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The regulatory role of erythropoietin in Diabetes Mellitus: A focus on oxidative and glycemic statuses

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Abstract

Background and Objectives. One of the leading causes of disability and death among the population is type 2 diabetes mellitus (T2DM), which is characterized by persistent hyperglycemia. The disease is associated with disorders including oxidative stress and resistance to insulin action, which are involved in the progression of other diabetic complications. Such complications strongly rationalize the need for advanced treatment strategies. Considering the antioxidant, and anti-inflammatory in addition to cytoprotective properties of erythropoietin (EPO), it may offer a new potential strategy for the management of these disorders in diabetic patients. This review aims to explore the effects of EPO on oxidative stress and insulin resistance and its impact on glucose metabolism to guide healthcare professionals to a novel approach for controlling diabetes complications.

Materials and Methods. This review was conducted by analyzing studies involved with oxidative stress, resistance to insulin, and glucose metabolism in T2DM published in Cochran Library, PubMed, and Google Scholar until February 2024.

Results. EPO shows promising beneficial effects in the management of these diabetes-associated disorders.

Conclusion. With this beneficial effect of EPO, it is considered a strong candidate and area of development for the creation of new choices in the management of diabetes.

Keywords: Diabetes Mellitus, Erythropoietin, Insulin Resistance, Oxidative stress.

Abbreviations:

DM: Diabetes Mellitus

T2DM: Type 2 Diabetes Mellitus

RBC: Red Blood Cell

EPO: Erythropoietin

PI3K: Phosphatidylinositol 3 Kinase

Akt: Protein Kinase B

EPO-R: Erythropoietin Receptor

POMC: Hypothalamic Pro-Opiomelanocortin

GLUT-4: Glucose Transporter-4

PC-1: Plasma Cell Differentiation Antigen-1

IRS-1: Insulin Receptor Substrate-1

ROS: Reactive Oxygen Species

AGEs: Advanced Glycation End Products

HOMA-IR: Homeostatic Model Assessment for Insulin Resistance

NF-κB: Nuclear Factor Kappa B

Introduction

Insulin resistance is regarded as a major hallmark of diabetes mellitus (DM). It can lead to chronic hyperglycemia with eventual organ failure in several body systems, including the circulatory, neurological, ocular, renal, and vascular systems [1]. Persistent hyperglycemia due to insulin resistance is considered an important factor for developing oxidative stress in T2DM. The development of oxidative stress results in worsening the course of the disease and predisposes to further levels of insulin resistance and diabetes complications. The deleterious effects of insulin resistance and oxidative stress are expected to extend beyond diabetes. Some studies have also linked insulin resistance to an increased risk of heart disease and anemia in those with or without diabetes [2,3]. Oxidative stress, on the other hand, has been shown to cause cation channel stimulation in red blood cells (RBCs), leading to iron loss and anemia. Both conditions, high oxidative stress level and resistance to insulin action, are the causes of the increased prevalence of hematological disorders in individuals with T2DM, in particular those with chronic kidney disease [4].

To manage anemia, erythropoietin (EPO) is frequently used as an essential therapeutic option. EPO, in addition to its beneficial blood impact, is involved in the regulation of several other processes including immunological response, vascular function, metabolic balance, and cell division [5]. Interestingly, EPO is being studied to treat several illnesses and it seems to be particularly effective in treating metabolic disorders, such as DM. It has been demonstrated that EPO has a role in the improvement of glucose metabolism and insulin intolerance in those patients [6]. Additionally, EPO was shown to improve heart function, lower tiredness, and enhance cognitive performance in diabetic patients [7]. Also, EPO administration improves glucose metabolism and decreases blood glucose levels in diabetic patients undergoing hemodialysis [8]. Furthermore, the reported cytoprotective properties of EPO on non-erythroid tissues, by alleviating oxidative stress, have been shown to be a suggested issue of a profound clinical importance [9]. Thus, the involvement of EPO deficiency in the pathophysiology of several disease-complications, in addition to its role in modulation of various organ deteriorations have dragged researchers attention to further investigate its potential benefits in patients with T2DM.

Accordingly, this review has explored the published articles in an aim to propose the beneficial impact of EPO on oxidative stress and insulin resistance, in order to reveal its probable potential on alleviating these disorders and to guide the healthcare professionals to a novel approach for controlling some diabetes-related complication.

Effect of EPO on Glucose Metabolism

Numerous observations proposed a connection between reduced EPO level and the development of DM [10,11] In nondiabetic individuals, EPO decreased glucose levels, and in rats, it reduced diet-induced obesity and repressed gluconeogenesis. Also, EPO increases the oxidative metabolism of adipose tissue, and obesity is caused by the decrease of EPO in adipocytes. Furthermore, in a range of tissues, including pancreatic beta cells, EPO has demonstrated cytoprotective, proliferative, and anti-inflammatory properties [12].

Phosphatidylinositol 3 kinase (PI3K) / protein kinase B (Akt) is the proposed pathway for the association between EPO and glucose metabolism. PI3K/Akt is an essential modulator of various biological processes, including glycolysis, lipogenesis, glycogen formation, glucose transportation, and protein synthesis. When Akt activation is disrupted, glucose intolerance and abnormal gluconeogenesis happen while restoring insulin-induced Akt phosphorylation facilitates insulin sensitivity and glucose metabolism [13]. EPO binds to and stimulates the EPO receptor (EPO-R), which recruits the p85 subunit of the PI3K through its Src homology 2 domain and activates the PI3K and Akt pathways resulting in reduced glucose intolerance and, as a result, a better glycemic control [14]. Indeed, some of the noticed metabolic effects on glucose may be related to the effects of EPO on beta cells rather than the direct effect on glucose metabolism [15]. However, systemic glucose metabolism is regulated by the high expression Of EPO-R in hypothalamic pro-opiomelanocortin (POMC) neurons [16]. In *vivo* studies with EPO demonstrated a significant weight loss, decreased fasting blood glucose and serum insulin levels, and reduced glucose intolerance. Such evidence suggested that EPO may contribute to a decreased glucose intolerance via activating the Akt pathway, which in turn inhibits gluconeogenesis and inflammation-related signaling in the liver [17,18]. Moreover,

it has been reported that both healthy and diabetic rats were affected by the acute metabolic action of EPO, which led to lower blood glucose levels. Additionally, the study found that under high glucose settings, adipocytes exhibited enhanced glucose uptake rates and glucose transporter-4 (GLUT-4) trafficking [19]. Furthermore, an additional investigation illustrated that the introduction of a single dose of the novel EPO-R agonist, CNTO 530, to mice with diet-induced obesity resulted in enhanced glucose tolerance and insulin sensitivity. The improved glucose tolerance was attributed, at least in part, to the enhanced absorption of glucose by skeletal and cardiac muscles. The precise molecular mechanism behind the translation of EPO-R signaling into enhanced glucose tolerance has yet to be fully elucidated. Nevertheless, it is plausible that EPO-R agonists may present a novel therapeutic approach for T2DM, on the condition that the medication can be administered at a dosage that elicits favorable metabolic outcomes without significantly elevating hematocrit levels [20]. Additionally, the beneficial effects of EPO on glucose metabolism were reflected indirectly by its correlation with selenium. In general, the concentration of selenium is lowered in diabetics, and a study found that treatment with EPO resulted in elevation of the concentration of selenium, accompanied with enhancement of its insulin-mimetic properties. Such improvement in glucose metabolism through the elevation of selenium level, may provide a plausible additional mechanism to the favorable effect of EPO on glucose metabolism [21].

Effect of EPO on Insulin Resistance

Insulin resistance in T2DM means a cell has a weakened insulin signaling pathway. As a result, muscle, fat, and liver cells uptake less glucose, and insulin-mediated processes within cells are impaired. This resistance is exacerbated by an extra deficiency in the ability of pancreatic beta cells to produce and secrete insulin [22]. In general, patients with T2DM have both insulin resistance as well as the inability to increase insulin secretion to overcome the resistance. Resistance to insulin action is a result of an interaction of environmental and genetic factors, which was shown to have a role in the progression of diabetes complications including central obesity, hypertension, dyslipidemia, and cardiovascular disease [23].

Several studies have shown that patients treated with EPO demonstrate a significant increase in insulin sensitivity [24,25]. The improvement of insulin resistance by EPO is still uncertain. However, research has shown that insulin resistance may be predisposed by overexpressing several potential inhibitors of insulin receptor tyrosine-kinase activity, a critical step in the signaling of insulin [26]. The plasma cell differentiation antigen-1 (PC-1) presents in many tissues, where it prevents the signaling of insulin in two ways, directly at the receptor of insulin, and indirectly at a post-receptor site. Insulin resistance in obese people and those with T2DM may be significantly influenced by an increase in PC-1 levels in insulin target tissues [27]. EPO therapy has revealed a successfully potential in lowering the PC-1 activity to normal levels. Accordingly, patients receiving EPO treatment may have an improvement in their insulin resistance as a result of altered PC-1 expression [8]. Additionally, the beneficial effect of EPO on the sensitivity to insulin may be linked to the management of anemia. Increased oxygen delivery and corrected tissue hypoxia may be regarded as indicators for enhanced insulin activity [28]. Moreover, investigation on EPO administration was revealed an association between increased EPO levels and reduced insulin resistance. The identified mode of action could involve the activation of downstream signaling pathways, leading to the phosphorylation of Akt, insulin receptor substrate-1 (IRS-1), and PI3K. This activation causes the GLUT-4 to translocate, regulate autophagy, and decrease apoptosis in the skeletal muscle cells [24]. Furthermore, the reduced responsiveness to the hypoglycemic effects of insulin is a common drawback in individuals with uremia, where it is commonly associated with either uremic toxins, anemia, or secondary hyperparathyroidism. The observed positive influence of EPO therapy on resistance to insulin in these individuals can be related to the direct effects of EPO, rather than only to the adjustment of anemia [29].

Effect Of EPO On Oxidative stress

The increase in the production of free radicals or a malfunction in the antioxidant mechanisms within cells can cause oxidative stress, which in turn can cause significant health problems [30]. Multiple studies have linked reactive oxygen species (ROS) to the development of insulin resistance, a hallmark of T2DM, suggesting that oxidative stress has a role in the onset and progression of the disease. Additionally, oxidative stress could

be directly involved in the development of subsequent complications associated with DM. In diabetic patients, oxidative stress can lead to DNA damage, nutritional impairment, and mitochondrial injury [31].

EPO may directly exert its antioxidant effects by exploiting intracellular antioxidant processes like glutathione peroxidase and heme oxygenase-1. Also, EPO might have an indirect effect by reducing iron-dependent oxidative damage by generating iron depletion. Moreover, because RBCs contain so many antioxidant enzymes, increasing RBC counts with EPO may have an indirect effect on lowering cellular oxidative stress [32]. In addition, EPO modulates many signal transduction pathways that can involve Janus-tyrosine kinase 2, Akt, Wnt proteins, mammalian forkhead transcription factors, caspases, and nuclear factor kappa B (NF-κB), which in turn reduces oxidative stress [33]. Epoetin beta, EPO derivative, is demonstrated to increase the serum activities of antioxidant enzymes such as glutathione peroxidase and superoxide dismutase while decreasing the blood level of the oxidative enzyme malondialdehyde in diabetic rats. Furthermore, it has been demonstrated that EPO may prevent ROS generation and high glucose-induced oxidative steers, resulting in preventing renal cell apoptosis in diabetic kidneys [34]. Additionally, the results of in vivo investigation showed that EPO and EPO-R expression were upregulated and maintained in response to free radical exposure caused by elevated glucose levels, which served to diminish oxidative stress and safeguard cells from apoptotic cell death [35].

Clinical significance

Elevated levels of both intracellular and extracellular glucose that resulted from a disturbance in glucose metabolism, cause proteins to undergo nonenzymatic and spontaneous reactions. Advanced glycation end products (AGEs) are the result of a series of complicated processes involving this nonenzymatic protein glycation [36]. In addition, glyoxal, a precursor for AGEs that promote cellular oxidative stress, is formed when glucose levels are consistently high [37]. Insulin resistance, when developed as a

result of oxidative stress, may lead to disruption of the insulin signaling pathway [38]. Insulin resistance is frequently observed in individuals diagnosed with T2DM, and it has been proposed that other metabolic risk causes, such as high blood pressure, high glucose levels, and dyslipidemia, may be made worse by this condition. Furthermore, several diseases are caused by insulin resistance which includes heart disease, kidney damage, and obesity [39]. On the other hand, resistance to insulin and DM complications are strongly associated with the development of oxidative stress in the cells, which can result in clinical impairment and several disorders, including stroke, dementia, and myocardial infarction [40].

There are restricted therapeutic options for the treatment and prevention of these conditions in diabetic patients which rationalize the need for advanced strategies to control the onset and progression of these disease complications. EPO by enhancing insulin resistance is considered as a potential novel therapy for T2DM to offer a prevention of its complications. Antioxidant administrations during increased glucose concentrations can inhibit the production of free radicals and AGEs, which are known to produce ROS. EPO with antioxidant properties may present a compelling option therapy to preserve appropriate cellular metabolism and mitochondrial membrane potential during T2DM [33]. Moreover, diseases of the nervous system, by affecting sensitive cognitive regions of the brain such as the memory-modulating hippocampus, might appear to be the most debilitating complications of DM. These diseases can result in significant functional impairment, dementia, and Alzheimer's disease. EPO by its cytoprotective and antioxidant properties can be recommended as a novel treatment for the prevention and management of such diseases [9]. Furthermore, previously highlighted role of EPO on glucose absorption in adipocytes, through an Akt-mediated pathway, suggests that EPO therapy in most diabetic patients is more effective than insulin alone in reducing hyperglycemia. This approach may provide a possible clinical implications and pose a promising strategy for lowering blood sugar levels [19].

In individuals with diabetes, who have severe resistant congestive heart failure, EPO cardio-protection has been shown to reduce dyspnea and/or fatigue, raise left ventricular ejection fraction, and significantly reduce hospitalization [41]. Similarly, treatment with

EPO analogue has been shown to have important potential as a medicinal intervention for decreasing the development of diabetic nephropathy via providing protection against insulin resistance and oxidative stress [34]. Additionally, the administration of EPO resulted in a decrease in body weight and homeostatic model assessment for insulin resistance (HOMA-IR), as well as a reduction in the buildup of white fat in diet-induced obese mice. This suggests that EPO can be a promising candidate to reduce obesity in humans [42].

However, Further research is required to investigate the controversial aspects surrounding the long-term effects of EPO on the progress and prognosis of diabetes, diabetic complications as well and its adverse effects. It is well-known that EPO, when used in high concentrations, may cause hypertension, thrombosis, and stroke. These issues are probably a consequence of hemodynamic alterations, in some instances, or a potentially fatal complications, in others. Dose reduction can minimize these adverse effects, and in severe situations, drug cessation is the best option [43]. However, conventional antihypertensive medication can control hypertension that occurs as a result of EPO therapy. Nevertheless, if the hypertension persists, a decrease in the dose of EPO or a transient withdrawal may be necessary. Switching from intravenous to subcutaneous dosing also helps in preventing blood pressure rise. Additionally, platelet aggregability is another concern for EPO administration; which if happens, antiplatelet medication may help in resolving it [44].

Conclusion

EPO, as a cytoprotective agent with a favorable metabolic effect may provide a therapeutic potential in T2DM. However, more research is needed to fully explain the mechanism by which it controls glucose metabolism, oxidative stress, and insulin resistance in people with T2DM. Additionally, the increased propensity for thrombogenesis and hypertension implies that the administration of EPO in individuals with diabetes should be approached with caution.

CONFLICT OF INTEREST:

Authors have no conflict of interest and are financially supported independently.

AUTHOR'S CONTRIBUTIONS:

Muthanna K. Zeki: Writing – review & editing, writing—original draft preparation, and conceptualization. **Mohammed N. Abed:** Supervision, project administration, formal analysis, and conceptualization. **Fawaz A. Alassaf:** Supervision, project administration, formal analysis, and conceptualization.

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