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RELATIONSHIP OF OBESITY WITH MICRONUTRIENT STATUS

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ABSTRACT: Background & objectives: Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems. Body mass index (BMI), a measurement which compares weight and height, defines people as overweight when their BMI is between 25 kg/m^2 and 30 kg/m^2, and obese when it is greater than 30 kg/m^2. A survey of the literature indicates that little is known about the influence of the obese condition on the tissue status and metabolism of essential trace metals; however, available data suggest that trace metal status of obese humans and animals is altered. Hence our aim was to study the changes in the micronutrient status in overweight and obese people in comparison with normal weight controls.

Methods: Ninety Adults of age 30-40 years were divided into three groups (30 each) into normal, overweight and obese individuals based on their BMI. The serum samples of all the three groups were used for estimation of micronutrient status (serum iron by Bathophenanthroline method, zinc and copper by Atomic Absorption Spectroscopy).

Results: We found that the mean iron levels in obese individuals were significantly decreased in overweight and obese individuals than those in the control group (P<0.0001), whereas the mean zinc levels were slightly lower than those of the control group (P=0.2080) but not statistically significant. Serum copper levels were significantly increased in obese individuals when compared to controls (P < 0.0003).

Interpretation & Conclusion: The presence of nutritional deficiencies in overweight and obesity may seem paradoxical in light of excess caloric intake, but several micronutrient deficiencies appear to be higher in prevalence in overweight and obese adults and children. Causes are multifactorial and could include decreased consumption of fruits and vegetables, increased intake of high-calorie, but nutritionally poor-quality foods, and increased adiposity, which may influence the storage and availability of some nutrients. Hence medical practitioners must be aware of nutritional deficiencies in overweight and obese patients and appropriately recognize and treat common and rare nutritional deficiencies.

KEY WORDS: BMI, copper, iron, micronutrients, obesity, zinc

INTRODUCTION

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems. [WHO, 2000][1].

WHO describes obesity as one of the most blatantly visible, yet most neglected, public-health problems that threatens to overwhelm both more and less developed countries. The problems of overweight and obesity have achieved global recognition only during the past 10 years, in contrast to underweight, malnutrition, and infectious diseases, which have always dominated our thinking. WHO[1] now accepts a body-mass index (BMI) of 25·0 kg/m^2 or higher as abnormal; the overweight category is classified as obese when the BMI is 30·0 kg/m^2 or more. The risks of diabetes, hypertension, and dyslipidaemia increase from a BMI of about 21·0 kg/m^2 [2], thereby reducing life expectancy and greatly increasing the health and societal economic burden[3]. Excess bodyweight is now the sixth most important risk factor contributing to the overall burden of disease worldwide[4].

Interest in trace elements has been steadily increasing over the last 25 years. Trace elements are accepted as essential for optimum human health, because of their diverse metabolic characteristics and functions. They serve a variety of catalytic, structural and regulatory functions, in which they interact with macromolecules such as enzymes, pro-hormones, pre-secretory granules and biological membranes.

A survey of the literature indicates that little is known about the influence of the obese condition on the tissue status and metabolism of essential trace metals; however, available data suggest that trace metal status of obese humans and animals is altered. The presence of nutritional deficiencies in overweight and obesity may seem paradoxical in light of the evidence of excess caloric intake, but a growing body of literature has documented that several micronutrient deficiencies may be higher in prevalence in overweight and obese adults and children, particularly in those suffering from extreme obesity (BMI > 40kg/m^2 in adults and ≥ 99th percentile in children).

Consumption of excess calories does not automatically equate with over-consumption of fruits, vegetables and other unprocessed, high quality nutrient-dense foods[5]. Much of the recent data on nutritional deficits in obese individuals are from studies of adults undergoing pre-operative evaluations for bariatric surgery, which indicate that baseline nutritional deficiencies are not negligible in extremely obese patients. As the obesity epidemic continues unabated and the popularity of bariatric surgery rises for both extremely obese adults and adolescents, clinicians must be aware of pre-existing nutritional deficiencies in overweight and obese patients[5]. Our aim was to study the changes in the micronutrient status (serum iron, copper and zinc Levels) in overweight and obese individuals in comparison with normal weight controls.

MATERIALS AND METHODS

- Ninety Adults of age 30-40 years were divided into three groups (30 each) into normal, overweight and obese individuals and were monitored for serum micronutrients (iron, zinc and copper).
- Participants in the study are recruited from the A.B.Shetty Memorial Institute of Dental Sciences, Mangalore. The study was approved by the Ethical and the Research Committee of the Institute.
- After obtaining informed consent from the subjects, their 2ml venous blood was collected in a plain bottle, centrifuged and serum was used for estimation of Iron. Serum iron was estimated by Bathophenanthroline method. Iron in serum is present as F^{e+++} bound to transferrin. In the assay, the proteins are precipitated and consequently the iron (F^{e3+}) bound to ferritin is released by mild acid treatment. The iron thus released is reduced to (F^{e2+}) by reducing agents. (F^{e2+}) in turn reacts with Bathophenanthroline to form pink color complex whose intensity is measured at 535 nm.
- Zinc and copper were measured using atomic absorption spectrophotometer. Five ml venous blood was collected in heparinized, zinc- and copper-free, polypropylene tubes in the fasting state from all subjects. Heparinized samples were centrifuged at 1500g for 10 min to separate the plasma for estimation of copper and zinc. Plasma was diluted with an equal volume of trichloroacetic acid to precipitate proteins. The precipitate was kept at 0°C for 10 min. The supernatant was directly aspirated into double beam atomic absorption spectrophotometer. The instrument was calibrated using standards.
- The height and weight was recorded and BMI was calculated. BMI = Body mass (kg) / height (m^2). Then participants were categorized into normal, overweight and obese.
- Body fat percentage was analyzed using a Body fat analyzer. The height and weight of the subject is entered into the body fat analyzer (Citizen BM 100) and the subject is made to place both the hands on the analyzer, arms are kept in a relaxed state and the percentage of body fat is measured.

Statistical Analysis:

Results are expressed as Mean ± Standard Deviation (S.D). Statistical significance was determined by one-way analysis of variance (ANOVA). Statistical analysis included standard methods for comparison among variables. A two-tailed p-value was used for calculating statistical significance. The p-value < 0.05 was considered as a significant value. All statistical analysis was carried out using the instant statistical package (Graph pad prism version 3.0).

RESULTS

Thirty healthy individuals (23 men, 7 women; mean age 35.6 ± 4.8 years), 30 Overweight subjects (21 men, 9 women; mean age 36.5 ± 4.7 years)and 30 obese subjects(19 men, 11 women; mean age 37.2 ± 2.8 years) comprised the study group as shown in Table 1. The mean BMI was 27.6 ± 2.1kg/M2 in the overweight group, 32.1 ± 1.9 kg/M2 in the obese group and 21.3 ± 3.2kg/M2 in the controls(Table 1). Forty three percent were diabetic in over weight group and 63% were diabetic in obese group. We found that the mean iron (Fe) levels in over weight and obese individuals were significantly decreased than those in the control group ($P<0.0001$), whereas the mean Zinc (Zn) levels were slightly lower than those of the control group ($P=0.2080$) but not statistically significant. Serum Copper (Cu) levels were significantly increased in over weight and obese individuals when compared to controls ($P < 0.0003$) as shown in Table 2.

Table 1: Clinical and biochemical characteristics of Normal, Overweight and Obese Individuals (figures given as means ± SD).

Characteristics	Normal	Overweight	Obese
Male to female ratio	23:7	21:9	19:11
BMI(Kg/M$^{2)}$	21.3 ± 3.2	27.6 ± 2.1	32.1 ± 1.9
FBS(mg/dl)	120.9 ± 22.9	124.8 ± 33.8	132.7 ± 40.2
Non-diabetic to Diabetic ratio	24:6	17:13	11:19
Body fat percentage(N:H:V.H)	27:3:0	10:16:4	0:25:5

N=Normal; **H**=High; **V.H**= Very High

Table 2: **Serum Iron, Copper and Zinc levels in Normal, Overweight and Obese Individuals**

	IRON(µg/dl)	COPPER(µg/dl)	ZINC(µg/dl)
NORMAL(n=30)	104.9±21.29	154.8±25.95	132.0±66.90
OVER WEIGHT(n=30)	84.37±25.84	164.1±11.79	108.5±5.772
OBESE(n=30)	75.79±24.98	180.2±29.40	98.20±65.24
P-VALUE	p<0.0001	p<0.0003	p=0.2080

Age Group 30-40 years
Values are expressed as (Mean ± SD).

DISCUSSION

Trace elements have long been accepted as essential for optimum health. The clinical significance of trace elements is still somewhat controversial. Among the trace elements, iron, copper and zinc are of particular interest. We found that the mean Fe levels in obese individuals were significantly decreased than those in the control group, whereas the mean Zn levels were slightly lower than those of the control group (p=0.2080) but not statistically significant. Serum Cu levels were significantly increased in obese.
Obesity is associated with low-serum iron concentrations. The inverse relationship between iron status and adiposity was first reported in 1962, when Wenzel et al.[6] unexpectedly found a significantly lower mean serum iron concentration in obese compared with non-obese adolescents. In a large study using National Health and Nutrition Examination Survey-I (NHANES-I) data, Micozzi et al.,1989[7] found that higher body mass index (BMI) was significantly associated with lower serum iron in women, and that transferrin saturation was significantly lower in the highest BMI quartile for both men and women. Most subsequent studies[8-10] have shown similar results.

However, the pathophysiological mechanisms leading to hypoferremia among obese individuals are unknown. One proposed mechanism is an iron-poor diet[11]. Humans obtain dietary iron in two forms: nonheme and heme. Nonheme iron is found mainly in enriched cereals and pasta, beans, and dark green leafy vegetables, while heme iron is derived primarily from hemoglobin and myoglobin in animal protein sources[12,13]. Separate pathways are involved in the absorption of nonheme-associated and heme-associated iron . Although uptake of heme iron by enterocytes is affected little by consumption of other foods, absorption of nonheme iron is relatively inefficient, and can be altered substantially by co-consumption of certain dietary elements[12]. Factors known to enhance nonheme iron absorption include animal protein, copper, and vitamin C. Factors known to inhibit nonheme iron absorption include vegetable protein, phytic acid, oxalic acid, zinc, calcium, eggs, tea, and coffee.

Another proposed cause of hypoferremia among the obese is a deficient iron store due to a greater iron requirement in obese adults because of their larger blood volume. Because obesity is considered a chronic inflammatory state, inflammatory-mediated sequestration of iron in the reticuloendothelial system, with resultant hypoferremia, despite adequate or even increased iron stores could also play a role in the hypoferremia of obesity[14]. A unifying explanation for hypoferremia may stem from the recently elucidated roles of two iron-regulating proteins that are made by adipocytes: hepcidin and lipocalin-2. Hepcidin is a small peptide hormone secreted by the liver and by adipocytes. Hepcidin is an acute-phase reactant, and its expression is increased in chronic inflammatory states including obesity[15]. Hepcidin can inhibit enterocyte iron absorption and has further been shown to inhibit the release of non-heme iron from macrophages. Because each of these actions diminishes the amount of bioavailable body iron, it has been suggested that when hepcidin is induced by inflammation, hepcidin is the key iron regulator that causes the hypoferremia and anemia of chronic disease[16]. Therefore, lower bioavailable iron among obese adults might potentially be related to the greater adipose hepcidin. Lipocalin-2 is a siderophore binding protein which is upregulated in inflammatory states and functions to limit the availability of iron to invading pathogens. Recent evidence suggests that white adipose tissue is the dominant site of expression of lipocalin-2. In humans circulating lipocalin-2 concentration is positively correlated with adiposity[17].

Insufficient iron bioavailability for metabolic requirements may also be a factor in the hypoferremia of obesity[11]. Since two-thirds of body iron is found in erythrocytes, and blood volume has been shown to be directly proportional to body mass, an increased need for iron in obese individuals is possible[8]. It thus remains possible that obese individuals do not meet their dietary iron requirements. Seltzer and Mayer, 1963[11] reported that serum iron level and the percentage iron saturation of transferrin were significantly lower in obese male and female adolescents than in lean individuals. Lean and obese individuals had similar hemoglobin and hematocrit levels, it was concluded that the obese adolescents had depleted body stores of iron and had symptoms of early iron-deficiency anemia. More recent studies[18] have also shown that obese infants and children are more prone to iron deficiency, but not anemia, than are lean individuals of similar age.

Zinc has important effects on metabolism, and on the thermoregulation of obese individuals. Di Martino G et al., 1993 evaluated the serum zinc levels in obese patients before and after severe hypocaloric diets and its correlation with the body mass index (BMI). Patients followed a severe hypocaloric diet (737 Kcal) for 60 days. Zn levels in obese patients were significantly ($p < 0.01$) lower than in controls, whereas the BMI values were significantly greater. At the end of a severe hypocaloric diet, serum Zn and BMI levels returned to normal values. They suggested a possible relationship of the serum Zn levels with the anabolic and catabolic mechanisms in obesity, although the exact metabolic role of this bio-element remains unclear[19].

Zinc plays an important role in appetite regulation also. Dildar K, et al., 2004[20] evaluated the relationship between leptin and zinc in obese and nonobese type 2 diabetic patients and its relationship with oxidative stress and insulin. They found that nonobese diabetic patients had significantly lower zinc levels than control subjects ($P<0.01$). There was no difference in plasma leptin levels between nonobese diabetic subjects and controls. Obese diabetic subjects had significantly lower plasma zinc levels than nonobese diabetic subjects ($P<0.01$). The univariate and multivariate analyses demonstrated a significant positive correlation between leptin and body mass index ($P<0.01$) and a significant negative correlation between leptin and zinc in obese subjects. They concluded that zinc may be a mediator of the effects of leptin, although the detailed mechanism is still unknown and requires further investigation[20]. Chandra and Kutty, 1980[21] reported significantly reduced plasma levels of zinc, iron, percent iron saturation of transferrin and serum ferritin in 38% of the obese children and adolescents in their study. Many of the individuals with subnormal zinc and iron status also exhibited impaired immunoresponsiveness. Daily oral supplementation of obese patients with iron and/or zinc for 4 wk elevated the plasma levels of zinc and iron to normal and markedly improved immunocompetence. Consequently, the authors suggested that some of the obese children were marginally deficient in zinc and/or iron. Reduced levels of plasma zinc and elevated levels of plasma copper have also been reported in obese adults[21].Copper is one of the essential trace elements, and has a particular role in cytochrome oxidase function at the terminal end of the mitochondrial electron transport chain. The loss of this activity may contribute to the characteristic swelling and distortion of mitochondria which can be observed in copper deficiency, particularly in metabolically active tissues such as pancreatic acinar cells, enterocytes, and hepatocytes. In trace element metabolism the best known interaction is the reported antagonism between zinc and copper. Excessive dietary zinc is reported to induce copper deficiency by several mechanisms, all involving induced synthesis of an intracellular binding protein, metallothionein. Excessive intake of zinc is thought to induce synthesis of the protein, resulting in sequestering of both metals, with subsequent excretion when cells are sloughed into the intestinal lumen. Thus, the protective mechanism preventing zinc toxicity also results in copper deficiency. Hormonal influences may also lead to apparently antagonistic zinc copper interactions. Both carbohydrate-active steroids and a mononuclear phagocyte produced hormone, interleukin-1, enhance intracellular zinc accumulation while increasing intracellular copper efflux as caeruloplasmin. The net result of these effects is a decreased plasma concentration of zinc and an increased concentration of copper[22]. We wonder whether any such interaction exists between zinc and copper in subjects with obesity which would explain the elevated plasma copper levels found in this study. Luque-Díaz MJ et al., 1982[23] studied iron, copper and zinc levels in serum and urine of obese patients. Hyperzincurie, hypocuprurie, hypozincemia, and hypercupremia were observed in the studied groups, in relation to normal controls. There were serious disturbances in the metabolism of the cited oligoelements. The diet had no influence on the observed values. Metin Ozata, 2002[24] concluded in their study that male obesity is associated with defective antioxidant status and hypozincemia, which may have implications in the development of obesity related health problems. In one of the prospective study[25], serum level of copper was evaluated by atomic absorption in a group of 32 obese (BMI > or = 30 kg/m2) compared to a group of 32 healthy subjects. The authors noted an elevation of serum copper in obese with a middle level of 133 mg/dl significantly superior to the middle level of serum copper of healthy subjects, 108 mg/dl ($p < 0.001$). In another hand, they noticed that the levels of serum cooper rise with the BMI. In fact, 58.3% of the obese that had a BMI > or = 40 kg/m2 showed a high concentration of serum copper although only 5% of obese with BMI < 40 kg/m2 showed this high concentration.

Summary points

* A complex interplay exists between micronutrients and Obesity
* Serum iron and Zinc levels are decreased in overweight and obese individuals
* Plasma copper levels are increased in overweight and obese individuals

Summary and Conclusion

Iron is a necessary constituent of several macromolecules involved in cell metabolism, but, at the same time, it could be a potentially dangerous element. For this reason iron balance must be finely regulated. At present, obesity has been recognized as a worldwide public health problem. Excess body fat is associated with increased all-cause mortality and increased risk for several medical morbidities.

Many studies have shown that obesity might increase the risk of iron deficiency but, at the same time, obese subjects exhibit high serum ferritin levels. Recent studies seem to indicate that obesity is associated with iron deficiency although the aetiology appears to be multifactorial and includes (i).

A decrease in iron food intake; (ii) An impairment of intestinal iron uptake and iron release from stores because of an overexpression of hepcidin and (iii) Inadequate iron bioavailability because of inflammation. In addition, abnormal ferritin concentrations can be explained by chronic inflammation rather than by iron overload. A known interaction is the reported antagonism between zinc and copper. Excessive dietary zinc is reported to induce copper deficiency by several mechanisms, all involving induced synthesis of an intracellular binding protein, metallothionein. Hence medical practitioners must be aware of nutritional deficiencies in overweight and obese patients and appropriately recognize and treat common and rare nutritional deficiencies. Routine screening should at least be triggered by the onset of symptoms of unexplained anemia, neurological impairment, unusual skin manifestations or cardiac dysfunction.

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