial effect of sequestering iron from invading microbes. This may elucidate the link of iron to diabetes that links to inflammation [58]. The complexity of the association among diabetes, inflammation and ferritin reflect the excess iron stores cause diabetes and reflect inflammation causes diabetes or both. Furthermore, if iron causes diabetes, the ability of the importance mechanisms could be cause oxidant stress and may also be linked to inflammation. This evidence suggests that iron overload can be cause diabetes.

Role of iron in the induction of diabetes

Evidence of the systemic iron overload in classic hereditary hemochromatosis (HH) was frequency increased diabetes mellitus. This evidence demonstrated that iron could contribute to abnormal glucose metabolism. In the genetic disorders of iron metabolism demonstrated iron overload resulting in the increased of type 2 diabetes. The role of iron in the pathogenesis of diabetes is uncertain but increased of type 2 diabetes in diverse causes of iron overload and improvement in diabetes with reduction in iron load by using iron chelation therapy. Recent studies demonstrated the association between increased dietary iron intake (eating red meat) and increased body iron stores with development of diabetes. These studies suggested frequent blood donation and decreased iron stores improve insulin sensitivity and insulin secretion [59,60]. Although the exact mechanism of iron-induced diabetes is unclear, it is likely to mediate by four key mechanisms: (i) oxidative stress and inflammation, (ii) insulin resistance, (iii) insulin deficiency and (iv) hepatic dysfunction. For the understanding of the pathogenesis of iron-induced diabetes pathways was derived from the animal models of hemochromatosis. In mouse model characterize of iron excess and oxidative stress mediate apoptosis of pancreatic islets resulting in decrease capacity of insulin secretion [61]. Pancreatic islets were caused oxidative damage, and may cause dysregulation of mitochondrial metabolism of glucose for glucose-induced insulin secretion and increased antioxidant defense using and low expression of the antioxidant defense system [62]. Increased expression of the divalent metal transporter proteins may addition with more accumulation of iron than other cells and potentiates with increased risk from iron catalyzed oxidative stress [63]. In study on transfusion-dependent β-thalassemic/HbE patient demonstrated the association of iron over load, increased oxidative stress, hepatic damage, dyslipidemia [64].

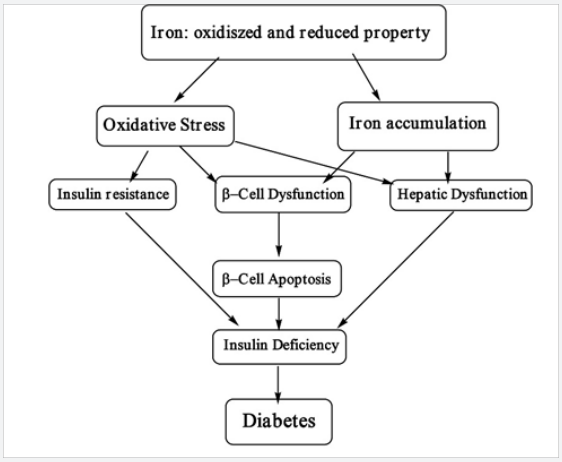

Figure 2: Schematic pathway of the iron induces oxidative stress and diabetes pathogenesis.

Oxidative stress plays an important role of the numerous pathologies in cardiovascular diseases, cancer and degenerative

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disease [65]. Oxidative stress is the deleterious factor leading to insulin resistance, β-cell dysfunction, impaired glucose tolerance, and type 2 diabetes mellitus [66,67]. McClain et al. [68] examined the high prevalence of abnormal glucose homeostasis in individuals with hemochromatosis by using glucose tolerance tests. They found that these hemochromatosis patients demonstrated not only impaired insulin secretion but also insulin resistance. Insulin resistance and impaired insulin secretion may cause from iron overload or through hepatic dysfunction [69]. The schematic of these processing were summarized in Figure 2.

Transfusional iron overload and diabetes risk

The most common acquired iron overload is typically found in transfusion-dependent β-thalassemia. Because of the ineffective erythropoiesis, decreased or impaired β-globin biosynthesis in β-thalassemia plays a crucial role in oxidative stress production [70]. Moreover, the heme-iron can free to generate H_2O_2 via the Fenton reaction. Anemia and excessive ROS are the hallmark of thalassemia [71]. Indeed, ROS and peroxidative tissue injury in these patients represent an unavoidable complication accelerated multi-organ damage, especially in excess iron accumulationin organs, such as liver, pituitary gland, pancreas and heart. Increased oxidative stress is the deleterious factor leading to insulin resistance, β-cell dysfunction, impaired glucose tolerance, and type 2 diabetes mellitus [66,67]. Many studies demonstrated impaired glucose tolerance and its progression towards overt diabetes mellitus which depended on the severity and duration of iron overload in β-TM patients [72-75]. These patients are often detected as impaired glucose tolerance in the second decade of life. In the study of Chern et al., they found 19.5% with diabetes and 8.5% with impaired glucose tolerance of the 80 transfusion-dependent β-thalassemia patients and demonstrated high serum ferritin and hepatitis C (HCV) infection as the risk factors for impaired glucose tolerance and type 2 diabetes mellitus [75]. While insulin deficiency may cause from iron accommodation in the interstitial pancreatic cells caused excess collagen deposition, obstructive the microcirculation and insulin resistance [76,77]. Glucose tolerance up to one-third of these patients was improved by intravenous or oral chelation treatment, these suggested the causal role of iron [78,79]. Our recent study demonstrated that transfusion-dependent β-thalassemia patients associated with iron overload, oxidative stress, and hyperinsulinemia or insulin resistance [80]. Loebstein et al. [81] demonstrated the direct role of iron-derived free radicals mediating organ damage of in transfusion-dependent diabetes patients with increased lipid peroxidation accelerated diabetic nephropathy onset.

Iron deficiency and diabetes risk

Approximately 75% of iron in human body is associated with hemoglobin, iron protein containing is responsible for oxygen transport of red blood cell (RBC). Anemia is a pathologic condition of decrease mass or amount of hemoglobin in red blood cell. Iron deficiency anemia (IDA) is the most common nutritional problem about 30 percent of people throughout the world [82]. Iron deficiency limits the synthesis of heme (a prosthetic group of hemoglobin) in the body, limits of hemoglobin synthesis and decreases the RBC production resulting in anemia. These are also affected the cellular energy metabolism of oxygen dependent. Iron deficiency also affects all of the Fe^{2+} containing proteins production such as myoglobin, catalase (CAT), peroxidase and cytochromes [83]. Anemia has a wide range of clinical consequences, especially in severe iron deficiency is a decrease RBCs- life span in circulation, it exacerbates the anemic condition [84-89]. The ID-RBCs were increased membrane stiffness and decrease in deformability, these may accelerated macrophages recognition [90-92], which decreases the ability of ID-RBCs to pass through the spleen without being removed. The deformability decreasing in ID-RBCs can increase cytosolic calcium levels which increase the ID-RBCs membrane stiffness to attribute oxidative stress [93-95]. Recent studies demonstrated the ID can accelerate RBCs eryptosis by increased the phosphatidylserine residue on the outer surface membrane for macrophages recognition resulting in the removed RBCs from circulation [89,93]. However, ROS of RBCs are one of the importance factors of anemia. ROS elevation in RBCs can occur either by activation of ROS production or by suppression of antioxidant or redox system. When RBCs cause an excessive ROS production, oxidative stress develops. Generally, 50% of anemia cause from iron deficien¬cy. More recent studies demonstrated that reduced iron stores were associated with increased glycation (hemoglobin A1C; HbA1c) [96-98].

Animal models: In ID-animal models were demonstrated glucose and lipid metabolism al¬terations. ID-animals present signs of the metabolic homeostasis disruption such as insulin signaling alterations evidenced of hyperinsulinemia, hyperglycemia and hyperlipidemia. Decreasing in oxidative capacity causes a shift in fuel utilization from fat to glucose [99-102]. These signs appeared as response grading associated with the hemoglobin reduction. However, in the non-severe hemoglobin reductions are not correlated with hyperglycemia and hyperlipidemia. These findings may suggest that these may have a certain threshold exists in order to develop these potentially negative meta¬bolic consequences [103-106]. However, other studies, in the moderate in¬duction of iron deficiency in ro¬dents are sufficient to disrupt normal metabolic homeostasis, to cause glucose and insulin elevations in both steady-state levels with the basal diet for-mulation in the ID-animals. High cortisol secretion, the secondary of the stress of anemia status, is not responsible for the hyperglycemia, while hyperglycemia was associated with de¬crease cortisol levels in the ID-animals [104-109].

The other studies demonstrated the hepatic genes expression was involved in stabilized glucose homeosta¬sis during ID.

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These studies demonstrated ID rats in each group had significant alterations in genes expression of glucose metabolism [110]. These gene expressions are also include those genes involve d in glycolysis and gluconeogenesis of metabolic pathways. The increasing of glucokinase (Gck) gene expression in ID-animals is relative increase insulin levels in cir¬culation. This insulin is the inducer of the hepatic Gck mRNA ex-pression. Increased Gck expression has been shown increased on the glucose levels as a metabolic substrate, to increase glucose phosphorylation rate in the liver, responsible for blood glucose elevations. Furthermore, Gck may involve in the multiple pathways such as glycogen synthesis, glycolysis, and de novo lipogenesis which may explain the enhancing of the glucose utilization and hyperlipidemia in the responsible to dietary ID-animals [110-116]. In the studies of metabolic gene expression alterations indicate an impaired hepatic insulin response in ID-animals, exhibited as insulin resistance. In this model, rapamycin complex 1 act as target of insulin to cause lipogenesis activation via the sterol regula¬tory element-binding protein-1c, while diminished insulin-induced phosphorylation of forkhead box protein O1 the transcription factor, inappropriate the glu¬coneogenic gene expression. Thus, mixed insulin resistance demonstrates as the candi-date mechanism responsible for these hyperglycemia and hyperlipidemia in ID-animals [117-122].

Human studies: Iron deficiency, the most common mi¬cronutrient deficiency remains in the world. General symptoms of IDApatients such as weakness, fatigue, impaired immune function, and reduced cognitive function, especially in children. Serum level of fer¬ritin was reflected the accurate iron status in the body. Many studies demonstrated the association of the reduction of iron stores with hemoglobin A1C (HbA1c) elevation. Many studies demonstrated the association of ID/IDA with the alteration of blood glucose, HbA1c and insulin levels [99,123,124].

Non-diabetic patients with IDA

In the cor¬rection of IDA study, 54 non-diabetic premenopausal women with IDA were corrected the Hb concentration from of 9.9±1.8g/dL to 13.1±1g/dL demonstrated fasting insulin reduction, insulin resistance and also found the positive correlation of fasting insulin levels with hemo¬globin levels after treatment [125]. The non-diabetic patients with IDA patients demonstrated the signifi¬cant reduction of HbA1c values after iron treatment [126,123]. While the study of Gram Hansen et al. [127] demonstrated normal HbA1c levels in IDApatients were dropped to subnormal levels after iron treatment. Many research studies were also demonstrated the association of HbA1C reduction with erythrocyte indices and iron metabolic indices after iron treatment [97,98,128,129].

IDA and type 2 DM patients

Many research studies demonstrated the association between IDA (patients with Hb: =9.4±1.3g/dL) with HbA1c levels, especially in dia¬betic women having FPG between 100-126mg/dl, or diabetic chronic kidney disease, or diabetic pregnancy with IDA (Hb≤10.5g/dl), which was reduced following iron treatment and increased Hb level [96,130-133]. Anemia in diabetic patient is always present as a biomarker for disease progression, the co-morbidities develop¬ment and quality of life. Hemoglobin (Hb) levels reduction may indicate increased risk of the renal disease progression. In type 1 diabetes mellitus, anemia is associated with micro- and macrovascular complications, the role of anemia may involve in the progression of these complications [133-136]. From the direct relationship of anemia and diabetic kidney disease, type 2 diabetes patients had reduced Hb levels to identify patients with increased risk for renal disease progression [132].

Anemia may play importance role in the mitogenic and fibrogenic process in kidney and the heart, these may associated with growth factors, hormones, and vasoactive reagents expressions. Many of these agents were involved in diabetic mi¬crovascular disease. Because RBCs act as importance antioxidant component in the circulation, thus, IDA patients had increase oxidative stress [132-135]. IDA patients are associated with increased oxidative stress and demonstration of increased triglycerides, decreased high-density lipoproteins (HDL) particles [136] and increased cholesteryl ester transfer protein (CETP) activity. IDA patients demonstrated lower arylester¬ase activity of paraoxonase-1 (PON-1) after received iron supplementation improved arylesterase activity of PON-1 and decreased malondialdehyde levels [136,137].

Anemia in diabetes patients

Type 2 diabetes mellitus is associated with increased oxidative stress and inflammation. Increased inflammatory cytokines plays the major role in insulin resistance and cardiovascular diseases risk as the micro- and macrovascular diabetic complication, renal disease and anemia. Interleukin-6 (IL-6) can limit the sensitivity of erythropoietin; an erythroid growth factor and also promotes immature erythrocytes apoptosis. The progression of nephropathy may effect erythropoietin reduction contributing the deterioration to anemia. Thus, diabetic patients with renal disease are at high risk for anemia. Many research studies reported the prevalence of IDA is signifi¬cant in type 2 diabetes mellitus patients, espe¬cially with nephropathy [138-142]. The clinical relevance of the effect of iron deficiency on glucose metabolism and HbA1c is still not elucidated. The reduction of iron ab¬sorption and gastrointestinal bleeding were the diabetic complications caused anemia [96-98].

Metformin, an antidiabetic drug is the most common prescription for diabetic patients. It may cause the adverse effects including diarrhea, dyspepsia, poor appetite, vomiting, lactic acidosis, and metallic taste. Long-term use of metformin may increase vitamin B 12 deficiency that has been indicated as a cause of hemolytic anemia [143]. However, drug-induced

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immunehemolytic anemia (DIHA) can be caused by many different mechanisms. Many drugs bind with proteins on the RBC membrane by covalent bond to cause hemolytic reaction on the presence of the drug and ceases shortly after discontinuation [144]. The DIHA is the immune complex reaction, which antibodies were formed to combine with proteins on RBC membrane and drugs to activate the complement resulting in acute intravascular hemolysis, DIHA may associate with drug-independent antibodies, these antibodies do not need drug to present in vitro reactions (e.g. fludarabine). Drug affects the immune system by causing the RBC autoantibodies production [144]. Although antibodies against the drug cannot be detected, based on the negative Coombs test with complement and no continuous hemolysis after the cessation of metformin, this hemolysis reaction was a drug-dependent reaction. A few cases of metformin-induced hemolysis were reported [143,145-148]. The recommendation on drug-induced hemolytic anemia, is to discontinue the potential drug treatment. In severe hemolysis case, may be operated further by RBC transfusion or plasmapheresis or dialysis in patients with renal failure [149].

Conclusion

Iron demonstrated the reversibly oxidized and reduced property, it play the importance role in the pathophysiology of disease by the generation of powerful oxidant species via the Fenton and Harber Weiss reactions. Oxidative stress is the deleterious factor leading to insulin resistance, β-cell dysfunction, impaired glucose tolerance, and type 2 diabetes mellitus. Human research and animal experimental studies have established the association of iron stores with diabetes risk. Many research studies suggest the relationship between higher iron and caused diabetes and iron demonstrate the multiplicity of effects in many tissues runs from iron deficiency to iron excess. The phenotypes of iron excess might be particularly prone to increase oxidative stress resulting insulin resistance and β -cell failure to cause insulin deficiency causing diabetes. Iron deficiency also affects all of the Fe^{2+} containing proteins production such as myoglobin, catalase (CAT), peroxidase and cytochromes. Oxidative stress elevation in RBCs can occur either by activation of ROS production or by suppression of antioxidant or redox system. ID-subjects present signs of the metabolic homeostasis disruption such as insulin signaling alterations evidenced of hyperinsulinemia, hyperglycemia and hyperlipidemia. These produce the possible of excess iron stores and ID/IDA contributes to cause diabetes. For further research is needed regarding the cut-off point for serum ferritin concentration in diabetes patients, and the affecting of body iron stores to cause insulin resistance, vascular resistance, blood viscosity and oxidative damage.

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Conflict of Interest

The author has no conflict of interest to report.

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