Iron status in diabetes mellitus

***Aseel Ghassan Daoud, *Huda Jaber, * Mayssaa E. Abdalah**
**** Clinical Laboratory Sciences Department/College of Pharmacy/Mustansiriyah University***

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Corresponding Author email:
ph.aseelbutti@uomustansiriyah.edu.iq
orcid: https://orcid.org/0000-0001-6309-6802

Abstract:

Diabetes mellitus can be defined as chronic metabolic disease which results from either relative or complete absence of insulin by the pancreatic beta islet cells. This in-turn may lead to hyperglycemia due to disturbances in the metabolism of glucose. In the human body, iron is considered to be an effective pro-oxidant and participates in the generation of reactive oxygen species (ROS) such as hydroxyl radical. Because of the poor antioxidant defense mechanism of beta cells (low production of antioxidant enzymes such as catalase, glutathione peroxidase and dismutase), so they are highly prone to iron-induced oxidative stress and iron deposition in it and this will lead to apoptosis, and subsequently insulin deficiency. This iron deposition in beta cells will also lead to insulin resistance by reducing insulin extracting ability of the liver and inhibiting glucose uptake in muscle tissues and fats, this in turn will result in high production of hepatic glucose. Ferritin which is an acute phase reactant protein, that responds to acute stress like trauma, infections, tissue necrosis and surgery, it can produce diabetes mellitus either through inflammation or by increasing iron stores.

Key words: diabetes mellitus, iron, insulin, beta cells, oxidative stress.

اسيل غسان داود،*هدى جابر وحيد،* ميساء عصام عبد الله
****فرع العلوم المختبرية السريرية/ كلية الصيدلة/ الجامعة المستنصرية***

الخلاصة:

ان داء السكري يمكن تعريفه بأنه مرض ايضي مزمن ناتج عن انعدام افراز الانسولين النسبي او الكلي من قبل خلايا بيتا الموجودة في البنكرياس. هذا بدوره قد يؤدي الى ارتفاع نسبة سكر العنب (الكلوكوز) في الدم نتيجة اضطرابات في عمليات ايض الكلوكوز. يعتبر عنصر الحديد عنصر موالي للاكسدة في جسم الانسان ويساهم في انتاج انواع الاوكسجين التفاعلية مثل جذور الهيدروكسيد. وبسبب الفعالية الدفاعية الضعيفة لخلايا بيتا كمضادات للاكسدة (ضعف انتاج الانزيمات المضادة للاكسدة مثل: كاتالايز، بيروكسيد الكلوتاثايون، دسميوتيز) ، لهذا السبب تكون هذه الخلايا اكثر عرضة للاكسدة من قبل الحديد وترسب الحديد فيها مما يؤدي الى موت الخلايا المبرمج وبالتالي نقص في الانسولين. ان ترسب الحديد في خلايا بيتا قد يؤدي ايضا الى مقاومة الانسولين من خلال تقليل قدرة الكبد على استخراج الانسولين وتقليل عملية اخذ او قبول الكلوكوز من قبل الانسجة العضلية والخلايا الدهنية والذي بدوره قد يؤدي الى زيادة انتاج الكبد للكلوكوز. ان الفيرتين، وهو البروتين المتفاعل للمرحلة الحادة الذي يستجيب للتوتر الحاد مثل: الصدمة، العدوى، نخر الانسجة والعمليات الجراحية ، قد يسبب مرض السكري اما من خلال الاتهاب او من خلال زيادة مخزون الحديد.

الكلمات المفتاحية: داء السكري، الحديد، الانسولين، خلايا بيتا، الاكسدة.

Definition of diabetes mellitus:

Diabetes mellitus can be defined as chronic metabolic disease which results from either relative or complete absence of insulin by the pancreatic beta islet cells. This in-turn may lead to hyperglycemia due to disturbances in the metabolism of glucose [1]. This may happen either when not enough insulin is produced or when there is insulin resistance by the tissues. It was found that about 8.3% of population worldwide had diabetes within the age between 20-70 years in 2013 and 10.1% in 2035 [2].

There are two main types of diabetes mellitus:

Type 1 DM:

Type 1 diabetes is a chronic disorder which is caused by autoimmune destruction of pancreatic beta cells that is thought to be mediated by T-cells [3]. Children and adolescents are the most common age groups that prone to type 1 DM [4]. The pro-inflammatory cytokines which are released by the immune cells cause beta- cell destruction and death by reactive oxidative species (ROS) formation within the cells [5, 6]. As a result, oxidative damage and beta-cell death may occur [5,7].

Type 2 DM:

It is considered a chronic disease that mostly affects elderly and to a lesser extent children and adolescents [8]. High blood glucose may lead to several complications like retinopathy, stroke, cardiovascular diseases, amputation of extremities, neuropathy and nephropathy. Type 2 DM may affect about 90 to 95% of the patients [9]. It is mainly characterized by insulin resistance [10]. Besides, the levels of trace elements such as copper, manganese, iron and zinc may be altered by type 2 DM [11].

Iron and diabetes mellitus:

Iron role in the body cells:

Iron is considered to be an essential microelement in human body. It plays a crucial role in the metabolic functions in the body either in oxygen transporting or as a cofactor for several enzymes [12]. It serves as potent toxicant (increases oxidative stress and cancer risk at high levels mainly colon cancer) [14,41] and essential nutrient to the cells (regulating the metabolism of tissues especially adipocytes and in intracellular signal transduction) [42]. Iron has an important function in several biochemical pathways in the body such as gene regulation, electron transfer reactions, regulation of cell growth, and differentiation, oxygen transport and binding by the formation of heme- and iron-containing proteins, and in immune system function [13-18]. The adult reference value of iron is about 60–170 μg/dL [19]. In addition, iron also plays an essential role in neurotransmitter generation and release [20], DNA synthesis [21], and steroid hormones and collagen [22, 23].

Iron and blood glucose:

Hepcidin is a peptide which consists of 25 amino acids that is found in urine, plasma and liver of human body in addition to its pancreatic source where it is stored in and released from the insulin granules with beta-cells are the main extrahepatic source of it [24,25]. Therefore, blood iron concentration may be regulated to some extent by the blood glucose in that when insulin secretion is increased, hepcidin will be released thus decreasing iron release to the blood. Besides, beta cells also contain ferroportin on its membrane [25,26]. Beta cells have an intracellular iron accumulation and ROS formation due to autocrine inhibition of iron efflux as a result of this insulin/hepcidin release, this may explain the association between overweight and diabetes [27].

The mechanism by which iron may produce diabetes mellitus:

In the human body, iron is considered to be an effective pro-oxidant and participates in the generation of reactive oxygen species (ROS) such as hydroxyl radical. Because

of the poor antioxidant defense mechanism of beta cells (low production of antioxidant enzymes such as catalase, glutathione peroxidase and dismutase), so they are highly prone to iron-induced oxidative stress and iron deposition in it and this will lead to apoptosis, and subsequently insulin deficiency. This iron deposition in beta cells will also lead to insulin resistance by reducing insulin extracting ability of the liver and inhibiting glucose uptake in muscle tissues and fats, this in turn will result in high production of hepatic glucose. The main cause of elevated iron stores in producing insulin resistance is well detected by the evidence that donation of blood will improve insulin sensitivity by decreasing iron stores [28-31]. In addition, high intake of iron in the diet may lead to its accumulation in body organs like liver, skin, heart and pancreas resulting in diabetes mellitus in hemochromatosis patients [25].

Ferritin:

Ferritin is a widely distributed protein that presents in almost all cells in the body which gives an idea of how much iron is stored in the tissues. In diabetic patients, the plasma ferritin levels are higher than its levels in non-diabetic individuals (reference level in males 30-300 ng/ml and 15-200 ng/ml in female [42]). It is also associated with the incidence of metabolic syndrome. Besides, its measurement gives an indication of insulin resistance together with other markers like insulin and high glucose levels [32]. There is a significant statistical correlation between type 2 DM and ferritin levels according to some epidemiological studies [33, 34].

Ferritin is an acute phase reactant protein, which responds to acute stress like trauma, infections, tissue necrosis and surgery [35]. Besides, it is also considered a globular protein which stores iron in non-toxic soluble form, its level in blood is associated with hyperglycemia and lowered with decreased blood glucose level. In case of oxidative stress, Fe^{2+} (ferrous ion) enters to cells and is converted to Fe^{3+} (ferric ion) which in turn links to ferritin and protects the cells from oxidative stress. However, insulin resistance and pancreatic beta-cells dysfunction can result from high ferritin and iron concentrations inside the cells. Increased serum ferritin level may occur as a result of insulin resistance induced-Hyperinsulinemia. It has been thought that iron metabolism disorders may lead to hyperinsulinemia, insulin resistance, hypertension, dyslipidemia, and central obesity [36].

Finally, it can be said that ferritin can produce diabetes mellitus either through inflammation or by increasing iron stores [42].

Disorder of iron metabolism:

Excessive accumulation of iron in the tissues may occur by genetic diseases of iron overload like hereditary hemochromatosis which may contribute to diabetes [28]. The relationship between type 2 DM and moderately increased iron level, which is less higher than that of genetic diseases of iron overload, have been studied [37] . In hemochromatosis patients, the main clinical features of iron overload are impaired glucose metabolism and diabetes mellitus [32].

Tumorigenesis and even cancer may result from iron metabolism disorders particularly excessive gain and retention of iron [38,39]. However, tumor death can be induced by the oxidative stress which results from high intracellular iron concentration. Together with reactive oxygen species (ROS), iron plays an important role in ferroptosis (regulated cell death) which depends on lipid peroxidation. As a part of iron metabolism disorders, iron deficiency may occur when the availability of iron is inadequate to meet the body's need and may lead to anemia [40].

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