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To study beta cell function, insulin resistance and the prevalence of impaired fasting glucose (IFG), impaired glucose tolerance (IGT), diabetes mellitus (DM) among children and adolescents with obesity in north-west Rajasthan

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Abstract

Background: Obesity has emerged as one of the leading global health problems. It is associated with co-morbidities, like DM, dyslipidemia, PCOD, hypertension, metabolic syndrome, which are increasingly becoming common among children and urban adolescents.

Methods: This study was conducted in north-west Rajasthan on 1000 school going children and adolescents, aged 10-18 years. Anthropometric measurements were taken & blood samples were collected for estimation of blood sugar, HbA1c and fasting plasma insulin level. For obese cases, the values of fasting plasma insulin and fasting glucose level were used in the computer based updated HOMA model (HOMA-2) calculator for calculating insulin resistance and ß-cell function.

Results: We found that 13.8% and 7.2% subjects were overweight and obese respectively. The overall prevalence of pre diabetes was 2.5% and that of diabetes 0.3%. The prevalence of pre diabetes (25%v/s5.1%) and diabetes (2.8%v/s0.7%) was higher in obese cases as compared to overweight. Mean fasting insulin level was higher in obese subjects with IGT (17.85±0.23 µU/ml) and IFG (17.54±0.11 µU/ml) as compared to those with normal blood sugar(17.41±0.22 µU/ml), whereas, lowest in diabetics (17.30±0.14 µU/ml); (P<0.001). Mean HOMA-IR was highest in obese individuals with diabetes (2.43±0.01), followed by IFG (2.40±0.01), IGT (2.30±0.04) and normal blood sugar (2.26±0.04); (P<0.001). Among obese, there was significant reduction in beta cell function in IFG and diabetic groups as compared to IGT group. Mean HOMA% B

(beta cell functioning) was lower in diabetics (76.65%±7.85) and IFG (93.76%±3.31) as compared to normal blood sugar (146.39%±8.60). It was highest in IGT (156.53%±17.24); (P<0.001).

Conclusion: As per our study, overweight and obese children and adolescents are at higher risk of developing prediabetes and diabetes. Hence, it is recommended that strategies for weight reduction, promotion of healthy lifestyles and regular monitoring should be enforced.

Key Words- Childhood obesity, diabetes, beta cell function, insulin resistance, HOMA

Introduction

Obesity is a leading global health problems which is associated with co-morbidities, like DM, dyslipidemia, PCOD, hypertension, metabolic syndrome, which are increasingly becoming common among children and urban adolescents[1-3]. The epidemic of childhood obesity is a substantial health burden worldwide[4-6] and its impact is being observed in developing countries as well[7, 8]. The problem is of more concern in developing countries like India where a significant proportion of the population belongs to younger age group[9]. Rising prevalence of obesity in India may be attributed to various factors, like sedentary life-style, unhealthy food habits, cultural practices and urbanisation[1-3, 10].

The International Association for the Study of Obesity (IASO) and International Obesity Task Force (IOTF) estimate that 200 million school children are either overweight or obese[11].

Rapid rise in the prevalence of childhood obesity in recent decades within a relatively stable population indicate that genetic factors are not the primary cause. Therefore, changes in the environment towards a more obesogenic society are the most likely cause for the rise in prevalence[12].

Insulin resistance and beta cell dysfunction occur due to various factors. Proposed mechanisms of insulin resistance are: (a) obesity, (b) inflammation, (c) mitochondrial dysfunction, (d) hyperinsulinemia, (e) lipotoxicity/ hyperlipidemia, (f) genetic background, (g) endoplasmic reticulum (ER) stress, (h) aging, (i) oxidative stress, (j) fatty liver, (k) hypoxia, (l) lipodystrophy, and (m) pregnancy[13]. Whereas, that of beta cell dysfunction are genetic factors, malnutrition in utero and early childhood, prolonged acute hyperglycaemia, increased free fatty acid, obesity and increased glucagon secretion. Many of these factors are associated with obesity.

In adults, type 2 diabetes mellitus develops over a long period and, most, if not all, patients initially have glucose intolerance, which is an intermediate stage in the natural history of type 2 diabetes and predicts the risk of development of diabetes and cardiovascular disease[14].

With appropriate timely action, progression from pre diabetes to frank diabetes and associated complications can be delayed or prevented[15], thereby reducing the burden on the community and the nation as a whole.

Hence, we aimed to conduct the study among obese children and adolescents.

Aims and Objectives

1. To study the prevalence of overweight and obesity in children and adolescents in North-Western Rajasthan.
2. To study the prevalence of IFG (Impaired Fasting Glucose), IGT (Impaired Glucose Tolerance) and DM (Diabetes Mellitus).
3. To study beta cell function and insulin resistance in pre diabetic and diabetic obese children and adolescents.

Material & Methods

A sample size of 1000 apparently healthy children and adolescents of 10-18 years of age of both genders, were taken from various schools of Bikaner district.

Inclusion Criteria

A. Age - 10-18 years

B. Diagnostic criteria for overweight and obesity-

Revised IAP growth chart for BMI is used[16] and values equivalent to adult BMI 23 kg/m^2 and 27 kg/m^2 were taken as overweight and obesity cut-off values.

C. Diagnostic criteria for abnormal glucose homeostasis

1. Diagnostic criteria for Impaired Fasting Glucose (IFG) –

Fasting plasma glucose level of 100-125 mg/dl

2. Diagnostic criteria for Impaired Glucose Tolerance (IGT) –

Two hour plasma glucose level of 140-199 mg/dl during an oral glucose tolerance test

3. HbA_1c 5.7- 6.4%

D. Diagnostic criteria for Diabetes Mellitus (DM)

1. Fasting glucose level ≥126 mg/dl

2. Two hour plasma glucose level ≥200 mg/dl during an oral glucose tolerance test

3. Random blood sugar ≥200 mg/dl plus symptoms of diabetes

4. HbA_1c ≥6.5

Exclusion Criteria

A. Subject with thyroid dysfunction

B. Secondary causes of obesity

C. Any acute or chronic illness

D. Subjects not willing to participate in the study or not giving consent

- Body weight was measured to the nearest 0.1 kg using a digital weighing machine with subjects barefoot.
- Body height was measured using calibrated stadiometer to the nearest mm with subjects barefoot.
- Body mass index (BMI) was measured as the ratio of body weight to body height squared, expressed as kg/m^2.

Revised IAP growth chart for BMI formulated by Khadilkar et al[16] is used. Values corresponding to 23 and 27 adult equivalent percentiles were taken as overweight and obesity cut-off, whereas value corresponding to less than 3 percentile was considered as underweight.

- The waist circumference was measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest, using a stretch-resistant tape.
- Hip circumference was measured around the widest portion of the buttocks, with the tape parallel to the floor.
- Waist to hip ratio was calculated by dividing waist by hip measurement.
- Blood glucose was measured by glucose oxidase method (one touch glucometer). Every 5th sample was calibrated by auto analyser.
- Fasting blood glucose was measured after 8 hr of overnight fast.
- For OGTT, glucose load in a dose of 1.75 g/kg of body weight (up to a max. of 75gm) was used and after 2hr blood sugar was again measured.
- Blood collection was done by clean venepuncture of a large antecubital vein using a 19 gauge needle for relevant investigations.

- Insulin resistance and ß-cell function of the participants, who were found to be obese were calculated by measuring fasting plasma insulin level by chemiluminescence immuno assay. The values of fasting plasma insulin and fasting glucose level were put in the computer based updated HOMA model (HOMA-2) calculator for calculating insulin resistance and ß-cell function.
- HbA_1c was measured by ion exchange chromatography.
- Statistical analysis was done using SPSS 17.0 software. Student's't' test, ANOVA test and Chi Square test were applied. P value <0.05 was considered as significant.

Observation and Results

Recent studies in India and other countries revealed that obesity is a growing health problem among children and adolescents, especially in urban population[17].

In our study, we found that 61 candidates (6.1%) were underweight, 138 candidates (13.8%) were overweight, while 72 (7.2%) were obese. Out of 386 female cases, 33 (8.6%) were underweight, 286 (74.1%) had normal BMI, 51 (13.2%) were overweight and 16 (4.1%) cases were obese. In males, out of total 614 cases, 28 (4.6%) were underweight, 443 (72.1%) were in normal range, 87 (14.2%) were overweight and 56 (9.1%) were obese. Significantly more females were underweight as compared to males ($p<0.05$).While, among obese adolescents, males had significantly higher prevalence in comparison to females ($p<0.01$). In normal and overweight children, no significant difference was found between females and males ($p>0.05$) (Table 1, Fig.1).

The overall prevalence of pre diabetes and diabetes was 2.5% and 0.3% respectively. We observed that the prevalence of pre diabetes and diabetes in overweight cases was 5.1% and 0.7% respectively, while in obese it was 25% and 2.8% respectively. No case of pre diabetes and diabetes was found in normal and underweight candidates. Thus, overweight and obese candidates were at higher risk of developing impaired glucose homeostasis and frank diabetes.

Out of 138 overweight cases, 7 had IGT, while, none had IFG. Out of 7 cases of IGT, 3, 2, 1 and 1 cases belonged to age 17, 18, 14 and 15 respectively, while only 1 case had diabetes, who was 18 years old (Table 2).

Out of 72 obese patients, 5 had IFG and 13 had IGT. Out of 5 IFG cases, 1 each belonged to age 12, 13, 15, 17 and 18 while out of total 13 IGT cases, 4 cases were of the age 16 years, 3 cases each were of the age 14 and 15 years, 2 cases had their age 18 years and 1 case had 12 years of age. 2 cases had diabetes and out of them 1 each belonged to age 17 and 18 years (Table 3).

In our study, mean fasting insulin levels in obese subjects with normal blood sugar, IFG, IGT and diabetes were 17.41±0.22 µU/ml, 17.54±0.11 µU/ml, 17.85±0.23 µU/ml and 17.30±0.14 µU/ml respectively. On applying ANOVA test, the difference was found highly statistically significant ($p<0.001$). Mean HOMA-IR in obese subjects with normal blood sugar, IFG, IGT and diabetes was 2.26±0.04, 2.40±0.01, 2.30±0.04 and 2.43±0.01 respectively and the difference was found highly statistically significant ($p<0.001$). Mean insulin sensitivity (%S) in obese subjects with normal blood sugar, IFG, IGT and diabetes was 44.29±0.68, 41.66±0.34, 43.51±0.82 and 41.30±0.14 respectively and it was statistically highly significant ($p<0.001$).

Similarly, mean beta cell function (%B) in obese subjects with normal blood sugar, IFG, IGT and

diabetes was 146.39±8.60, 93.76±3.31, 156.53±17.24 and 76.65±7.85 respectively, which was highly statistically significant ($p<0.001$) (Table 4, fig2).

Discussion

The number of people with diabetes mellitus has increased substantially, making it one of the most important public health challenge. Prediabetes and Type 2 diabetes mellitus are increasingly observed among children and adolescents.

India is a fast growing economy and undergoing major epidemiological, nutritional and demographic transitions. These transitions tend to promote obesity in all age groups.

Therefore, identifying obese children at risk for developing diabetes is of prime importance in order to interrupt its progression and the diabetes related complications.

In our study, we have tried to find out the prevalence of overweight, obesity, pre diabetes and diabetes among children and adolescents in north -west Rajasthan. We also studied beta cell function and insulin resistance in obese children and adolescents.

We found that 61 candidates (6.1%) were in under nutrition category, out of them 33 (54.1%) were females while 28 (45.9%) were males. 729 cases (72.9%) were in the normal BMI range. Females had significantly higher prevalence in underweight group as compared to males ($p<0.05$). While in obese children, males had significantly higher prevalence in comparison to females ($p<0.01$). In normal and overweight children, no significant difference was found between females and males ($p>0.05$). These findings throw light on the social stigma still prevalent in our region.

Unfortunately, identifying cut-off point of BMI for overweight and obesity in children is difficult as they have less disease related to obesity than adults. Asian adult populations are more prone to adiposity and central obesity at a lower BMI than their western counterparts. As the pattern of growth of population changes over time so the growth references should be updated regularly. In our study we have used latest revised IAP growth charts[16] formulated specifically for 5-18 year old Indian children for defining overweight and obesity. This will help in showing the real picture of obesity problem among children in our community than using WHO defined cut-off point of 25kg/m^2 and 30kg/m^2 which is for adults.

Our results were comparable to various earlier studies done across the country. Narayanappa et al[18] in 2011 in Mysore city showed the prevalence of overweight and obesity to be 11% and 5%, respectively. In Rohtak city, Rohilla et al[19] showed the prevalence of overweight and obesity to be 11.0% and 5.7% respectively, in the age group 10-19 years in 2014.

There are very few studies conducted in Rajasthan. One of the studies by Jain et al[20] in 2012 in Jaipur, showed the prevalence of overweight to be 12.5% and that of obesity 5.6%. Another study by Choudhary et al[21] in 2017 in Jaipur, showed the prevalence of overweight to be 32.65% in males and 34.15% in females. They also found that 33.67% males and 32.93% females belonged to the obese category. The high prevalence of obesity and overweight in their study can be attributed to very small sample size of 180 candidates.

Continuous rising trend of the problem can be attributed to sedentary life style, increase consumption of junk food and stress.

Prevalence of pre diabetes and diabetes

Globally, there has been an increase in the burden of pre diabetes and diabetes among children and adolescents.

In our study, the overall prevalence of pre diabetes and diabetes was 2.5% and 0.3% respectively.

Results of our study were comparable to the study done by Narayanappa et al[18] in 2011 in Mysore city. They found the prevalence of pre diabetes and diabetes to be 3.7% and 0.6% respectively. Taranikanti et al[22] in 2014 found the prevalence of pre diabetes to be 7.1% in South Indian school children, however their sample size was very small.

Study conducted by Choudhary et al[21] in 2017 in Jaipur reported the prevalence of IGT to be 13.89% while that of diabetes to be 0.5%. The higher prevalence of IGT can be attributed to small sample size in their study.

Association between obesity and diabetes:

We observed that the prevalence of pre diabetes and diabetes in overweight cases was 5.1% and 0.7% respectively, while in obese it was 25% and 2.8% respectively. No case of pre diabetes and diabetes was found in normal and underweight candidates. Thus candidates with overweight and obesity were at higher risk of developing impaired glucose homeostasis and frank diabetes.

Sinha et al[23] in 2002 studied prevalence of IGT and diabetes in children and adolescents with marked obesity and reported prevalence of IGT to be 25% in children (age 4-10 yr) while 21% in adolescent (11-18 yr). They also reported 4% prevalence of diabetes in obese adolescent.

Choudhary et al[21] reported that 15% of overweight student and approximately 26% of obese students had IGT and they found the association of IGT and increased BMI to be highly significant.

Beta cell function and insulin resistance

Mean fasting insulin level in obese subjects with normal blood sugar, IFG, IGT and diabetes was 17.41 ± 0.22 µU/ml, 17.54 ± 0.11 µU/ml, 17.85 ± 0.23 µU/ml and 17.30 ± 0.14 µU/ml respectively. On applying ANOVA test, the difference was found statistically highly significant ($p<0.001$).

The mean fasting insulin level of IGT group was significantly higher than NGT, IFG, DM groups and that of DM group was lower than NGT, IFG and IGT group ($p<0.001$). It could be explained by compensatory increase in beta cell mass and hypertrophy of existing beta cells to meet the increased demand and to avoid more severe hyperglycemia in IGT subjects whereas decline in the function in diabetic subjects.

Mean HOMA-IR in obese subjects with normal blood sugar, IFG, IGT and diabetes was 2.26±0.04, 2.40±0.01, 2.30±0.04 and 2.43±0.01 respectively and the difference was found statistically highly significant ($p<0.001$).

There was progressive increase in insulin resistance across the glucose tolerance levels ($p<0.001$). The mean HOMA-IR in DM group was significantly higher than that of NGT, IFG, IGT groups and the mean HOMA-IR of IGT group was significantly higher than that of NGT group ($p<0.01$).

Our observations of fasting insulin level and HOMA-IR were supported by the study done by Than et al[24], Shalitin et al[25] and H. Zelada et al[26].

There was significant decline in beta cell function in IFG and DM groups as compared to IGT groups ($p<0.001$).The same patterns of changes in HOMA-β were found in other international studies. A Thai study also found that subjects with IFG and DM had a significantly lower beta-cell function than those with IGT[27]. This was also seen in study conducted by Than et al[24].

Conclusion

Prevalence of obesity is increasing in children and adolescents across the country including north -west Rajasthan. Obesity increases insulin resistance and causes beta cell dysfunction which results in impaired glucose tolerance and frank diabetes. As obesity is increasing in children and adolescents of our society, therefore the incidence of pre diabetes and diabetes is also on rising trend. Based on observations of our study, it is recommended that strategies for obesity prevention, weight reduction, promotion of healthy lifestyles and regular monitoring are necessary during childhood and adolescence else the implications of this global phenomenon on future generations will be serious.

Limitations

As the sample size was small, the prevalences obtained may not be truly reflective of the heterogeneity in the population. Larger sample size is required to obtain a better and more representative overview of prevalence of pre-diabetes and diabetes in children and adolescents in north-west region of Rajasthan.

Table 1: Prevalence and gender wise distribution of underweight, overweight and obesity among study subjects

Sex	BMI Group								Total	
	Under weight		Normal		Over Weight		Obese			
	No.	%	No.	%	No.	%	No.	%	No.	%
Female	33	54.1	286	39.2	51	37.0	16	22.2	386	38.6
Male	28	45.9	443	60.8	87	63.0	56	77.8	614	61.4
Total	61	100	729	100	138	100	72	100	1000	100
χ^2	6.5839		0.4531		0.1825		8.7809			
P	<0.05		>0.05		>0.05		<0.01			

Table 2: Age and sex wise distribution of pre-diabetic and diabetic overweight subjects

Age (years)	No. of Overweight	IFG				IGT				Diabetics			
		Girls		Boys		Girls		Boys		Girls		Boys	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
10	4	0	-	0	-	0	-	0	-	0	-	0	-
11	6	0	-	0	-	0	-	0	-	0	-	0	-
12	4	0	-	0	-	0	-	0	-	0	-	0	-
13	17	0	-	0	-	0	-	0	-	0	-	0	-
14	35	0	-	0	-	0	-	1	2.9	0	-	0	-
15	24	0	-	0	-	0	-	1	4.2	0	-	0	-
16	11	0	-	0	-	0	-	0	-	0	-	0	-
17	25	0	-	0	-	2	8.0	1	4.0	0	-	0	-
18	12	0	-	0	-	0	-	2	16.7	1	8.3	0	-
Total	138	0	-	0	-	2	1.5	5	3.6	1	0.7	0	-

Table 3: Age and sex wise distribution of pre diabetic and diabetic obese subjects

Age (years)	No. of Obese	IFG				IGT				Diabetics			
		Girls		Boys		Girls		Boys		Girls		Boys	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
10	0	0	-	0	-	0	-	0	-	0	-	0	-
11	1	0	-	0	-	0	-	0	-	0	-	0	-
12	3	0	-	1	33.3	1	33.3	0	-	0	-	0	-
13	4	1	33.3	0	-	0	-	0	-	0	-	0	-
14	21	0	-	0	-	0	-	3	14.3	0	-	0	-
15	20	1	5.0	0	-	1	5.0	2	10.0	0	-	0	-
16	8	0	-	0	-	1	12.5	3	37.5	0	-	0	-
17	8	0	-	1	12.5	0	-	0	-	0	-	1	12.5
18	7	0	-	1	14.3	1	14.3	1	14.3	0	-	1	14.3
Total	72	2	2.8	3	4.2	4	5.6	9	12.5	0	-	2	2.8
Mean		14.00		15.67		15.25		15.33		-		17.50	
SD		1.41		3.21		2.50		1.32		-		7.07	

Table 4: Fasting serum insulin and homeostasis model assessment for insulin resistance index (HOMA-IR), insulin sensitivity (%S) and beta cell function (HOMA-B) in obese subjects

Parameters	Blood Sugar Status								F	P
	Normal (n=52)		IFG (n=5)		IGT (n=13)		Diabetic (n=2)			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Fasting Insulin Level (µU/ml)	17.41	0.22	17.54	0.11	17.85	0.23	17.30	0.14	15.269	<0.001
HOMA-IR	2.26	0.04	2.40	0.01	2.30	0.04	2.43	0.01	38.460	<0.001
Insulin Sensitivity (%S)	44.29	0.68	41.66	0.34	43.51	0.82	41.30	0.14	33.835	<0.001
Beta Cell Function (HOMA-%B)	146.39	8.60	93.76	3.31	156.53	17.24	76.65	7.85	72.783	<0.001

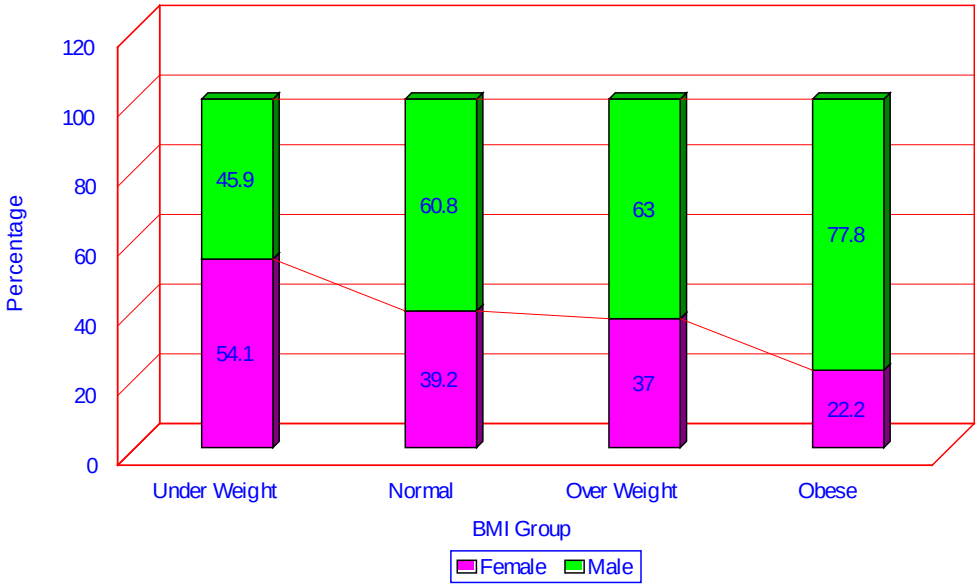

Fig. 1: Prevalence and gender wise distribution of underweight, overweight and obesity among study subjects

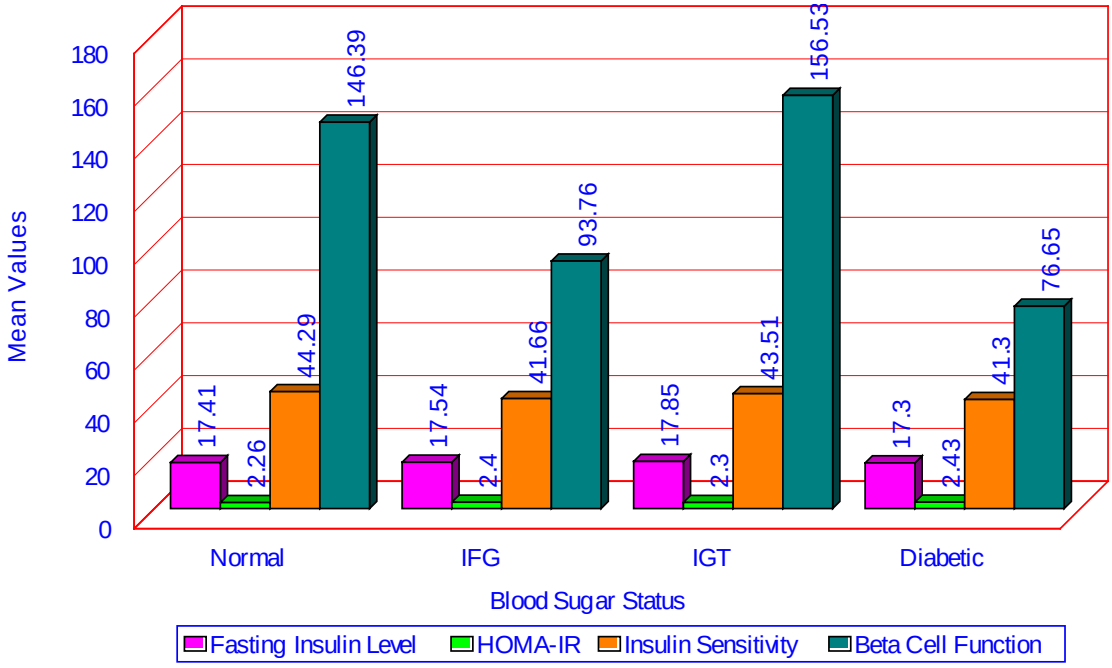

Fig.2: Fasting serum insulin and homeostasis model assessment for insulin resistance index (HOMA-IR), insulin sensitivity (%S) and beta cell function (HOMA-B) in obese subjects

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