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Influence of Obesity and Family History of Type 2 Diabetes Mellitus on Serum Ferritin and Insulin Levels in Young Adults

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Authors' contributions

This work was carried out in collaboration between all authors. Author HVS designed the study, wrote the protocol, and wrote the first draft of the manuscript. Authors SMRU and NC managed the literature searches, analyses of the study and author KSM performed the statistical analysis. All authors read and approved the final manuscript.

Original Research article

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ABSTRACT

Aim: Obesity and family history of Type 2 Diabetes mellitus are the major risk factors for the development of type 2 Diabetes mellitus in youth. The purpose of this study is to investigate the association between serum ferritin and insulin resistance in healthy young obese with and without family history of type 2 Diabetes mellitus.
Place and Duration of Study: Department of Biochemistry, Rajarajeswari Medical College and Hospital, Kambipura, Bangalore, Karnataka, India, for eight months period in the year 2012.
Material and Methods: A small group study was undertaken in 90 students who were in the age group of 17-22 years. The study population was divided into two groups based on body mass index, Group I /non-obese group (n=46) and Group II/ overweight & obese group (n=44). Fasting and postprandial blood glucose, Serum ferritin, serum insulin and lipid parameters were estimated and Homeostasis Model Assessment-Insulin resistance (HOMA-IR) was calculated for all the ninety students.
Results: Statistically significant differences in Total cholesterol ($p=0.05$), Triglycerides ($p=0.05$), serum insulin ($p<0.01$) and HOMA ($p<0.01$) were observed between the two groups. Mean serum ferritin values were increased in group II (overweight/obese) but not statistically significant. Serum insulin and serum ferritin showed a significant correlation

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with BMI for the whole study group.
Serum ferritin and insulin levels significantly correlated with waist to hip ratio in students with family history of Type 2 Diabetes mellitus as against individuals without family history. 59% of the obese students with family history of Diabetes mellitus had insulin resistance.
Conclusion: Our study has shown that a significant proportion of obese students with family history of type 2 diabetes mellitus had insulin resistance and elevated levels of ferritin, highlighting the importance of early screening for obesity associated co morbidities like metabolic syndrome, Type 2 Diabetes mellitus and cardiovascular diseases in these individuals.

Keywords: Serum ferritin; obesity; type 2 diabetes mellitus (T2DM); diabesity; insulin resistance (IR).

1. INTRODUCTION

Obesity is a complex, multifactorial chronic disease involving genetic, physiological, metabolic, behavioural, psychological and environmental components. The global epidemic of overweight and obesity-'globesity' is rapidly becoming a major public health problem and is an important causative factor for metabolic disorders like hypertension, diabetes mellitus(DM) and cardiovascular disease(CVD) [1].

Diabetes occurring in the context of obesity is termed as 'diabesity'. World Health Organisation has forecast that by 2015 approximately 2-3 billion adults will be overweight and more than 700 million will be obese. India is said to have the highest number of people with type-2 diabetes mellitus (T2DM), with China occupying the second position [2]. Linked to various pathophysiological mechanisms, revolving around insulin resistance, diabesity has important diagnostic and therapeutic implications.

In obesity there is progressive hypertrophy and hyperplasia of adipocytes which causes local hypoxia and this results in the development of a pro-inflammatory state with the release of cytokines like tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) [3]. This pro-inflammatory state can cause IR in adipose tissue, skeletal muscle and liver by inhibiting insulin-mediated signal transduction, which is the most common feature of childhood obesity and the key risk factor for the development of the T2DM in obese youth [4].

The metabolically triggered inflammation or meta inflammation seen in obesity leads to elevation of serum ferritin which is an acute phase reactant. Serum ferritin in turn releases catalytic iron which participate in free radical reactions thus setting in a vicious cycle of oxidative stress. There is increasing evidence that moderately elevated iron stores reflected by serum ferritin, may be associated with IR syndrome and glucose intolerance[5].

One other factor that has also been hypothesized to increase risk of T2DM is a positive family history of T2DM.Family history reflects both genetic and environmental factors, it may serve as a better predictor of diabetes risk than either factor alone. But this has not been widely studied especially in young adults.

Currently not many studies have emphasized the role of obesity, influence of family history of T2DM and the relationship between ferritin and IR. Therefore we aimed to evaluate the

association between serum ferritin and insulin resistance in healthy young obese with and without family history of T2DM.

2. MATERIALS AND METHODS

The study was carried out in Rajarajeswari Medical College and Hospital, Kambipura, Bangalore, Karnataka, India,for eight months period in the year 2012. We studied ninety healthy MBBS students who were between 17 and 22 years of age. Students with history of juvenile diabetes, anemia and any acute or chronic illness were excluded from our study. The study design was approved by the Ethics board of our Institution and an informed consent was obtained from all subjects participating in the study.

The participants were asked to furnish the details about their family history of T2DM (only first degree relatives), life style characteristics (dietary habits, physical activity, etc) in a questionnaire that was provided to them.

This is a cross sectional study and the subjects were divided into following two groups:

Group I (Non obese group)- Forty six students having Body mass index (BMI)<23 were included in this group.

Group-II (Overweight & obese group)- Forty four students having Body mass index (BMI)≥23 were included in this group [6].

After 12 hours overnight fasting, blood samples were drawn from all the subjects for the estimation of Fasting blood glucose (FBG), lipid parameters which included total cholesterol (TC), high density lipoprotein (HDL) and triglycerides (TGL), serum insulin and serum ferritin. A postprandial blood sample (two hours after breakfast) was obtained on the same day and post prandial blood glucose (PPBG) was estimated.

Blood glucose (FBG and PPBG), serum total Cholesterol. HDL and Triglycerides were estimated on fully automated analyzer from Transasia company, ERBA EM 360.

Blood glucose (FBG and PPBG) was estimated by Glucose oxidase-Peroxidase (GOD-POD) method. Total Cholesterol by Cholesterol oxidase-peroxidase method, HDL was estimated by direct method, Triglyceride was estimated by Glycerol 3-phosphate oxidase method. VLDL was calculated by the formula VLDL=TGL/5. LDL was calculated using Freidwald equation.

Serum insulin and serum ferritin were analyzed on Roche Cobas fully automated instrument by Chemiluminescence Immuno assay.

We estimated hemoglobin (Hb) concentration in the students in order to rule out anemia. The concentration of Hb was estimated by cyanmet-hemoglobin method using EDTA blood sample.

Insulin resistance (IR) was derived using the Homeostasis Model Assessment equation (HOMA=fasting serum insulin (μunits/ml)×fasting plasma glucose (mmol/l)/22.5). Students who had a HOMA score of more than 2.5 were taken as individuals with insulin resistance [7].

Body weight and height were measured using standardized procedures. BMI was calculated as weight in kg divided by the square of height in meters and was used as an indicator of total body fat [6].

Waist and hip circumferences were measured according to WHO guidelines and waist to hip ratio (WHR) was calculated [8].

2.1 Statistical Analysis

Values were expressed as Mean±SD. Statistical comparisons were carried out by student 't' test. Correlations were done by calculating Pearson's correlation. All statistical analysis was done at 5% level of significance using statistical software SAS 9.2 and SPSS 15.0.

3. RESULTS AND DISCUSSION

Table 1 is a comparative table of different biochemical and anthropometric parameters of the two groups. Statistically significant differences in total cholesterol, TGL, BMI, WHR, serum insulin and HOMA values were observed when the two groups were compared.

Table 1. Comparison of Biochemical and Anthropometric parameters between group I and group II

Parameter	Group I(n=46) [Non-obese] Mean±SD	Group II(n=44) [Overweight/obese] Mean±SD	P value
FBG(mg/dl)	84.76±9.19	85±7.49	0.910
PPBG(mg/dl)	97.62±20.53	104.11±17.29	0.108
Blood Urea(mg/dl)	18.96±4.21	19.84±6.52	0.435
S creatinine(mg/dl)	1.06±0.16	1.05±0.17	0.774
Total cholesterol(mg/dl)	149.0±19.56	160.68±26.60	0.019*
HDL(mg/dl)	40.41±8.87	39. 86±6.59	0.740
LDL(mg/dl)	90.56±13.20	96.36±16.58	0.069
VLDL(mg/dl)	18.46±6.29	22.97±13.72	0.046*
TGL (mg/dl)	92.74±30.50	115.20±68.20	0.05*
S.Ferritin(ng/ml)	44.86±37.49	49.97±44.04	0.55
S insulin(µIU/ml)	9.22±9.24	14.89±8.90	0.004**
WHR	0.86±0.07	0.89±0.07	0.045*
HOMA	1.94±2.03	3.13±1.92	0.005**

*** P value 0.01 suggests strong significance*

Table 2 is correlation analysis of serum ferritin with BMI, WHR and Lipid parameters for the whole group of ninety students. There is significantly positive correlation between ferritin and TGL, BMI, WHR.

Table 3 contains Pearson correlation of Serum Insulin with BMI, WHR and Lipids for the entire group of ninety students. We have observed a positive correlation between insulin levels and BMI.

Tables 4 and 5 are comparative tables enumerating the 'r' and 'p' values when serum ferritin and serum insulin were correlated with BMI and WHR in students with and without family history of T2DM. Both serum ferritin and insulin positively correlated with WHR in students with family history of T2DM.

Table 2. Correlation analysis of serum ferritin with Lipid paramaters, BMI and WHR for the whole study group (n=90)

Pair	Pearson Correlation	P value
Serum ferritin vs Total cholesterol(mg/dl)	0.061	0.491
Serum ferritin vs HDL(mg/dl)	-0.177	0.271
Serum ferritin vs LDL(mg/dl)	0.025	0.817
Serum ferritin vs VLDL(mg/dl)	0.241	0.022*
Serum ferritin vs TGL(mg/dl)	0.210	0.047*
Serum ferritin vs BMI(kg/m^2)	0.247	0.019*
Serum ferritin vs WHR	0.332	0.001**

**Moderately significant (P value:0.01<P 0.05), ** Strongly significant (P value : <0.01)*

Table 3. Correlation analysis of serum insulin with Lipid paramaters, BMI and WHR for the whole study group (n=90)

Pair	Pearson Correlation	P value
Serum Insulin vs Total cholesterol(mg/dl)	0.194	0.07
Serum Insulin vs HDL(mg/dl)	-0.097	0.362
Serum Insulin vs LDL(mg/dl)	-0.103	0.332
Serum Insulin vs VLDL(mg/dl)	0.190	0.073+
Serum Insulin vs TGL(mg/dl)	0.199	0.060+
Serum Insulin vs BMI(kg/m^2)	0.205	0.00002**
Serum Insulin vs WHR	0.214	0.042

*+ Suggestive significance (P value: 0.05<P<0.10), ** Strongly significant (P value 0.01)*

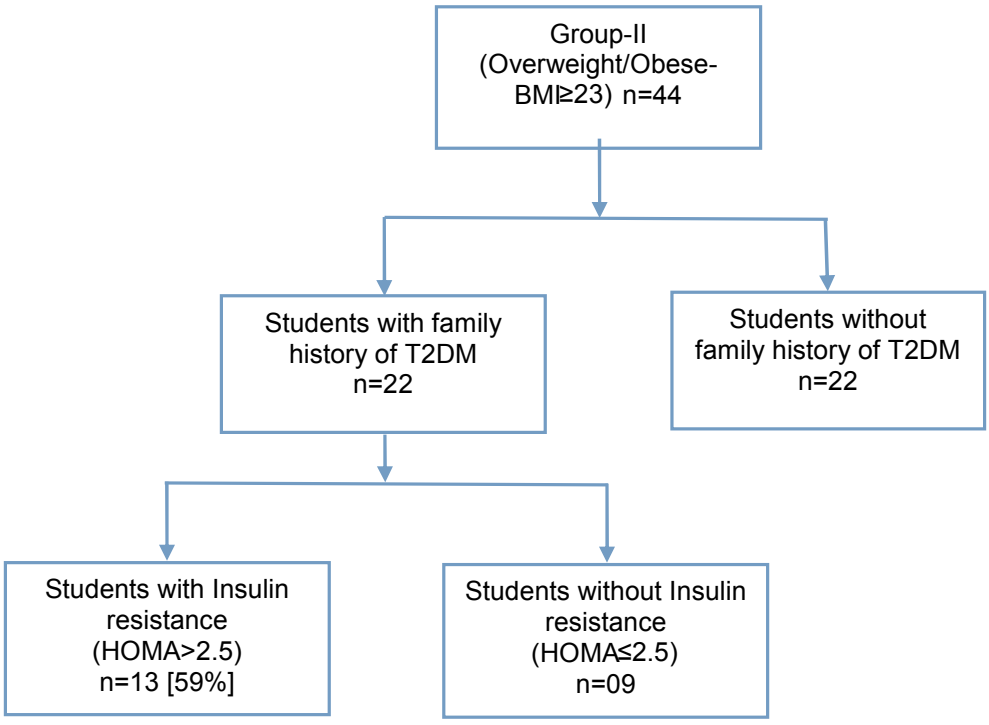

Fig. 1. Data furnishing the findings of students in Group II

Table 4. Pearson correlation of Serum Ferritin with BMI and WHR in students with and without family history of Type 2 Diabetes mellitus

Pair	With Family history (n=43)		Without family history (n=47)	
	r value	p value	r value	p value
Serum ferritin vs BMI(kg/m^2)	0.244	0.114	0.242	0.103
Serum ferritin vs WHR	0.448	0.002*	0.182	0.220

** Moderately significant (P value:0.01<P 0.05)*

Table 5. Correlation analysis of Serum Insulin with BMI and WHR in students with and without family history of Type 2 Diabetes mellitus

Pair	With Family history (n=43)		Without family history (n=47)	
	r value	p value	r value	p value
Serum Insulin vs BMI(kg/m^2)	0.392	0.009**	0.152	0.307
Serum Insulin vs WHR	0.278	0.068+	0.045	0.762

*+ Suggestive significance (P value: 0.05<P<0.10), ** Strongly significant (P value 0.01)*

3.1 Discussion

Diabesity, a term coined by Dr. Francine Kaufman, to cover a constellation of signs, including obesity, insulin resistance, metabolic syndrome and Diabetes mellitus is ready to become the largest rapidly escalating pandemic in human history. The future of diabetes in 'young' countries such as India, where half the population is under 25 is chilling. WHO predicts that, by 2030, developing countries will have three fourths of the world's estimated 900 million diabetics.

The diabesity complex originates from the interaction of modern western sedentary life style, dietary and environmental toxins, micronutrient deficiencies, chronic stress and altered gut microflora with our unique genetic susceptibilities. These root causes are intricately linked to each other. The best news–they are 100% preventable and in most cases, entirely reversible [9].

The most common feature of childhood obesity is insulin resistance and is the key factor for the development of type 2 diabetes mellitus and metabolic syndrome in obese youth. Insulin resistance is defined as a decreased response of the peripheral tissues to insulin action. Insulin resistance, dyslipidemia and obesity are integral components of metabolic syndrome, which by itself predisposes to type 2 diabetes mellitus.

Obesity is a pro-inflammatory state which triggers the release of acute phase reactant like ferritin. Serum ferritin in turn releases catalytic iron which is an important catalyst in the formation of highly reactive hydroxyl radicals and reactive oxygen species and modest iron overload (iron markers within the normal range) may be involved in the induction of insulin resistance early in the pathogenesis of type 2 diabetes mellitus [10].

It is clear that type 2 diabetes mellitus has a strong genetic component and is partly an inherited disease. Familial studies have revealed that first degree relatives of individuals with T2DM are about three times more likely to develop the disease than individuals without a positive family history of the disease [11].

In our study, we have observed significantly raised triglycerides, increased serum insulin levels and insulin resistance among overweight/ obese group of students compared to the non obese group. Similar findings were observed in studies by Lara Naserridin et al. [12].There was also an increase in mean values of serum ferritin in overweight/ obese group of students compared to the non obese group, though not statistically significant. This is in accordance with the findings of Sharma et al and Jee-Yon Lee et al. [13,14].

We observed a significant association when serum ferritin was correlated with triglycerides, body mass index and waist to hip ratio for the whole study group of ninety students. This is in accordance with the findings of the studies done by C. E. Wrede et al. where serum ferritin levels were significantly increased in subjects with high BMI [15]. A study done by Gastaldelli et al have shown that morbidly obese individuals (BMI=44.4±0.4kg/m^2) had increased plasma ferritin concentration that are associated with insulin resistance and elevated Liver function tests. Weight loss reduced liver enzymes and insulin resistance but did not significantly change the plasma ferritin levels, which remained correlated with insulin resistance [16]. Another study by Gillum R.F have similar finding as in our study, where they have reported that serum ferritin concentration is positively associated with waist to hip ratio [17].

The possible explanation for the raised ferritin levels in obesity is probably due to the inflammation mediated sequestration of iron in reticuloendothelial system with resultant hypoferremia, despite adequate or increased iron stores. The pro-inflammatory markers like IL-6 and TNF-α also induce ferritin production in macrophages, hepatocytes and adipocytes. In addition the pro-inflammatory cytokine induced by the obese state increase iron regulating proteins hepcidin and lipocalin-2 secreted by adipocytes. Hepcidin specifically inhibits the release of non- heme iron from macrophages and lipocalin upregulates ferritin synthesis in reticuloendothelial cells [18].

Serum insulin levels showed a positive and strongly significant correlation with BMI for the entire group of ninety students. Lara Nasreddin et al have shown that 88.5% of obese adolescents in their study group were insulin resistant based on HOMA-IR [12]. Druet et al. have shown that 71.8% of obese children and adolescents in their study group had insulin resistance [19]. Juarez et al in 2010 have also reported similar findings [20].

Obesity induced pro-inflammatory state releases one of the important cytokines TNF-α, which activates a variety of serine protein kinases. These activated protein kinases increase serine phosphorylation of insulin receptor substrate-1 and 2.This will lead to decreased activity of phosphotidyl inositol-3 kinase. Hence the downstream effects of insulin signalling are inhibited leading to insulin resistance, which explains the findings in our study [21].

A strong hereditary component has been suggested for the development of type 2 diabetes mellitus. A family history of type 2 diabetes mellitus increases the risk and its high concordance in identical twAll authors declare that ‘written informed consent was obtained from the patient for the publication of this case report.ins and the aggregation of this disease in families support the existence of genetic determinants for type 2 diabetes mellitus in families.

Of the ninety students in our study group, forty three had family history of diabetes mellitus. Both serum ferritin and serum insulin positively correlated with waist to hip ratio in individuals with family history of T2DM. In the obese group 50% of the students had family history of T2DM, out of which 59% had insulin resistance as depicted in Fig. 1.

Studies done by Adeela Shahid et al. have shown that insulin resistance estimated by HOMA-IR was significantly higher in offsprings of diabetic parents than in off springs of non diabetic parents [22]. 41% of the obese students with family history of T2DM did not have IR. IR in an individual with family history of T2DM depends on locus and allelic heterogeneity, degree of penetrance (not everyone with genes will get T2DM or have IR), age of onset, degree of interaction between environmental and genetic factors. In short its etiopathogenesis is complex and multifactorial [23]. These factors explain the absence of IR in obese individuals with family history of T2DM.

4. CONCLUSION

In our study we have found that serum ferritin and serum insulin positively correlated with waist to hip ratio in individuals with family history of T2DM which supports the fact that genetic predisposition and obesity are the foremost risk factors for the development of T2DM. Obesity leads to hyperferritinemia, hyperinsulinemia and insulin resistance which over a period of time results in glucose intolerance and ultimately Type 2 Diabetes mellitus.

A cross sectional design and a small study group are the limitations of the current study. The ferritin levels in the obese group did not reach significance because of the small sample size. A calculated sample size of 800 to 1000 is necessary to obtain validresults. Prospective studies in a larger sample size is required to eludicate the role of ferritin in obesity.

CONSENT

All authors declare that written informed consent was obtained from the subjects who participated in this study for the publication of this article.

ETHICAL APPROVAL

All authors hereby declare that all investigations have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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