Short Communication

Diabetes, HbA_{1C} and Iron levels – An Overview

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Abstract:

Diabetes, the most common non-communicable disease is approaching epidemic proportions globally. The prevalence of impaired glucose tolerance is likely to go up to 6.0 by 2025. Maintaining glycemic control and monitoring the glucose levels periodically is mandatory in preventing long term complications. The role of iron metabolism and its impact on glucose levels is widely studied nowadays. Iron deficiency anemia influences theHbA_{1C} levels there by questioning the value of this parameter as a marker of glycemic status. Poor glycemic control is the most important factor for formation of advanced glycation end products. This short communication will give an overview on the link between iron metabolism, diabetes and HbA_{1C}.

Keywords: anemia, diabetes mellitus, glycated hemoglobin, iron

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Introduction:

Diabetes mellitus is a growing global health burden affecting over 400 million people worldwide, crippling the quality life of people. Good glycemic control and regular follow up are the corner stones in the management of the disease. The American Diabetes Association recommends to check HbA_{1C} value at least twice a year. As a disease with chronic phase, the complications of diabetes are mainly attributed to the overall glycemic status.

Nowadays the incidence of diabetes is more among young adults. Maintaining the HbA_{1C} values less than 6.5-7% and tittering the drugs, diet and exercise protocols to maintain good glycemic status prevents the complications of diabetes mellitus thus improving the life expectancy and quality of life.

Glycation is the non-enzymatic attachment of aldehyde group of carbohydrate to amino group of proteins. Formation of advanced glycation end products (AGE) is controlled by various physiological factors like temperature, pH, substrate concentration (glucose level) and lifetime of protein (quality and quantity of Hb).[1]

Glycation alters the structure and function of isolated basement membrane components, several soluble and insoluble proteins, contributing for most of the diabetic complications.

HbA_{1C}- Its reliability in anemia:

The amount of HbA_{1C} at any given glucose level is decided by factors like the mean age of Hb, the type of Hb, the rate of glycation of Hb, and the percentage of glycation when released as reticulocyte.[2] Anemia is most prevalent in our population and henceforth, reliability of HbA_{1C} as a biomarker monitoring the glycemic status and altering the treatment protocols in patients with diabetes is questionable. Studies show that any anemia that increases the red blood cell turnover will increase glycation of Hb leading to higher HbA_{1C} values as observed in blood loss, hemolysis, red cell disorders, hemoglobinopathies, and myelodysplastic disease.[3] On the contrary there are reports showing low levels of HbA_{1C} in patients with hereditary spherocytosis, elliptocytosis, auto-immune hemolytic anemia and anemia of chronic renal failure. The authors attribute low $HbA_{1C}$for the given level of blood sugar, to reduced RBC survival and reduced availability of Hb for glycation.[4-7] Potential glycation sites of the hemoglobin molecule include the N-terminal amino acid mostly valine of the beta chain. Glycation can also occur in lysine residues or in alpha chain. These Hb are designated as glycated HbA0 and cannot be separated from non-glycated hemoglobins by certain methods of assay. In hemoglobinopathies the altered structure will affect the glycation sites and therefore give spuriously increased or decreased results. The variants of hemoglobin like HbF, HbS and HbC require specific methods for assay and should be considered while interpreting the HbA_{1C} values.

Influence of iron on HbA_{1C} levels:

Iron, the micronutrient is the sheet anchor of hemoglobin synthesis. Iron deficiency anemia (IDA) is more prevalent among diabetic patients also.[8] In patients suffering from iron deficiency, HbA_{1C} values spuriously increases with no corresponding change in blood glucose. Rajagopal and co-workers demonstrated a statistically significant difference in HbA_{1C} values between cases of mild, moderate, and severe IDA, in non-diabetic individuals.[9] In iron deficiency anemia, increased HbA_{1C} is attributed to increased glycation by malondialdehyde. This was also the finding by Brooks et al who reported that relative absence of iron results in the alteration of quaternary structure of the Hb molecule leading to excessive glycation of the beta globin chain.[10] El Agouza et al also reported that at a constant glucose level, lower levels of Hb can lead to an increase in the glycated fraction because HbA_{1C} is measured as a percentage of total HbA.[11] Later, Mitchell TR reported the work of Heyningen et al that there were no differences between the HbA_{1C} levels of anaemic patients and controls.[12] On the other hand, a significant drop in HbA_{1C} was noticed with iron substitution therapy in various populations.

Above studies show that anemia perse affects the formation of AGE products irrespective of the glycemic status. Therefore, the effects of anemia in diabetic patients and its influence on HbA_{1C} levels are being studied extensively by researchers now. Studies by Fernandez et al establishes the link between diabetes and iron metabolism.[13,14] The interactions between iron and glucose metabolism is bidirectional with iron affecting glucose metabolism and glucose interfering in iron metabolic pathways.

Influence of Iron on Diabetes:

Iron influences insulin secretion, its action and glucose metabolism, thereby affecting the glycemic status.[4] The CLEVER trial evaluates the relationship between iron deficiency and HbA_{1C}in Type II diabetic patients.[15] It states that excessive iron is a risk factor for the development of diabetes. Iron stores, expressed as serum ferritin concentration, have been proposed to be a component of the insulin-resistance syndrome. The association between serum ferritin and insulin resistance has been studied by many

researchers.[16-19] Ferritin has antioxidant properties and beta cells of pancreas are more prone to oxidative stress. This is given as the reason for more ferritin accumulation in beta cells by studies done by Macdonald MJ et al and Rahier JR et al.[20,21] Iron overload and increased beta cell mass in non-diabetic subjects was reported by Rahier et al. He also reported that in type 2 diabetic patients with increased serum ferritin, there is increased basal and stimulated C-Peptide secretion.

Normally iron increases insulin secretion in pancreatic beta-cells. Insulin in turn decreases the glucose production in liver but iron interferes with this action. It has been suggested that iron increases oxidative stress and prevents insulin action by decreasing the internalisation of insulin into the cell.[22] Therefore, with increased iron there is hyperinsulinemia and insulin resistance.

Frequent blood donation and phlebotomy has shown to decrease the iron overload thereby protecting the subjects from diabetes. Decreased iron stores, have been demonstrated to reduce postprandial hyperinsulinemia in healthy volunteers and to improve insulin sensitivity.[23] But, lower levels of serum iron or serum ferritin have been linked with increased glycation of HbA_{1C}. Thus, even though low iron has a protective role in diabetic patients by increasing insulin sensitivity it increases the rate of glycation of HbA_{1C}, leading to its false-high values in diabetic as well as non-diabetic individuals.[24] Therefore, with less iron even-though the glucose levels are normal, subject may present with higher levels of HbA_{1C} and treating them based on HbA_{1C} levels may precipitate hypoglycemia in these patients.

Influence of Diabetes on Iron metabolism:

In the previous section, we have seen that iron affects insulin and diabetic status. But insulin in turn influences iron metabolism by stimulating ferritin synthesis and iron uptake. This is mediated by facilitating translocation of transferrin receptors from intracellular compartment to cell surface. In diabetic individuals with hyperglycemia, there is glycation of iron binding protein transferrin decreasing its ability to bind ferrous iron. This increases free iron levels and ferritin synthesis.[13] As discussed earlier, ferritin is a known factor to increase insulin resistance and thereby hyperglycemia.

Hyperglycemia contributes to the oxidative stress by inducing the formation of oxygen free radicles and impairment of endogenous oxidative defense system. Iron acting as pro-oxidant increases the production of oxygen free radicals and also potentiates the depletion of endogenous anti-oxidants. Increased iron contributes to macro vascular disease. Iron also increases fibrinogenesis and vascular smooth muscle proliferation in animal models. Thus, high levels of iron and ferritin in diabetic patients augments the microvascular and peripheral nerve complications. Iron even-though is a co-factor for many metabolic pathways, in higher dose it has deleterious effects. Being a pro-oxidant, causes oxidative damage and cellular toxicity.

Conclusion:

There is bidirectional interaction between diabetes and iron overload, each augmenting the deleterious effects of the other mutually. Iron and hyperglycemia both increases oxidative stress and produces tissue damage. Even-though HbA_{1C} is the gold standard test for monitoring glycemic status in diabetic patients, there are limitations and it should be interpreted with caution.

- Low iron will favor more HbA_{1C} production and propensity to correct the glycemic status based on this alone may precipitate hypoglycemic episode.
- Correction of anemia with hematinic should be monitored in diabetic patients as increased iron and ferritin also will interfere with insulin sensitivity causing hyperglycemia.

- Iron overload and hyperglycemia both contribute to the vascular and neurological complications in diabetic patients.

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