INTRODUCTION

Iron essentially a trace element; also possess properties of transition during mostbiological processes. Body iron is sourced from duodenal absorption, specifically in the heme form (Fe$^{3+}$) and is released from both macrophages and liver.1 South Asian diet up to 90-95% comprises of non-heme iron of total daily iron requirement which is rather poorly absorbed by the gut.2 Researchers have shown that body iron is known to have a negative association withbody mass index (BMI).3,4 Increased plasma volume and more significantly, inflammation induced by increased adiposity is suggested to be a link between iron status and adiposity.5 The C-reactive protein (CRP) is the first cytokine to

ABSTRACT

Objective: Obesity causes subclinical inflammation which results in the secretion of various bioactive peptides that are key players in metabolic regulation of iron homeostasis. We sought to establish correlation of one such peptide (ferritin) with marker of subclinical inflammation (CRP) in various BMI.

Methods: Total 150 subjects between the ages of 20-60 years were included in the cross-sectional study conducted at Basic Medical Sciences Institute, Jinnah Post Graduate Medical Centre, Karachi, Pakistan. Body Mass Index (BMI) was calculated by weight (kg) /height (m$^2$). The given values were used as reference for Group A: normal weight (18.0-22.9 kg/m2), Group B: overweight (23.0-24.9 kg/m2), Group C: obese (>25.0 kg/m2) according to South Asian criteria. Serum Iron, Total Iron Binding Capacity, serum Transferrin Saturation, serum Ferritin and C-reactive protein were measured by commercially available kits. ANNOVA with Tukey's minimum significant difference and Spearman Rho correlation were used considering p<0.05 significant.

Results: The results identified an increased serum Ferritin and CRP in obese versus lean subjects (p < 0.001). BMI showed significantly positive correlation with serum CRP (r = 0.815; p-value < 0.01) and Ferritin (r = 0.584; p-value < 0.01). However, serum Iron levels and Transferrin saturation decreased in obese versus normal weight individuals (p < 0.001).

Conclusion: This integrated new data reveals that individuals with high BMI had high levels of Serum Ferritin despite low levels of iron with high levels of C-reactive protein. This might be caused due to inflammatory conditions prevailing in the presence of increased adipose tissue.

KEY WORDS: Obesity, Inflammation, Ferritin, Iron, CRP.

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be elevated in inflammatory conditions such as obesity. A strong relationship between obesity and CRP has been observed in all populations. This is because of the inflammatory changes in obese individuals. Concentration of CRP in serum decreases significantly after massive weight reduction. The pathophysiological mechanisms linking obesity to elevated levels of CRP are well recognized in obesity, the accumulation of free fatty acid metabolites activates pro-inflammatory serine kinase cascades.

Among the many metabolic effects of obesity, higher BMI is also correlated with incongruity in iron parameters as this finding is attributed more to being physiological rather than due to dietary deficiency. Adipose tissue, the endocrine organ contributes to the development of inflammation process by secreting various pro-inflammatory cytokines and adipokines i.e. IL-6, TNF-α, leptin, C-reactive protein etc. Certain cytokines/chemokines influence food intake through direct effect of hypothalamus (Kershaw and Flier, 2004; Arslan et al., 2010). According to Zimmermann and Kohrle, chronic inflammation due to obesity results in low iron status. An inverse relationship has been found between physical activity and weight gain, and it has been suggested that physical inactivity could be another factor associated with decreased body iron in obesity in adults. It seems that increased body adipose tissue, particularly visceral depots, is associated with increased risk of iron deficiency which may be masked by high serum ferritin levels, presumably because the increase cytokines result in increased acute phase reactants synthesis resulting in increased macrophage sequestration and/or decreased intestinal iron absorption.

Transferrin saturation and serum ferritin are the preferential indicators for estimation of iron status. Ferritin expression is stimulated by several factors, such as cytokines released during inflammation and liver diseases. Inflammation in turn induces hepatic synthesis of acute phase proteins. Obesity is one of the most common and prevalent conditions that promote this low-grade inflammatory environment within the body.

A relationship between iron status and inflammation utilizes C-reactive protein as an indicator of inflammation. Serum CRP concentration is utilized to support and authenticate the relationship between high ferritin levels in obesity with persistent low iron levels. However, no study has been carried out in South Asia up till now which establishes relationship between iron profile with South Asian BMI criteria. Keeping this in view, this proposed study aimed to elucidate whether obesity associated hypoferemia is correctly judged by serum levels of ferritin in obese individuals of South Asian and if it is correlated with subclinical inflammation. Thus we sought to estimate and correlate between low grade inflammatory marker (CRP) and iron marker (ferritin) in individuals with different BMI categories.

**METHODS**

This cross-sectional study was conducted in Basic Medical Sciences Institute (BMSI), Jinnah Postgraduate Medical Centre, Karachi, Pakistan. The study was approved by the institutional ethical review board. Informed written consent was obtained from all study participants.

Total 380 healthy individuals between the ages of 20-60 years irrespective of gender were interviewed in detail regarding their medical, surgical and personal history to validate/confirm their suitability for inclusion in this study. Two hundred thirty individuals were excluded on the basis of conditions which influence the body iron stores such as pregnancy, alcoholism, hemoglobinopathies, diabetes mellitus, bleeding disorders, any acute illness during last one month, as well as iron deficiency as seen on complete blood picture (CP). Finally, 150 subjects were included in the present study. The subjects were divided into three groups with 50 individuals in each. Group A: normal weight (18.0-22.9 kg/m²), Group B: overweight (23.0-24.9 kg/m²), Group C: obese (>25.0 kg/m²) according to South Asian criteria of BMI.

The weight and height of all the subjects were measured in kilograms and meters respectively, using a weight scale with a built-in Stadiometer (ZT -120 Health Scale, Nanjing Everich China). Subjects were asked to stand in an erect posture wearing light clothing. Hip and waist circumference was measured by standard techniques. BMI was calculated using the following formula: (weight in kg / height in m²).

About 6ml of blood was collected using all aseptic measures into EDTA vaccutainer (2 ml) and serum separator SSTs (4 ml). SST’s were centrifuged after complete clotting at 2000xG for 10 minutes. Clear serum was separated and stored in eppendorf at -80°C until assayed. Hemoglobin (gm/dl) was measured on Sysmex (21 Cat No. KX21 manufactured by Kobe, Japan). Serum iron (mg/
dl) and TIBC (mg/dl) were analyzed by enzymatic colorimetric method (kit Cat. No.61075 and kit Ref 61631 supplied by Bio Merieux S.A., France). Serum Ferritin (ng/dl) and CRP (mg/dl) were determined by Enzyme Linked Immuno-Sorbent Assay kit method (Cat No. BC- 1025 provided by BioCheck and Cat No. KAPDB 4360, manufactured by DIA Source, Immuno Assay S.A., Belgium), while transferrin saturation was calculated as 100x serum iron /TIBC.24

Statistical Analysis: Data was analyzed using SPSS- version 19 (version 19; SPSS Inc., Chicago, IL, USA). Mean ± SD were calculated for quantitative variables. ANOVA with Tukey’s minimum significant difference was used as a post hoc test, assuming homogeneity of variances. Spearman Rho correlation was applied to measure the relationship of obesity (as depicted by BMI) with ferritin, TIBC, iron and CRP and significance was considered at the level of p<0.05.

RESULTS

The mean biophysical parameters of all three groups are shown in (Table-I). Mean weight was found significantly different between Group C when compared to Group A (p<0.001). The meanwaist and hip circumference among the three groups were also significantly different (p-value < 0.001), whereas no significant difference was observed in the waist to hip ratios among all three groups (p = 0.387). BMI in all three groups was significantly different (p<0.001).

![Box plot showing mean, 25th and 75th quartiles for ferritin, iron, TIBC and transferrin saturation in three groups.](image)

Fig.1: (A-D): Hemoglobin and iron parameters among all groups. Box plot shows the mean, 25th and 75th quartiles for Ferritin (a), Iron (b), TIBC (c) & Transferrin saturation (d) in three groups. X axis shows the study groups of normal weight (n= 50), overweight (n= 50) and obese (n= 50). Y axis shows the BMI obtained. Annovaposthoc test was applied for significant difference between Control vs. Overweight, Control vs. Obese and Overweight vs. Obese. P value<0.05 is considered significant.
The biochemical parameters are illustrated in (Table-II and Fig.1 A-D). No difference was observed in the mean hemoglobin values in all three groups. Serum ferritin levels were high while serum iron were low in group C subjects as compared to groups A and B (p < 0.001). TIBC was found to be significantly lower in group B (p < 0.001) as compared to group A while significantly higher in group C as compared to group B (p < 0.001). Transferrin saturation percentage was high in group B as compared to group A (p = 0.001), and decreased in group C as compared to group A and group B (p < 0.001). The serum CRP levels depicted a rising trend from group A to C and showed significantly positive correlation with BMI (r = 0.815; p-value < 0.01) and Ferritin (r = 0.584; p-value < 0.01). Ferritin showed a positive correlation with increasing BMI (r = 0.614; p-value < 0.01) while negative correlation were observed for iron (r = -0.476; p-value < 0.01) and transferrin saturation percentage (r = -0.419; p-value < 0.01). (Table-III)

DISCUSSION

Obesity accounts for iron deficiency with or without anemia. This could be attributed to certain mechanisms associated to the pathogenesis of obesity, such as low grade inflammation. The trend noticed in this study was an increase in TIBC in overweight individuals when compared to normal weight, while iron concentration decreased. However, in obese individuals the TIBC levels tend to maintain near the normal values with persistent decreased iron levels (Table-II). These findings are contradictory to what has been reported by Ghadiriet al., who described no change in TIBC with increase in BMI.

Studies have previously revealed lower levels of iron and transferrin saturation in obese as
Iron status in varying degrees of adiposity

determined the baseline values of the iron parameters in our population. However, this study proposes a causal relationship between obesity, inflammation and low iron levels.

CONCLUSION

Obese individuals show a unique picture of high ferritin and C-reactive protein, low serum iron and transferrin saturation. This may be an indication of fat cells playing a vital role in the production of acute phase reactants like ferritin which may not be the gold standard for the evaluation of iron status in obese individuals.

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Faiza Alam conceived, designed and did statistical analysis & drafting of manuscript.

Abdul Shakoor Memon was involved in manuscript writing.

Syeda Sadia Fatima interpreted data, drafted and revised final manuscript.

Faiza Alam takes the responsibility and is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.