

Age- and body mass index-dependent relationship between correction of iron deficiency anemia and insulin resistance in non-diabetic premenopausal women

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BACKGROUND: No prospective studies have evaluated the effects of correction of iron deficiency anemia on insulin resistance in non-diabetic premenopausal women. We investigated this relationship in 54 non-diabetic premenopausal women with iron deficiency anemia.

SUBJECTS AND METHODS: All patients were treated with oral iron preparations. Insulin resistance was calculated with the Homeostasis Model Assessment formula. All patients were dichotomized by the median for age and BMI to assess how the relationship between iron deficiency anemia and insulin resistance was affected by age and BMI.

RESULTS: Although the fasting glucose levels did not change meaningfully, statistically significant decreases were found in fasting insulin levels following anemia treatment both in the younger age (<40 years) ($P=0.040$) women and in the low BMI (<27 kg/m²) ($P=0.022$) subgroups but not in the older age (≥ 40 years) and the high BMI (≥ 27 kg/m²) subgroups. Post-treatment fasting insulin levels were positively correlated both with BMI ($r=0.386$, $P=0.004$) and post-treatment hemoglobin levels ($r=0.285$, $P=0.036$). Regression analysis revealed that the factors affecting post-treatment insulin levels were BMI ($P=0.001$) and post-treatment hemoglobin levels ($P=0.030$).

CONCLUSION: Our results show that following the correction of iron deficiency anemia, insulin levels and HOMA scores decrease in younger and lean non-diabetic premenopausal women.

It is well known that complex interactions exist among insulin, insulin resistance, iron and anemia. A mutual relationship has been identified between insulin and iron metabolism. Insulin both stimulates the synthesis of ferritin and causes a rapid and marked stimulation of iron uptake of cells by redistributing transferrin receptors from the intracellular compartment of the cell membrane to the cell surface. Regulation of iron uptake by insulin occurs in parallel with its effects on glucose transport.² On the other hand, insulin action is also influenced by iron. Iron causes hyperinsulinemia and insulin resistance by inhibition of insulin internalization and actions.³ In fact, the initial and most common abnormality seen in conditions with iron overload is hepatic insulin resistance.⁴ In previous animal studies, it has been shown that glucose turnover

increases in iron deficiency, and this increase is primarily due to enhanced peripheral insulin responsiveness.⁵⁻⁸ Interestingly, there are some reports indicating that low iron status increases insulin sensitivity in lacto-ovo vegetarians. In addition, phlebotomy is followed by decreases in serum glucose as well as by improvements in both beta-cell secretion and peripheral insulin action.^{9,10}

Insulin plays an important role in regulation of erythropoiesis both with its ability to boost activity of the transcription factor, hypoxia-inducible factor-1A (HIF-1A), and more directly as a growth factor influencing development of reticulocytes.¹¹ On the other hand, some recent reports suggest that rising hemoglobin/hematocrit (hemoglobin/hematocrit) levels are a component of insulin resistance syndrome, presumably

due to the facilitative effect of insulin on erythropoietin synthesis.¹²⁻¹⁴ Conversely, in patients with chronic renal failure, anemia has been suggested to be responsible for the insulin resistance commonly seen in these patients.¹⁵⁻¹⁸

Hyperinsulinemia and insulin resistance constitute a risk factor for atherosclerotic heart diseases.¹⁹ It is commonly accepted that premenopausal women carry less risk for cardiovascular diseases essentially due to the protective effect of intrinsic estrogen hormone.²⁰ In premenopausal women, iron deficiency, which is usually caused by menstrual loss, is a very common health problem. Some animal and human studies indicate that iron deficiency increases glucose tolerance and insulin sensitivity. In that case, low iron status in premenopausal women may exert an independent and additional protective role besides hormonal status for atherosclerotic heart diseases. To the best of our knowledge, there have not been any prospective studies reporting the effects of correction of iron deficiency anemia on insulin resistance in non-diabetic premenopausal women. In this prospective study, we investigated how insulin resistance is affected by correction of anemia and how this relationship might be affected by anthropological parameters such as age and BMI.

SUBJECTS AND METHODS

We recruited 54 anemic premenopausal women (menstruating women of reproductive age) who had iron deficiency anemia due to menstrual loss (median age, 40 years; mean age, 36.28±10.64 years; range, 15 to 52 years) for this study. Serum ferritin values below the normal range and transferrin saturation below 15% were accepted as indicators of iron deficiency. Blood hemoglobin and hematocrit values below the normal range (≤ 12 g/dL and $\leq 35\%$, respectively) were accepted as indicators of anemia. All patients were treated with oral iron preparations (daily 225 mg ferroglycine sulfate), and the median duration of treatment was three months. Patients were excluded from the study if they had family histories of diabetes mellitus, repeatedly had fasting venous serum glucose levels >110 mg/dL or were previously placed on iron replacement treatments. Previous medications other than iron preparations that had already been used by the patients were continued. Informed consent was obtained from each subject after approval of the experimental protocol by the local human ethics committee. For each patient included in this study, hemoglobin, hematocrit, serum iron, transferrin saturation and serum ferritin were measured in 12-hour fasting blood both prior to the onset of iron replacement and 15 days after stopping iron treat-

Table 1. Pre- and post-treatment laboratory parameters of all patients.

	Pre-treatment	Post-treatment	P
Hemoglobin (g/dL)	9.76±1.73	13.13±1.04	<0.001
Hematocrit (%)	30.26±4.25	39.11±2.92	<0.001
Iron (μ g/dL)	20.94±15.14	83.80±27.09	<0.001
Ferritin (ng/mL)	5.56±4.07	33.40±23.76	<0.001
Transferrin saturation (%)	4.77±4.00	25.94±8.85	<0.001
Glucose (mg/dL)	94.89±12.50	94.26±10.70	0.693
Insulin (μ IU/mL)	9.94±6.56	7.90±3.60	0.007
HOMA score	2.40±1.80	1.86±0.91	0.009

Table 2. Pre- and post-treatment laboratory parameters of low and high BMI subgroups.

		Lean BMI	High BMI	P
Pre-treatment	Hemoglobin (g/dL)	9.92±1.97	9.62±1.50	0.538
	Hematocrit (%)	30.55±4.95	30.00±3.55	0.639
	Iron (μ g/dL)	19.58±15.79	22.21±14.67	0.527
	Transferrin saturation (%)	4.58±3.92	4.94±4.15	0.747
	Ferritin (ng/mL)	5.25±3.36	5.83±4.67	0.613
	Fasting glucose (mg/dL)	92.15±8.52	97.43±15.08	0.123
	Insulin (μ IU/mL)	9.18±7.35	10.64±5.79	0.419
	HOMA score	2.13±1.89	2.64±1.71	0.304
Post-treatment	Hemoglobin (g/dL)	13.18±1.04	13.08±1.07	0.742
	Hematocrit (%)	39.42±2.87	38.81±2.98	0.449
	Iron (μ g/dL)	80.85±26.96	86.54±27.42	0.446
	Transferrin saturation (%)	24.97±7.76	26.85±9.81	0.442
	Ferritin (ng/mL)	30.05±16.21	36.38±28.87	0.338
	Fasting glucose (mg/dL)	91.85±9.31	96.50±11.56	0.111
	Insulin (μ IU/mL)	6.29±2.82	9.39±3.65	0.001
	HOMA score	1.43±0.67	2.26±0.93	<0.001

ment due to improvement of anemia. Both pre-treatment and post-treatment insulin and glucose levels were measured in three different venous serum samples taken within intervals of 5 minutes after 12 hours of fasting. Insulin level was measured with the ECLIA (ElectroChemiluminescence ImmunoAssay) method using a Roche Modular Analytics E170 machine (Elecsys insulin kit No. 12017547). Insulin resistance (IR) was calculated according to the Homeostasis Model

Table 3. Pre- and post-treatment laboratory parameters of younger and older age subgroups.

		Younger age	Older age	P
Pre-treatment	Hemoglobin (g/dL)	10.08±1.80	9.49±1.66	0.217
	Hematocrit (%)	31.25±4.40	29.41±3.99	0.114
	Iron (µg/dL)	19.48±15.89	22.21±14.61	0.514
	Transferrin saturation (%)	4.47±3.98	5.02±4.08	0.621
	Ferritin (ng/mL)	5.28±3.08	5.79±4.79	0.656
	Fasting glucose (mg/dL)	95.04±11.16	94.74±13.80	0.935
	Insulin (µIU/mL)	10.27±7.20	9.65±6.08	0.734
	HOMA score	2.47±1.93	2.33±1.71	0.776
Post-treatment	Hemoglobin (g/dL)	13.18±0.87	13.08±1.19	0.717
	Hematocrit (%)	39.32±2.45	38.92±3.30	0.623
	Iron (µg/dL)	83.96±25.65	83.66±28.73	0.968
	Transferrin saturation (%)	26.24±8.84	25.69±9.01	0.824
	Ferritin (ng/mL)	27.85±12.06	37.98±29.67	0.123
	Fasting glucose (mg/dL)	91.80±10.08	96.38±10.93	0.118
	Insulin (µIU/mL)	7.55±3.02	8.20±4.07	0.516
	HOMA score	1.74±0.79	1.97±1.00	0.355

Assessment (HOMA) formula: $HOMA-IR = \text{fasting glucose (mmol/L)} \times \text{fasting insulin (mU/L)} / 22.5$.

In all patients, we searched for the existence of a possible relationship between iron deficiency anemia and insulin resistance. All patients as a whole group were dichotomized by the median for age (<40 years, n=25 and ≥40 years, n=29) and BMI (<27 kg/m², n=26 and ≥27 kg/m², n=28) to assess how this relationship, if it existed, was affected by age and BMI.

Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS, Inc, Chicago, IL, USA) for Windows 10.0 programs. Results were expressed as mean±standard deviation. Comparisons between pre- and post-treatment levels were made by the paired T test. Simple (Pearson) correlation coefficients between HOMA-IR and measures of variables were calculated, and a multiple linear regression analysis was performed, considering HOMA-IR as a dependent variable and all others as explanatory variables. Since the levels of HOMA-IR strictly depended on fasting insulin and glucose concentration, we did not consider these parameters in the multiple regression analysis. Results

were analyzed with 95% confidence intervals and probability levels less than 0.05 were considered significant.

RESULTS

The patients included in this study had a mean BMI of 26.84±5.95 kg/m², a mean waist/hip ratio of 0.82±0.10 and mean age of 36.28±10.64 years. When all 54 patients were assessed as a whole, statistically significant decreases were found in fasting insulin levels and HOMA scores following the correction of iron deficiency anemia while pre-and post-treatment fasting glucose levels did not change meaningfully (Table 1). In the presence of anemia, neither fasting insulin levels nor HOMA scores were found to be significantly correlated with either hematological or iron parameters. After correction of the anemia, both fasting insulin levels and HOMA scores were found to be positively correlated with both BMI and post-treatment hemoglobin levels, with statistical significance. In the regression analysis, the factors affecting post-treatment insulin levels were found to be BMI (P=0.001) and post-treatment hemoglobin levels (P=0.030).

When all the patients were dichotomized by the median for BMI into two subgroups as low (mean BMI, 21.90±2.62; range, 17 to 26 kg/m²) and high (mean BMI, 31.43±4.22; range, 27 to 44 kg/m²) subgroups, the high BMI subgroup consisted of older patients than the low BMI subgroup (42.50±5.51 and 29.58±10.82 years, P<0.001, respectively). Neither pre-treatment nor post-treatment levels of hemoglobin, hematocrit, serum iron, transferrin saturation, serum ferritin and fasting glucose differed significantly between the high and the low BMI subgroups. Also, pre-treatment fasting insulin levels and HOMA scores in the high and low BMI subgroups did not differ significantly from each other, but the mean post-treatment fasting insulin levels and HOMA scores were found to be significantly lower in the low BMI subgroup than in the high BMI subgroup (Table 2). The fasting glucose levels of the low and high BMI subgroups did not change meaningfully following iron treatment. After correction of the anemia, both insulin levels (from 9.18±7.35 to 6.29±2.82, P=0.022) and HOMA scores (from 2.13±1.89 to 1.43±0.67, P=0.032) in the low BMI subgroup decreased significantly, whereas decreases in insulin levels (from 10.64±5.79 to 9.39±3.65, P=0.150) and HOMA scores (from 2.64±1.71 to 2.26±0.93, P=0.145) in the high BMI subgroup were less evident and statistically insignificant.

When all patients were dichotomized by the median for age into two subgroups as younger (mean age, 26.92±8.16; range, 15 to 39 years) and older (mean age

44.34±3.38; range, 40 to 52 years) age subgroups, the subjects in the older age subgroup also had a higher BMI (29.52±5.50 and 23.74±4.91 kg/m², $P<0.001$). Neither pre-treatment nor post-treatment levels of hemoglobin, hematocrit, serum iron, transferrin saturation, serum ferritin, fasting glucose, serum insulin and HOMA scores differed significantly between the older and younger age subgroups (Table 3). Although statistically insignificant, post-treatment fasting glucose levels in the younger age subgroup had a tendency to fall (from 95.04±11.16 to 91.80±10.08, $P=0.064$), whereas post-treatment fasting glucose levels showed a tendency to rise in the older age subgroup (from 94.76±13.80 to 96.38±10.93, $P=0.529$). Fasting insulin levels and HOMA scores in the younger age subgroup decreased significantly after iron treatment (from 10.27±7.18 to 7.55±3.02, $P=0.040$ and from 2.47±1.93 to 1.74±0.79, $P=0.032$, respectively), but the decreases in these parameters in the older age subgroup were lesser and statistically insignificant (from 9.65±6.06 to 8.20±4.07, $P=0.081$ and from 2.33±1.71 to 1.97±1.00, $P=0.146$ respectively).

DISCUSSION

The most important result of this study is that the relationship between iron deficiency anemia and insulin levels (and HOMA scores, which are accepted as indicators of insulin resistance) seen in non-diabetic premenopausal women is multi-factorial. Our results show that some anthropological parameters such as age and BMI have an influence on the relationship between iron deficiency anemia and insulin levels.

When all 54 patients were assessed as a whole, the results of this study differed from the results of animal and similar, but not identical, human studies, which reported that iron deficiency increases glucose tolerance and insulin sensitivity.⁵⁻⁹ According to our results, in general, following treatment of iron deficiency anemia, insulin levels and HOMA scores in premenopausal women decreased, with statistical significance. Our results showed that the decreases in insulin levels and HOMA scores actually occurred in patients of younger age and lower BMI. However, these parameters also showed a tendency to decrease rather than to increase in patients of older age and high BMI.

To the best of our knowledge, there are no published human studies that assess the relationship between iron deficiency anemia and insulin resistance other than reports indicating that low iron status enhances insulin sensitivity in lacto-ovo vegetarians.⁹ Previously reported human studies investigating the relationship between anemia and insulin resistance usually consist-

ed of patients with diagnoses of either thalassemia²¹⁻²⁴ or aplastic anemia,²⁵ and in general, subjects with these diagnoses are considered to have simultaneous iron overload. The relationship between iron overload and insulin resistance is well known.²⁶ Patients with thalassemia and aplastic anemia have only the anemia factor as the common denominator with iron deficient patients, and therefore, it would be a mistake to consider these patients anemic, but at the same time iron overloaded patients are in the same category with iron deficient patients when evaluating insulin resistance. Our results also differ from the results of animal experiments showing that iron deficiency increases glucose tolerance primarily due to an increase in peripheral insulin responsiveness.⁵⁻⁸ Similar studies have also been done with chronic renal failure patients in whom insulin resistance is accompanied with many other factors,^{15,17,27} and anemia has been suggested as the causal factor for insulin resistance in these patients. Moreover, it has been reported that insulin resistance is reduced or improved in these patients due to either the direct effect of erythropoietin treatment or the indirect effect of anemia correction.^{15,16,27} With respect to anemia, our results are similar to the results of the studies done with patients with chronic renal failure. However, our results indicate that neither low iron status itself nor the resultant anemia of iron deficiency are the causes of the higher insulin levels and HOMA scores.

In this study, the results of the subgroup analysis for age and BMI suggest that the anthropological characteristics of a study population may affect the relationship between iron deficiency anemia and insulin resistance, so the contrary results found in this study could be due to the different anthropological characteristics of the study population. The reason for the different responses in means of insulin resistance to iron treatment exerted by the younger age/low BMI and the older age/high BMI subgroups is not clear given that subjects were of the same gender and had similar hormonal status. We speculate that patients of younger age and low BMI are more energetic and active following the treatment of anemia compared to patients of older age and higher BMI, and the expenditure of more energy might be an additional factor contributing to the reduction of insulin resistance. Also, the therapy duration of three months is not long enough to see the changes in the levels of insulin and HOMA scores in patients with older age and high BMI who already have established insulin resistance when compared with patients of younger age and low BMI. The results of these subgroup analyses indicate both the necessity of taking the anthropological characteristics of the study population into account

while assessing the relationship between iron deficiency and insulin resistance, and the need for further studies with different population groups.

On the other hand, there are some recent reports suggesting that the rising of hemoglobin/hematocrit values might be a component of the insulin resistance syndrome.¹²⁻¹⁴ In this study, we also found that there were statistically significant positive correlations between post-treatment hemoglobin levels and insulin levels as well as between post-treatment hemoglobin levels and HOMA scores. Also, regression analysis revealed that the factors affecting post-treatment insulin levels were BMI and post-treatment hemoglobin levels. These results of regression and correlation analyses provide support for the existence of a relationship between insulin resistance and hematological parameters. Therefore, when considering the treatment of iron deficiency anemia, targeting lower hemoglobin/hematocrit levels may be a suitable and a necessary action for patients of older age and higher BMI who already have established insulin resistance, and particularly for the patients in whom impaired glucose tolerance accompanies iron deficiency.

We do not know the exact underlying mechanism that explains the significant decrease in fasting insulin levels and HOMA scores after the treatment of iron deficiency anemia in premenopausal women. Also, we do not know whether the decrease in insulin levels and HOMA scores following iron therapy is due to iron replacement itself or correction of the resultant anemia. Although there are some reports showing that insulin promotes the synthesis of erythropoietin by boosting the activity of HIF-1A, which functions physiologically as a detector of both hypoxia and iron-deficiency,¹¹ and induces the synthesis of glucose transporters as well as glycolytic enzymes, it is not known whether diminished activity of HIF-1A following iron therapy af-

fects the synthesis and secretion of insulin or not. Such a relationship, if it exists, could be responsible for the decrease in insulin levels and HOMA scores following iron replacement, so it is clear that this topic merits further investigation.

Due to the role of insulin resistance and iron-dependent oxidative stress in the onset and progression of atherosclerosis, the relationship between iron deficiency and insulin resistance has importance. Despite some contrary reports,^{28,29} it has been shown that there is a link between iron status and the pathogenesis of atherosclerosis.³⁰⁻³⁵ Also, some evidence from previously published data show that the progression of an atherosclerotic plaque can be decelerated by reducing body iron stores with phlebotomy.^{31,36} When the results of our study are assessed in this perspective, it can be concluded that iron deficiency has a reducing effect on insulin levels in patients of younger age and lower BMI in whom atherosclerosis and its complications are expected to be less prevalent, whereas such an effect was not evident in patients of older age and higher BMI in whom atherosclerosis and its complications are expected to be more prevalent. This result is not compatible with the hypothesis that low iron status in premenopausal women may play an independent and additional protective role for atherosclerotic heart diseases.

In conclusion, our results show that an age- and BMI-dependent relationship exists between iron deficiency anemia and insulin levels (and HOMA scores) in non-diabetic premenopausal women. When considering the treatment of iron deficiency anemia, targeting lower hemoglobin/hematocrit levels may be an appropriate and a necessary action for the patients of older age and higher BMI, particularly for patients in whom impaired glucose tolerance accompanies iron deficiency.

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