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International Journal of Dentistry and Oral Health

Research Article ISSN 2471-657X

Serum Resistin and its Relation to Hemoglobin levels in Obese Patients Suffering from Iron Deficiency Anemia. (A clinical study)

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Abstract

Background: Overweight or obesity within the last few decades has become a complex health problem, that's why The World Health Organization (WHO) in 1997 considered obesity a worldwide epidemic. Obesity was considered to be related to high socioeconomic status, nowadays it is also a widespread disorder in developing countries Several studies indicated the correlation between obesity and abnormal iron homeostasis. Iron Deficiency Anemia (IDA) is a frequent and main finding in obese patients. This was explained by the fact that adipose tissue can create an "inflammatory milieu" that release multiple inflammatory mediators such as interleukin-1 (IL-1), IL-6, tumer necrosis factor α (TNF-α), also adipokines like leptin, resistin. Also the peptide hormone Hepcidin, the main regulator of iron metabolism can be secreted by adipocytes.

Subjects and Methods: This study included sixty patients divided among three groups. Group I: This group included adults whose body mass index (BMI) was less than 25%, and their hemoglobin level was less than 11 gms/dl.(Non-obese patients with iron deficiency anemia). Group II: This group included adults whose BMI was more than 30 % and their hemoglobin level is less than 11gms/dl.(Obese with iron deficiency anemia). Group III: This group included healthy controls with body mass index less than 25 %. (Non- obese healthy subjects). A venous blood sample was collected from each patient for the detection of serum resistin levels.

Results: There was a statistically significant difference between Resistin levels in the three groups (P-value <0.001). Pair-wise comparisons between the groups revealed that Group II showed the statistically significantly highest mean Resistin level. Group I showed statistically significantly lower value. Group III showed the statistically significantly lowest mean Resistin level. Also there was a statistically significant difference between Hb levels in the three groups (P-value <0.001). Group III showed the statistically significantly highest mean Hb level. Group II showed statistically significantly lower value. Group I showed the statistically significantly lowest mean Hb level. In Group II There was a statistically significant direct correlation between serum Resistin level and BMI. There was a statistically **significant inverse** *correlation between Resistin level and Hb level indicating that an increase in Hb level is associated with a decrease in Resistin level and vice versa.*

Conclusion: *There is a direct relation between the elevated serum resistin levels in patients suffering from both obesity and IDA. Serum resistin levels were not higher in patients with anemia and normal body weight. This increase was attributed to the inflammatory condition created by the adipose tissues.*

Keywords: Iron Deficiency Anemia (IDA), Obesity, Adipokines, Resistin

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Citation: Shaymaa M. Hassan et al. (2018), Serum Resistin and its Relation to Hemoglobin levels in Obese Patients Suffering from Iron Deficiency Anemia. Int J Dent & Oral Heal.4:5, 58-63

Received: April 13, 2018
Accepted: April 23, 2018
Published: May 17, 2018

Introduction:

Anemia defined by the World Health Organization when hemoglobin (Hb) concentration is <13g/dl in men, < 12g/dl in non-pregnant women and < 11g/dl in pregnant women in patients above 15 years of age [1]. These values are controversial as they miss the patients suffering from colorectal cancer mainly by men. Therefore, men with Hb levels< 12g/dl and post-menopausal women with Hb levels < 10g/dl should be diagnosed accurately with more accurate investigations since these lowered Hb values will suggest more serious medical conditions [2,3].

The incidence of iron deficiency anemia (IDA) is usually 2-5% affecting men and postmenopausal women in the developed countries [1,4]. IDA is a multifactorial disorder, the main cause of IDA is menstrual blood loss, other causes like asymptomatic colon cancer, malabsorption as in patients with celiac disease, poor dietary iron intake, the use of non- steroidal anti-inflammatory drugs (NSAID), or on patients with gastrectomy. It also can be due to Dual pathology which means the presence of bleeding related to both the upper and lower gastrointestinal tract, this case ours in 1-10% of the patients and should always be suspected in elder patients [5,6]. Several laboratory tests can be used to diagnose IDA, but reduced mean cell hemoglobin (MCH, is the more reliable value. Also microcytosis and hypochromia can be reliable indicators for the diagnosis of IDA especially when there isn't any underlying chronic disease or any other type of anemia like folate deficiency anemia [7-8].

A term is known as " Functional iron deficiency," it is a condition where there is insufficient iron-supplying the bone marrow, in spite of the presence of iron-storing cells the monocyte-macrophage system. It is usually associated with patients with renal failure, or those with chronic inflammatory diseases, e.g. rheumatoid arthritis, anemia with Cardiovascular diseases, or inflammatory - bowl disorder. Reduced reticulocyte Hb level usually confirms the diagnosis of functional iron deficiency cases [9-10].

Patients with IDA are commonly seen in the dental office suffering from different symptoms that vary from the pale mucous membrane, dry mouth (Xerostomia), depapillated tongue; with great sensitivity to spicy and acidic food, Also angular cheilitis can be seen in those patients as a result of candidal infections or due to mucous dehydration. Also, they usually complain of recurrent aphthae ulcers affecting non-keratinized oral mucosa [11,12,13].

Obesity is a serious medical disorder characterized by the accumulation of body fat and causing multiple health issues. It has been suggested to be one of the predisposing factors to Type II diabetes mellitus, hypertension, dyslipidemia, sleeping apnea, and multiple gynecological problems. Several studies also documented that obese people are more liable to suffer from cancer, multiple infections and delayed wound healing especially after surgeries.[14,15,16]. According to data provided by the World Health Organization (WHO), there are more than 1 billion adults that are considered overweight, 300 million of which are obese. Also, its prevalence is alarmingly increasing among children and teenagers [17]. Obesity is measured according to the person's body mass index (BMI);(body weight/ height^2). In adults when the BMI < 18.5 then the person is considered underweight. The person is considered overweight when the BMI ranges from 25- 29.9. In case of obese adults their BMI > 30 [18, 19].

Adipose tissue is recently known to act as an endocrinal organ, and its morphology differs significantly in obese than in lean persons. In obese people, the adipose tissue becomes infiltrated by macrophages that are stimulated to release pro-inflammatory mediators, e.g. interleukin -1(IL-1), IL-6, Tumor necrosis factor α (TNF-α). Furthermore, hormone-like peptides known as adipokines are also released, all these biologic mediators create what is known as " Inflammatory milieu " [20]. These adipokines include Adiponectin, which acts as an- anti-inflammatory and insulin-sensitizing agent; whose levels are decreased in obesity. Another adipokine is Leptin, which acts as an indicator for energy storage fullness under normal physiological conditions, but during obesity, it is significantly increased and associated with leptin hypothalamic resistance. Also, Resistin which is released mostly from adipose tissue macrophages and monocytes rather than adipocytes, and is related to insulin resistance together with its increase in serum levels of obese persons [21].

All these bioactive mediators are released from the adipose tissue and spread to multiple body organs including liver, which is the main organ for iron homeostasis; developing multiple systemic conditions, e.g. iron deficiency anemia, together with fat accumulation in the liver leading to liver cirrhosis [22].

Several studies discussed the relationship between obesity and abnormal iron metabolism leading to anemia. According to this fact, it was worth to choose one of the recently known adipokines; Resistin and try to use it as a marker in an attempt to relate anemia to obesity, as it was proved that Resistin serum levels are relatively high in obese people. Also to prove whether or not Resistin levels can be used as a predictor whether or not an obese person is more likely to develop iron deficiency anemia.

Subjects and methods:

This research was revised and approved by the Research Ethics Committee of Faculty of Dentistry, Cairo University and was given the code number 18235. All patients signed a consent form after full and detailed explanation of their role and the aim of the research. Complete blood count was performed as a regular check-up to healthy subjects to make perfect use of their samples.

Patients Selection:

This study included patients that were selected according to the following criteria:

Inclusion Criteria: Adults, males, and females whose ages range from 20-40 years.

Exclusion Criteria: Any adults that suffered from any other diseases like diabetes mellitus, or taking any medications, e.g. Lipid decreasing drugs, or any iron supplements. Also, smokers and pregnant females were excluded from the study.

Individuals joined this research were recruited from both Diagnostic centers of Faculty of Dentistry, Cairo University, or were referred from the Central laboratory of Clinical and Chemical Pathology Department, Faculty of Medicine, Cairo University.

Research Design:

This study included 60 patients that were divided among three groups; these groups were classified as follows:

Group I: This group included adults whose body mass index (BMI) was less than 25%, and their hemoglobin level was less than 11 gms/dl.(Non-obese patients with iron deficiency anemia).

Group II: This group included adults whose BMI was more than 30 % and their hemoglobin level is less than 11gms/dl.(Obese with iron deficiency anemia).

Group III: This group included healthy controls with body mass index less than 25 %. (Non- obese healthy subjects).

For All groups, complete blood count was carried out to confirm the diagnosis of Iron deficiency anemia (microcytic anemia) especially in groups I and II, was mean cell hemoglobin (MCH) were less than 27 pg/cell, and mean cell hemoglobin concentration (MCHC) less than 33g / dl.

Serum Collection:

A venous blood sample was collected from each patient by the registered nursery. The collected samples were centrifuged to obtain

serum. All samples were also stored at a temperature not less than -20$_o$C until further use.

Quantitative assessment of Resistin of the collected serum samples was carried out by the commercially available ELISA Kit " Resistin (human) ELISA Kit, AdipoGen, Incheon, South Korea" for all the three groups according to the manufacturer's instructions. All samples were diluted by using the kit's diluent provided, A microtiter plate was used, where its wells were pre-coated with the specific monoclonal antibody followed by pipetting of the samples into the wells to bind to the antibody. Incubation of the samples at 37$_o$C was done for one hour followed by extensive washing of the unbound compounds. This latter step was performed two times again to make sure of the removal of any unbound compounds. After the final washing, a substrate was added at room temperature. A Stop solution was then added for 20 minutes to control further reaction. A color reaction was then produced; whose intensity depends directly on the resistin concentration in the serum samples.

Results:

Statistical Analysis

Numerical data were explored for normality by checking the distribution of data and using tests of normality (Kolmogorov-Smirnov and Shapiro-Wilk tests). All data showed normal (parametric) distribution. Data were presented as mean and standard deviation (SD) values. One-way ANOVA followed by Tukey's post-hoc test was used to compare between the three groups. Pearson's correlation coefficient was used to determine correlations between different outcomes in the three groups. Qualitative data (Gender) was presented as frequencies and percentages. Chi-square test was used to compare between the three groups. Spearman's correlation coefficient was used to determine correlations between different outcomes in the three groups.

The significance level was set at $P \leq 0.05$. Statistical analysis was performed with IBM® SPSS® Statistics Version 20 for Windows.

Demographic data

The mean and standard deviation values of age were 31.3 (5.6), 31.2 (5.5) and 30.4 (6.7) years old for Groups I, II and III, respectively. There was no statistically significant difference between mean age values of the three groups (P-value = 0.886).

Group I included 8 males (40%) and 12 females (20%), Group II included 11 males (55%) and 9 females (45%) while Group III included 8 males (40%) and 12 females (60%). There was no statistically significant difference between gender distributions in the three groups (P-value = 0.545).

The mean and standard deviation values of BMI were 22.7 (0.8), 30.5 (2) and 22.2 (0.8) Kg/m2 for Groups I, II and III, respectively. There was a statistically significant difference between mean BMI values of the three groups (P-value <0.001). Pair-wise comparisons between the groups revealed that Group II showed the statistically significantly highest mean BMI. There was no statistically significant difference between Group I and Group III; both showed the statistically significantly lowest mean BMI values.

Resistin level

One-way ANOVA test showed that there was a statistically significant difference between Resistin levels in the three groups (P-value <0.001). Pair-wise comparisons between the groups revealed that Group II showed the statistically significantly highest mean Resistin level. Group I showed statistically significantly lower value. Group III showed the statistically significantly lowest mean Resistin level. (Figure 1).

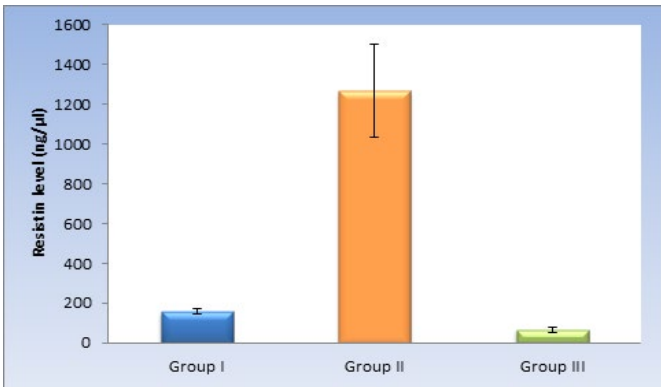

Figure 1: Bar chart is representing mean and standard deviation values for Resistin levels in the three groups.

Hemoglobin level

One-way ANOVA test showed that there was a statistically significant difference between Hb levels in the three groups (P-value <0.001). Pair-wise comparisons between the groups revealed that Group III showed the statistically significantly highest mean Hb level. Group II showed statistically significantly lower value. Group, I showed the statistically significantly lowest mean Hb level. (Table 1).(Figure 2).

Outcomes	Group I (n = 20)		Group II (n = 20)		Group III (n = 20)		*P*-value
	Mean	SD	Mean	SD	Mean	SD	
Resistin level (ng/µl)	157.9 ^{B}	13.8	1267 ^{A}	233.2	65.3 ^{C}	12.4	<0.001*
Hb level (g/dL)	8 ^{C}	0.6	9.8 ^{B}	0.6	13.7 ^{A}	1	<0.001*

*: Significant at P ≤ 0.05, Different superscripts in the same row are statistically significantly different:

Table 1: Descriptive statistics and results of one-way ANOVA test for comparison between different outcomes in the three group

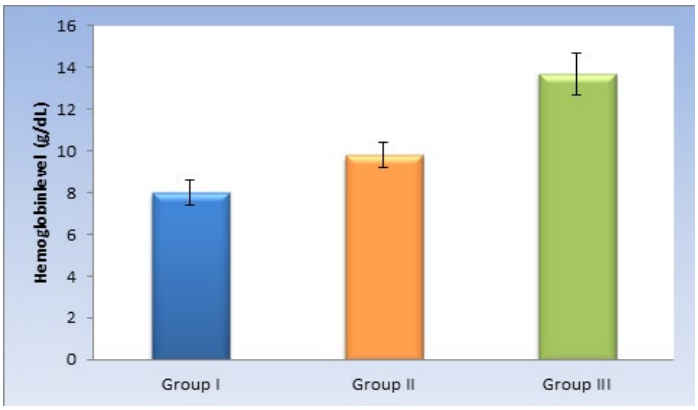

Figure 2: Bar chart is representing mean and standard deviation values for Hemoglobin levels in the three groups.

Correlation between different outcomes:

Group I: there was no statistically significant correlation between Resistin level and age (P-value = 0.458).

There was a statistically significant direct correlation between serum Resistin level and BMI (P-value <0.001) indicating that an increase in BMI is associated with an increase in Resistin level and vice versa.

There was no statistically significant correlation between Resistin level and Hb level (P-value = 0.988).

Group II: there was a statistically significant direct correlation between Resistin level and age (P-value <0.001) indicating that an increase in age is associated with an increase in Resistin level and vice versa.

There was a statistically significant direct correlation between serum Resistin level and BMI (P-value <0.001) indicating that an increase in BMI is associated with an increase in Resistin level and vice versa.

There was a statistically significant inverse correlation between Resistin level and Hb level (P-value = 0.020) indicating that an increase in Hb level is associated with a decrease in Resistin level and vice versa.

Group III: there was a statistically significant direct correlation between Resistin level and age (P-value = 0.001) indicating that an increase in age is associated with an increase in Resistin level and vice versa.

There was no statistically significant correlation between Resistin level and BMI (P-value = 0.951).

There was no statistically significant correlation between Resistin level and Hb level (P-value = 0.307). (Table 2).

Outcomes	Group I (n = 20)		Group II (n = 20)		Group III (n = 20)	
	Correlation coefficient	*P*-value	Correlation coefficient	*P*-value	Correlation coefficient	*P*-value
Resistin & Age	0.176	0.458	0.820	<0.001*	0.668	0.001*
Resistin & BMI	0.797	<0.001*	0.782	<0.001*	0.015	0.951
Resistin & Hb	-0.004	0.988	-0.516	0.020*	-0.240	0.307

*: Significant at P ≤ 0.05.

Table 2: Results of Pearson's correlation coefficient for the correlation between Resistin levels and different outcomes:

Discussion:

The regulatory mechanism of physiologic iron homeostasis has been elucidated over the past few years. In the proximal duodenum, iron is absorbed as Fe^{2+} where it gets incorporated into transferrin for further transport into the circulation. Iron is vitally required for the biosynthesis of heme in the erythropoietic bone marrow and other enzymes such as cytochromes, where the excess iron become stored in the liver cells (hepatocytes). Iron is transported from the hepatocytes, macrophages and most of the cells by the iron exporter ferroportin (FPN). FPN is considered the only known iron exporter [23]. Iron homeostasis is also maintained by a negative feedback mechanism via the hormone Hepcidin[24] Hepcidin is a peptide hormone which is released from liver hepatocytes in response to inflammation, hypoxia, iron overload or anemia. It exerts its function through binding to FPN, therefore leading to FPN degradation and consequently blocking the iron export, and thus reducing iron serum levels [25]. Hepcidin has also been proved to be secreted from other cells like macrophages, pancreatic cells and adipose tissue [26,27]. The relation between the factors that regulate the iron homeostasis and adipose tissue encouraged the investigators to carry out this study to find the relation between obesity and its impact on the iron homeostasis abnormal pattern that leads to iron deficiency anemia, using resistin as an indicator.

Sixty patients participated in the study, 33 males and 27 females their age range was 20-40 years, that were divided into three groups. There was no statistically significant difference between gender distributions in the three groups (P-value = 0.545).

After analyzing Resistin serum levels in the three groups, Group II showed the statistically significantly highest mean Resistin level compared to all other groups. Group, I showed statistically significantly lower value than the other two groups. Group III showed the statistically significantly lowest mean Resistin level (P-value <0.001). Also, there was a statistically significant difference between Hb levels in the three groups (P-value <0.001). Group III showed the statistically significantly highest mean Hb level (healthy individuals). Group II showed statistically significantly lower value. Group, I showed the statistically significantly lowest mean Hb level.

On comparing the serum resistin levels to the levels of Hb in the three groups, In group II there was a statistically significant direct correlation between serum Resistin level and BMI (P-value <0.001) indicating that an increase in BMI is associated with an increase in Resistin level and vice versa There was a statistically significant inverse correlation between Resistin level and Hb level (P-value = 0.020) indicating that an increase in Hb level is associated with a decrease in Resistin level and vice versa. The other two Groups I and Group III, There was no statistically significant correlation between Resistin level and BMI, and there was no statistically significant correlation between Resistin level and Hb level, where the P values were P-value In Group I = 0.458, 0.988), Group III (P= 0.951, 0.307) respectively. Meaning that Resistin levels were the highest in the group which had the obese and anemic patients, while the other two groups that included anemia patients together with healthy individuals, but not obese the levels of resistin were not statistically significant. These results came in accordance with a series of investigations carried out along several years; which proved the relation between lower serum iron concentrations in individuals with higher BMI [28-30]. The relation between adult obesity and anemia (Low iron stores) has been discussed in a meta-analysis of all controlled studies carried out by Cheng el al. in 2012. In this study, IDA appeared to be a typical finding in severely obese patients. On the other hand, that review concluded that in most of the studies, Hb levels and ferritin concentrations in obese patients were relatively higher when compared to normal weight adults. However, the anemia in obese patients was due to the decreased serum iron and transferrin concentration [31]. Also in 2014, Lefebvre et al. studied the correlation between morbid obesity and bariatric surgery clinical studies and found out that IDA is one typical and frequent finding in these patients [32].

In 2010, a study was done by De Luis et al., correlated the increased serum resistin levels in morbidly obese patients, this was attributed to the fact that macrophages and monocytes are infiltrating the adipose tissue release inflammatory mediators including resistin [33]. Richardson et al. in2009 conducted a study to relate low iron levels with the occurrence of the inflammation process. In this study he evaluated C-reactive protein (CRP), iron metabolism parameters and BMI in children and adolescents their ages range from 2 to 19 years. There was an inverse relation between BMI and CRP; leading to the conclusion that chronic inflammation in adipose tissue resulted in a low iron condition causing anemia [34].

The relation between IDA and obesity was also attributed to the fact that il-6 and CRP had a direct effect on the expression of Hepcidin gene expression in obese patients. Also, leptin which is one of the adipokines leads to up-regulation of Hepcidin gene expression; contributing to iron deficiency in obese patients [35].

On another level, some studies tried to investigate the effect of proper nutrition on the improvement of iron levels. Gong et al. observed the improvement in iron homeostasis along with the improvement of inflammatory markers in response to weight loss [36].

In this study there was no significant difference between the levels of serum resistin and IDA in normal-weight patients, this observation may lead to the fact that resistin is not one of the markers that can indicate the presence of IAD due to improper dietary iron intake only. Resistin levels may increase when IDA is more likely to be due to a systemic inflammatory condition such as adipose tissue accumulation or anemia associated with rheumatoid arthritis or cardiovascular diseases.

This study also had its limitations; the sample size wasn't large enough. Also the iron homeostasis parameters used were lacking the serum iron and transferrin saturation levels which are more reliable that Hb levels only.

Conclusion:

This study concluded that obese patients are more likely to develop IDA than normal weight individuals. Serum resistin levels are increased in obese patients suffering from IDA, but this is not likely related to normal weight anemic subjects.

The Role of a dental specialist can be crucial in the early diagnosis of IDA case that can be due to a serious underlying medical condition through proper interpretation of the existing oral manifestations.

Acknowledgment:

Authors of this research are genuinely grateful to Mr. Mohamed Gamal, the technician at the Central Laboratory of Clinical and Chemical Pathology, Faculty Of Medicine, Cairo University. His meticulous work with the samples made this study possible

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