REVIEW ARTICLE

Serum Ferritin and Type-2 Diabetes Mellitus

Sumeet Smotra, V.R.Tandon*, Sanjay Sharma, R. P. Kudyar**

Introduction

Diabetes Mellitus is a predominant public health concern, affecting millions of people worldwide. The disease causes substantial morbidity and mortality and long term complications. Recently, it is recognized that, increased body iron stores are associated with the development of glucose intolerance, gestational diabetes & Type-2 diabetes(1). Increased Serum Ferritin (SF) have been reported to negatively correlate with insulin sensitivity(2,3) and the presence of insulin resistance syndrome(4). Furthermore insulin resistance, compensated by hyperinsulinemia, sets in early even before the onset of frank diabetes mellitus and correlate well with indicators of iron overload and SF(5).Frequent blood donation lead to decrease iron stores, which in turn reduces post-prandal hyperinsulinemia in healthy volunteers and improves insulin sensitivity(6).Insulin resistance, correlate well with total units of blood transfused, splenomegaly and SF in chronically transfused patients of thalassemia major(5). Phlebotomy is followed by drop in serum glucose, serum cholesterol, serum triglycerides and improvement in both beta cell secretion and peripheral insulin action in type-2 diabetes mellitus(7,8). Epidemiological studies also suggest that high body iron stores are associated with insulin resistance and type 2 diabetes(9,10).In a trial of poorly controlled diabetic patients, hyperferritinemia co-related with diabetic retinopathy(11). A similar influence of the increase body iron stores on diabetic nephropathy and vascular dysfunction have been suggested(12,13).The present review discusses how raised serum iron levels can influence the patients of type-2 diabetes.

SF and its Influence on Serum Insulin levels

Wrede *et al* (4) reported a significant correlation between SF and the presence of IRS (Insulin Resistance Syndrome) criteria in a large representative population. Suvarna *et al* (5) from India reported similar results and suggested that insulin resistance, sets in early even before the onset of frank diabetes mellitus and correlate well with total units of blood transfused, splenomegaly and SF in chronically transfused patients of thalassemia major(5). Fernandez *et al* (1) found that in general population increased body iron stores are possibly associated with occurrence of glucose intolerance, type-2 diabetes and gestational diabetes. Facchini, (8) found significant reduction in serum insulin concentration after performing a 550 ml phlebotomy in healthy volunteers. Blood letting of 1500 ml has been demonstrated to improve insulin sensitivity and to decrease C-peptide secretion in type -2 diabetes subjects who had increased SF concentration. Similarly Dmochowski *et al* (2) reported in a study on thalassemic patients that SF concentration correlated negatively with insulin sensitivity and the conclusion of the study showed a major & significant insulin resistance which may be compensated for by an elevated circulating insulin level. Dymock *et al* (7) reported significant reduction in total daily insulin dosage following phlebotomy and improvement in diabetic status of patients following venesection. Further epidemiological studies also support these findings which suggest that high body iron stores are associated with insulin resistance and type 2 diabetes(9,10).

Mechanism

Rai Jiang *et al* (14) have reported elaboration of Hydroxyl radical in iron overload which causes cell damage. This leads to insulin resistance - hyperinuslinemia initially followed by decrease secretion and diabetes. Deferroxamine, a chelating agent with antioxidant properties improves fasting blood glucose in chronically transfused patients of thalassemia major, thus it supports

From the Department of G. Medicine ASCOMS, Sidhra, **Govt Medical College, Jammu, *Health Services, Jammu (J&K) .
Correspondence to : Dr V.R. Tandon, 5B, Bakshi Nagar, Jammu

above hypothesis(5). Recently, it has been suggested that transferrin and iron induce insulin resistance of glucose transport in adipocytes is through a mechanism independent of fatty acids(15). However, further studies are required to investigate the pathophysiological mechanism and consequences of increased SF levels in patients with Insulin resistance syndrome.

SF and its Influence on Various Biochemical parameters

In the diabetic patients, a positive correlation between increased SF and poor glycemic control reflected by higher HbAIC, has been suggested by Eschwege *et al* (16). They reported that haemoglobin AIc values measured in diabetic patients with idiopathic haemochromatosis tended to be lower than in diabetics without haemochromatosis which may be ascribed to the venesection therapy, which induces an increased turnover of red cells, and consequently a decrease time available for their glycosylation.

Metabolic syndrome(17) or syndrome X are terms used to describe constellation of metabolic divulgements that include insulin resistance, hyper tension, dislipidemia with low HDL-C and elevated triglycerides, central or visceral obesity, type-2 diabetes mellitus or IGT/IFT and accelerated cardiovascular disease. Iron stores expressed as SF concentration, have been proposed as component of insulin resistance syndrome. SF concentration is also directly associated with serum uric acid another component of the insulin resistance syndrome and inversely related with HDL concentration.

Phlebotomy is followed by drop in serum glucose, serum cholesterol, serum triglycerides and improvement in both beta cell secretion and peripheral insulin action in type-2 diabetes mellitus(7,8). Wrede *et al* (4) suggested that SF values are significantly increased in men and women with high BMI (> 25 kg/m2), increased cholesterol (> 200 mg/dl), and increased systolic (> 160 mmHg) blood pressure, in women with diabetes, and in men with increased diastolic (> 95 mmHg) blood pressure(4).

SF and its Influence on Diabetic Complications

DyMock *et al* (7) reported influence of the increase body iron stores on diabetic nephropathy and vascular dysfunction. Diabetic nephropathy is currently single commonest indication for renal replacement therapy world wide and patients developing end stage renal disease in diabetes is increasing (18). Tight blood glucose control reduces the risk of developing nephropathy.

In patients with increased SF, glycemic control is poor and there is vascular damage. Insulin resistance has been documented by Ralpha A, (19). They found impaired tissue sensitivity in uraemic patient .In diabetic nephropathy, there is decrease in the GFR & albuminuria. Once proteinuria has occurred, it is treated by ACE inhibitor or Angiotensin receptor biockers, but it is a progressive condition and it leads to end stage renal disease.

In a trial by Cantur KZ *et al* (11) poorly controlled patients of diabetes had hyperferritinemia. This confirmed that SF was increased in diabetes as long as glycemic control was not achieved. They also found correlation between ferritin level and diabetic retinopathy.

Whereas persistent hyperglycemia appears to be the primary factor in the pathogenesis of neuropathy, several functional disturbances are found in the microvasculature of the nerves of diabetic patients Vinik. *et al* (20). These include decreased neural blood flow, increase in vascular resistance and altered vascular permeability. This dysfunctional phase in the nerves as in the small vessels, is also associated with elements of metabolic syndrome such as insulin resistance, elevated systolic blood pressure and diabetic dyslipidemics Vinik *et al* (20). Supporting evidence also comes from animal models and analysis of atherosclerotic lesion in men. The evidence from prospective human studies is inconsistent; some patients with increased levels have shown risk of coronary heart disease while others have not. Discrepancy may be due to environmental bias and variability in response. Studies by Beyar (21) and Ascherio (6) showed inconsistent effect on coronary heart disease. So, nothing conclusively could be established about the relationship between SF level and cerebrovascular disease.

Conclusion

It is abundantly clear from the review of studies that increased SF levels are associated with increased S. Insulin levels reflecting insulin resistance, poor glycemic control and increased TC, S. Triglyceride and Uric Acid levels in diabetic patients and complications of type-2 diabetes like nephropathy, retinopathy, neuropathy and hypertension except for which data is insufficient vascular disease and

ischemic heart disease. Many measures are taken for prevention, treatment of anemia, but it is important to realize that raised levels of iron above physiological requirement serve no useful purpose in Diabetes Mellitus patients. Anemia is very prevalent in Indian population and continuous efforts are being made to prevent and treat anemia at physician, Government and community levels which can influence the coexisting diabetic state.

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