Mal J Nutr 16(3): 369 - 377, 2010

Ferritin and Soluble Transferrin Receptors in Type 2 Diabetic and Non-diabetic Post-menopausal Women in Dhaka, Bangladesh

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ABSTRACT

This cross-sectional comparative study was aimed at investigating the iron status of a group of post-menopausal women with and without diabetes. Thirty-five post-menopausal women in each group were selected purposively from among patients attending the out-patient department of Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), a specialist hospital, and two of its satellite clinics, all in Dhaka. Patients were enrolled based on their existing records. The subjects were matched on age, menstrual status and fasting status at blood draw. Ferritin, serum soluble transferrin receptors (sTfR) and fasting plasma glucose were measured by standard methods. Dietary information was collected by a specific food frequency questionnaire. No significant difference in plasma ferritin [62.02 ng / ml, (range: 4.68-288.89) vs 54.25 ng / ml (range: 4.58-137.17); p=0.28] was observed between the groups. But a higher level of plasma sTfR was found in diabetic women [(21.12 nmol / l (range: 7.91-39.79) vs 17.63 nmol / l (range: 10.30-110.00); p<0.01]. TFR-F index showed no difference between diabetic and control (p=0.25). Significantly a lower hemoglobin level [10.58±0.67 g / dl vs11.76±1.5 g / dl; p<0.01] was detected in diabetic women. Plasma sTfR (log) did not show any significant association with the dietary parameters and iron indices. No significant association between fasting glucose, ferritin and sTfR was seen except for haemoglobin (r=0.39, p=0.05). Total iron intake recorded was more than the requirement, and was significantly higher in control group [38.11mg / day (range: 19.83-105.63) vs 56.65 mg / day (range: 29.75-109.54); p<0.01)]. More than 97 % of total iron was of plant origin. No differences in heme iron [0.85 mg / day (range: 0.09-4.07) vs. 0.96 mg / day (range: 0.04-4.34), p= 0.17] and vitamin C intake was observed between the groups. Iron indices of non-diabetic women were within the normal range. A higher level of sTfR and a lower level of hemoglobin in diabetic cases is suggestive of iron deficiency anaemia rather than iron overload.

Keywords: Iron, iron deficiency anemia, T2 diabetes, menopause, ferritin, sTfR

INTRODUCTION

Several epidemiological studies have reported an association between high iron stores and increased risk of metabolic syndrome (Sheu *et al*., 2003; Hua, Stoohs & Facchini, 2001; Jehn, Clark & Guallar, 2004), gestational diabetes (Lao & Tam ,1997; Lao,

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Chan & Tam, 2001) and type 2 diabetes (Jiang *et al*., 2004; Ford & Cogswell ,1993; Hernandez *et al*, 2000; Hughes *et al*, 1998; Thomas *et al*, 2004; Kaye, Guay & Simonson ,1993). Iron is a strong pro-oxidant and high body iron levels are associated with increased level of oxidative stress that may elevate the risk of type 2 diabetes. Positive associations have been reported between high body iron stores as measured by circulating ferritin levels and the risk of T2 diabetes. In addition, increased dietary intake of iron, specially that of heme iron, is associated with the risk of T2 diabetes in apparently healthy populations (Swapnil *et al*., 2009). Heme iron is more bioavailable, because of its higher absorption independent of iron status of body , unlike the absorption of non-heme iron, which is well regulated (Monser, 1988).

Therefore, it is probable that a chronically high intake of heme iron can lead to high body iron stores and thus may elevate the risk of diabetes. Suggested iron intakes drop from 18mg per day in women aged 19 to 50 to 8 mg per day after age 50, due to iron conservation and decreased losses in post-menopausal women. Ferritin is a widely used marker of iron status in epidemiological studies. Serum ferritin levels are affected by age and sex. Its concentration generally reflects total body iron status in most persons (Cook *et al*., 1974) and serum sTfR concentration is closely related to cellular iron demands, and therefore the higher the ferritin levels, the lower the sTfR concentration. The serum ferritin levels are lower and more stable in females during the reproductive period, and only increases after menopause. Ferritin and transferrin are more saturated in post-menopausal women. Serum ferritin is now proposed to be a component of the metabolic syndrome (Fernandez-Real *et al*., 1999). Mean serum ferritin levels are found to be higher in post-menopausal women who have a higher risk of atherosclerosis and an increased risk of ischaemic strokes (Daphne *et al*., 2005; Kraml *et al*., 2000). An elevated ferritin concentration and a low ratio of transferrin receptors to ferritin is associated with an increased incidence of T2 diabetes in apparently healthy women independent of known diabetes risk factors (Jiang *et al*., 2004).

To our knowledge, there are no other reported studies relating iron stores to the incidence of T2 diabetes among post-menopausal women in Bangladesh. We conducted a small comparative study to evaluate biomarkers reflecting iron status, including plasma ferritin level, sTfR concentration, the ratio of transferrin receptors to ferritin, and dietary iron intake in relation to T2 diabetes in post-menopausal women.

METHODOLOGY

Study population

This comparative study was designed to investigate the association between iron status in relation to diabetic status among the post-menopausal women. A total of thirty-five post-menopausal T2 diabetic women were selected from among the patients attending the out-patient department of Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), a specialist hospital, and two of its satellite clinics. Patients were enrolled based on their existing records. Post-menopausal status was applied to women who have not experienced a menstrual bleed for a minimum of twelve consecutive months, assuming that they do still have a uterus, are not pregnant or lactating and are usually between 45 to 55 years of age. Those who experienced menopause within the last 5 years were considered eligible for inclusion in the study. All diabetic women had a history of diagnosed (fasting plasma glucose $\geq$126mg / dl, ADA 2003) type 2 diabetes mellitus and had taken oral anti-diabetic agents. Most of them reported suffering from T2 diabetes for more than 10

to 15 years. An equal number of non-diabetic post-menopausal women were recruited matched to the cases on age, menstrual status and fasting status at blood draw for comparison. Fasting was defined as 8-hours or longer since last meal prior to sample collection. Control subjects were apparently healthy individuals who volunteered to take part in our study, and were recruited through clinic staff. All participants received a clinical evaluation. The exclusion criteria for this study were having complications like nephropathy, retinopathy and cardio-vascular diseases. Informed written consent was obtained from all the patients and control subjects.

Laboratory analysis

All laboratory measurements were performed on fasting blood samples. The iron and diabetic status of the subjects was assessed by assaying venous blood sample for serum ferritin, serum transferrin receptors (sTfR), haemoglobin and fasting plasma glucose (FPG). The sTfR / log ferritin ratio (TfR-R index) was also determined. Plasma ferritin concentration was estimated by Microparticle Enzyme Immunoassay (MEIA) technology (Crichton, 1971) (reference range: 14.0 to 233.1 ng / ml for post-menopausal women). Plasma sTfR was measured by Enzyme Linked Immuno-sorbent Assay (ELISA) (Beguin, 1992) (reference range: 8.7 to 28.1 nmol / litre, mean 18.4 nmol / litre in both sexes). Iron deficiency (ID) was defined as sTfR>28.1 nmol / l. The ratio of the concentrations of sTfR to log ferritin (TFR-F index, reference range: 0.63-1.8) was used an additional marker of iron deficiency anemia. Plasma glucose was estimated by Glucose-Oxidase (GOD-PAP) method by an Auto analyser (Auto lab, Analyzer Medical System, Rome, Italy) using reagents of Randox Laboratories, UK (Barham & Trinder, 1972) (reference range: $\geq$7 mmol / l in fasting condition, and $\geq$11 mmol / l for non fasting condition).

Dietary and anthropometric data

A semi-quantitative food frequency questionnaire was specially designed in which commonly consumed foods and drinks were listed to assess the usual pattern of food intake of the study subjects. The respondents were asked for the frequency and portion size of the food and drinks consumed over the past seven days. The portion sizes used in the food frequency questionnaire were based on typical or natural portion consumed (e.g., slice, piece, cup etc.). When a typical or natural portion was uncertain, the amount of food eaten was recorded demonstrating various types of standardised utensils and food models in natural size in recalling and assessing portion size of the food eaten with the help of qualified personnel. From the food frequency questionnaire, foods and drinks providing similar types of nutrients were grouped into cereal, meat, dairy, vegetables and fruit groups. Emphasis was given to collecting information on food sources rich in iron, protein and vitamin C. The nutritive values of food intake by the subjects were determined from portion size estimated by consulting Bangladeshi food composition data published by HKI (Darnton-HI *et al.*, 1998). Qualified and trained female personnel were employed to do the interviews and take the anthropometric measurements.

The weights and heights of each patient and control were examined with light clothing in the morning before drawing blood. Body mass index(BMI) was calculated as kg / m^2.

Statistical analysis

Normal distribution of the variables was evaluated using the Kolmogorov-Smirnov test. Given their skewed distribution, serum ferritin and sTfR are expressed as median (range). Comparisons between two groups were done using Student *t*-tests for normally distributed data and Man-Whitney U tests

Table 1. Characteristics of the subjects included in the study

	Diabetic group (n=35)	*Control group(n=35)*	*p*
Age (years)	52.60 ± 3.15	51.03 ± 3.67	0.06
Weight (kg)	62.86 ± 10.51	57.69 ± 11.73	0.06
Height (cm)	155.06 ± 4.67	153.74 ± 7.13	0.37
BMI (kgm^{-2})	26.12 ± 4.13	24.33 ± 4.31	0.08
Ferritin (ng / ml)	62.02 (4.68-288.9)	54.25 (4.58-137.17)	0.28
sTfR (nmol / l)	21.12 (7.91-39.79)	17.63 (10.30-110.00)	<0.01
Hemoglobin (g / dl)	10.58 ± 0.67	11.76 ± 1.51	<0.01
FPG (mmol / l)	9.93 ± 3.66	5.13 ± 0.51	<0.01
sTfR / log Ferritin (TfR-F index)	1.00 (0.31-3.23)	0.89 (0.44-14.13)	0.25

Data are mean ± SD and median (range); sTfR- Serum Soluble Transferrin Receptors; FPG - Fasting Plasma Glucose; log - logarithmically transformed

for skewed data. The relationship between normally distributed variables was examined by the Pearson's linear correlation test. Spearman's coefficient correlation analysis was performed for skewed data. Multiple regression analysis was performed to explore the variables that were independently related to ferritin levels. Significance was accepted at $p<0.05$ level. Statistical analyses were performed with the SPSS (version 10.0).

RESULTS

The physical characteristics and iron indices of diabetic women and control group (non-diabetic) are presented in Table 1. No significant differences in age, weight and height were observed between the groups. Mean BMIs seem higher among cases than controls, but the difference was insignificant. Diabetic women were to be found overweight by their BMI score, whereas the control group was within normal limits. No notable difference among diabetic and non-diabetic women was found for plasma ferritin concentration [62.02 ng / ml, (range: 4.68-288.89) vs 54.25 ng / ml (range: 4.58-137.17); $p=0.28$]. But the diabetic women had higher sTfR levels [(21.12 nmol / l (range: 7.91-39.79) vs 17.63 nmol / l (range: 10.30-110.00); $p<0.01$]. The TFR-F index showed no difference between diabetic and non-diabetics groups. A significantly lower hemoglobin level [10.58±0.67 vs11.76±1.5; $p<0.01$] was noted among the diabetic women. Mean Hb level of the non-diabetic control group was within the normal range. As expected, type 2 diabetic subjects had higher fasting plasma glucose level [9.93±3.66 mmol / l vs 5.13±0.51 mmol / l; $p<0.01$] compared to the non-diabetes women.

Nutrient (iron, protein and vitamin C) intake of the study participants are shown in Table 2. Total dietary iron intake was observed to be significantly high among non-diabetic women [38.11mg / day (range: 19.83-105.63) vs 56.65 mg / day (range: 29.75-109.54); $p<0.01$)]. More than 97% of the iron intake was contributed by plant sources. Intake of heme iron was observed to be very poor for both case and control groups. No virtual difference in heme iron intake was detected between the groups [0.85 mg / day (range: 0.09-4.07) vs. 0.96 mg / day (range: 0.04-4.34), $p= 0.17$]. Protein and vitamin C are known enhancers for iron absorption and utilisation. Total protein consumption was remarkably poor among the diabetic women in terms of recommended dietary intake ($p<0.01$). Only 17% met the requirement, while it was 63% among the

Table 2. Dietary intakes of iron, protein and vitamin C per day

Nutrients	*Diabetic group*	*Control group*	*p*
Total iron (mg)	38.11 (19.83-105.63)	56.65 (29.75-109.54)	<0.01
Heme	0.85 (0.09-4.07))[2.7]*	0.96 (0.04-4.34)[2.4]	0.17
Non-heme	37.42 (18.69-104.71)[97.2]	56.00 (27.74-107.04)[97.5]	<0.01
Protein (g)	41.83 (17.12-85.23)	68.75 (25.68-323.18)	<0.01
Plant	27.87 (13.67-56.68)[68]	49.96 (20.93-287.14)[76]	<0.01
Animal	13.13 (2.89-49.25)[31]	17.14 (2.17-60.16)[23.1]	0.17
Vitamin C (mg)	113.68 (17.70-316.64)	133.93 (18.4-717.37)	0.30

Data are median (range); * Figures in parentheses are percentages of total intake

Table 3. Correlation of sTfR (log) with different parameters in diabetic and control groups

	Diabetic group		*Control group*	
	r	*p*	*r*	*p*
BMI	0.01	0.97	-0.12	0.51
Hemoglobin	-0.02	0.90	0.51	0.77
Ferritin (log)	-0.27	0.11	-0.46	<0.01
Total iron	0.11	0.52	0.02	0.91
Heme iron	0.08	0.65	-0.24	0.17
Non-heme iron	0.11	0.51	0.02	0.87
Vitamin C	0.01	0.95	0.32	0.06
Total protein	0.05	0.76	-0.04	0.80
Plant protein	0.02	0.90	0.05	0.79
Animal protein	0.06	0.73	-0.20	0.26

BMI, Body Mass Index

control group. The non-diabetic women reported considerably higher consumption (p<0.01) of dietary protein of plant origin, which is of low bioavailability. Consumption of animal protein was observed to be very low by both the groups. No differences in the intake either for animal protein or vitamin C were observed between the groups.

No significant association of sTfR (log) with dietary variables and iron indices except for ferritin (log) was found in any of the groups (Table 3). A significant negative correlation between sTfR (log) and ferritin (log) was found in the control group (r=-0.46, p<0.01)(Figure 1). No significant association among fasting glucose, ferritin or sTfR was detected in both groups. A significant positive correlation was observed between plasma fasting glucose and hemoglobin in diabetic post-menopausal women (r=0.34, p=0.05)(Table 4). Multiple regression analysis showed sTfR (log) to be an independent predictor of ferritin level in the control group(Table 5).

DISCUSSION

Ferritin levels in females increase considerably after menopause. There may ba an increment of two to three-fold from before menopause to after menopause. Elevated

Figure 1. Correlation of sTfR (log) with ferritin (log) in post-menopausal diabetic and non-diabetic women

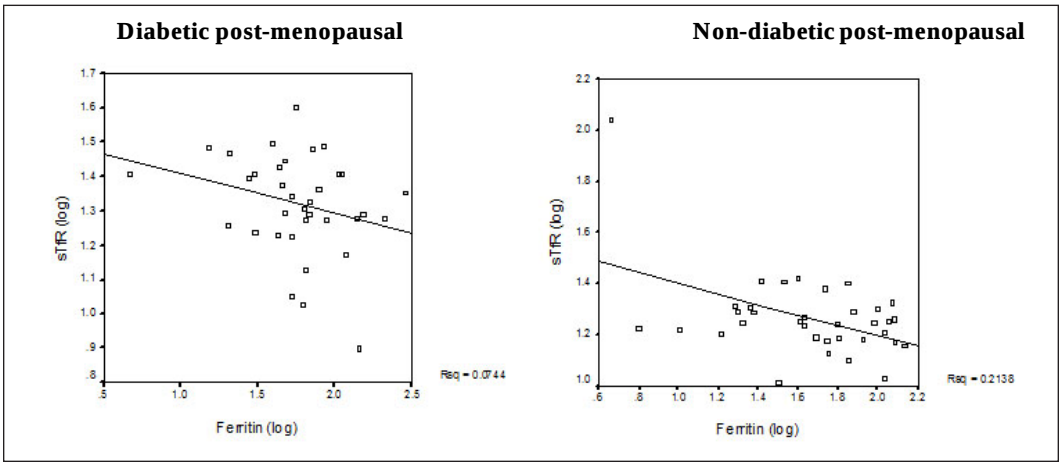

Table 4. Correlation of fasting plasma glucose (FPG) with iron indices

Iron indices	*Diabetic group*		*Control group*	
	r	*p*	*r*	*p*
Ferritin	0.14	0.41	-0.09	0.61
sTfR	-0.03	0.88	0.13	0.46
Hemoglobin	0.39	0.05	0.14	0.43

sTfR- Serum Soluble Transferrin Receptors

Table 5. Multiple regression analysis of independent variables associated with ferritin concentrations in diabetic and non-diabetic menopausal subjects

	Dependent variable: Ferritin (log)					
	Diabetic subjects			*Control subjects*		
	ß	*T*	*P*	*ß*	*T*	*P*
Age	0.001	0.005	0.99	-0.222	-1.258	0.21
BMI	0.157	0.764	0.45	0.050	0.303	0.76
sTfR (log)	-0.269	-1.469	0.15	-0.544	-3.141	<0.01
Heme iron	-0.077	-0.237	0.81	-0.158	-0.723	0.47
Nonheme iron	-0.035	-0.149	0.88	-0.064	-0.335	0.74
Total Protein	0.114	0.338	0.73	0.272	1.340	0.19
Vitamin C	0.136	0.664	0.51	-0.278	-1.351	0.18
R^2		-0.09			0.33	

iron reflects the development of insulin resistance and diabetes (Salonen *et al*., 1998). Epidemiological studies showed that the diabetic patients had higher serum ferritin levels than the control subjects (Hernandez *et al*., 2005). Serum ferritin level of our study population was found to be within the normal range and no differences were observed in ferritin level between diabetic and non-diabetic post-menopausal women [62.02 ng / ml, (range: 4.68-288.89) vs 54.25 ng / ml (range: 4.58-137.17); p=0.28]. The findings do not reflect the prevailing understanding that plasma ferritin concentration is elevated in persons with prevalent diabetes as compared with non-diabetic control. A normal or higher concentration of ferritin does not rule out the existence of iron deficiency in diabetic cases. sTfR is a sensitive measure in the differential diagnosis of anemia of chronic disorder and iron deficiency anemia. Because of its very small day-to-day variation, it predicts the iron profile more accurately than serum iron and transferrin saturation levels, which showed large day-to-day variation (Borel *et al*., 1991). Moreover, the concentration of sTfR is not influenced by inflammatory diseases and is independent of liver parenchymal status and hormonal status. The sTfR more accurately reflects the demands of bone marrow for iron, that is, high sTfR concentration indicates iron deficiency anemia. Individuals with T2 diabetes, who show elevated body iron stores, do have low sTfR concentration. High sTfR concentration and low hemoglobin among diabetic women in our cases is suggestive of iron deficiency anemia. High sTfR indicates iron deficient erythropoiesis leading to low hemoglobin concentration. The hemoglobin (Hb) level of diabetic cases was significantly lower than in the control group ($p<0.01$). Women with high sTfR hence have impaired iron availability. Iron indices are strongly correlated with Hb, which represents an important risk factor for morbidity and mortality in patients with diabetes (Thomas *et al*., 2003; Keane & Lyle, 2003). Correlation between low levels of hemoglobin with fasting plasma glucose in diabetic women was detected in our study. In Finland, it was reported that serum ferritin concentration had a significant correlation with blood glucose concentration (Salonen *et al*., 1992).

Transferrin saturation index (TFR-F index), a marker of iron overload, increases the risk of diabetes to 2.5 times (Jiang *et al.*, 2004). In our study, only 4 diabetics and one non-diabetic was found to have a ratio >1.8, otherwise no differences could be ascertained between the groups. When we examined each case separately, we found one diabetic and three non-diabetic had ferritin concentrations below the reference limit (<14ng / ml) suggesting a depleted iron store. Only one diabetic women was detected with high ferritin level (>233 ng / ml). In the case of sTfR , 6 diabetic and 1 non-diabetic women had sTfR levels greater than 28.1 nmol / l, while only one diabetic was found to have a sTfR level less than 8.7 nmol / l.

We examined the dietary variables of iron (heme and non-heme) intake, and intake of potential enhancers (vitamin C and meat) of iron absorption, in relation to serum ferritin. Non-heme iron dominated the total iron intake by the study population, but a significantly lower amount was found in diabetic women. A restricted dietary regimen might have contributed to such a low intake among the women.

We found diabetic women to be 'overweight' compared to their control peers based on their BMI score, and were anemic. A moderate degree of iron deficiency in obese post-menopausal women has been reported by Albert *et al.* (2006). However, though they were unable to elucidate the mechanism, they showed an association between BMI and sTfR in this group of population. But in our study, no such association between sTfR with independent variables like BMI, iron and dietary indices could be established. Multiple regression analysis showed that

ferritin levels are not independently associated with age, BMI, and dietary variables but sTfR (log) was found to be an independent predictor of ferritin levels in non-diabetic (R^2= 0.33) women.

This cross-sectional comparative study documents prevalence of anemia in post-menopausal diabetic women. Iron deficiency rather than iron overload dominated in diabetic post-menopausal women. The small size of the study complicates interpretation of findings. However, restricted dietary intakes by the diabetic post-menopausal women do have a probable interpretation in the causation of anemia. Future studies are needed with a larger sample to elucidate the mechanisms that underlie iron deficiency in post-menopausal diabetic women.

ACKNOWLEDGEMENTS

We are grateful to the women who took part in this study. Special thanks are extended to Shuhana Sultana, Fadia Afnan, Shirin Jahan Mumu, Fatema Akter, Sanzida Akter, Kajol Boron Biswas, Kalam, Biomedical Research Group, BIRDEM, Dhaka.

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