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Evaluate Cardiovascular Risk Factor in Indian Insulin Sensitive &Resistant Subjects Using Lipid Profile & Visceral Fat Measurement

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Abstract India is considered as capital of diabetes because India already leads the world with the largest number of diabetic subjects (nearly 40 million) and it is predicted that this numberwould reach almost 80 million by the year 2030. There are research works those indicate towards the genetic liability of Indians towards theinsulin resistance, diabetes & obesity. Indians also show much body fat than other ethnic groups.Central or abdominal obesity has been shown to be an important predictor for increased morbidity and mortality from diabetes and coronary heart disease. The constellation of insulin resistance, impaired glucose tolerance, atherogenic dyslipidaemia, hypertension and intra-abdominal adiposity (IAA) is called metabolic syndrome. Even though there is very little research work is done in direction of insulin resistancein India. The objective of the study was to evaluate whether visceral fat & lipid profile was associated with insulin resistance in centrally obese people of Bhavnagar, Gujrat . This cross-sectional study was conducted on 70 individuals with normal glucose tolerance (38 males and 32 females). The major criteria for selection of subject were that person should be having metabolic syndrome. Visceral fat measurement was done by body composition monitor. Insulin resistance was measured by HOMA-IR formula with the help of fasting insulin & glucose level. Subjects were divided in to insulin resistant people (cases) & non-insulin resistant people (controls). Lipid profile was analysed in each subject. Lipid profile contains total cholesterol, serum triglycerides, serum high density lipoprotein (HDL), serum low density lipoprotein (LDL), serum very low density lipoprotein (VLDL). Analysis of data with unpaired t-test using graph pad software revealed that there was significant difference in visceral fat, HDL & VLDL ($P< 0.05$) in between insulin resistant & insulin sensitive people. Insulin resistant people show higher visceral fat score & abnormal lipid profile which are potential cardio vascular risk factors. Outcome of the study indicate that insulin resistant people show more cardiovascular liability. Implication of study tells that as, insulin resistance is reversible at this phase we can take preventive step & focus our preventive guide lines to the insulin resistant people who are high risk subjects. So, the insulin resistance is subject of prime importance & subjects having metabolic syndrome should be primarily focused with preventive guide lines.

Keywords Diabetes, Insulin Resistance, Metabolic Syndrome, Central Obesity, Visceral Fat, Lipid Profile, Cardio Vascular Risk Factors, Ischemic Heart Disease

1. Introduction

India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the “diabetes capital of the world”. According to the recent projections of World Health Organization (WHO), India already leads the world with the largest number of diabetic subjects (nearly 40 million) and it is predicted that this number would reach almost 80 million by the year 2030[1].

The International Diabetes Federation (IDF) estimates the number of people with diabetes in India currently around 40.9 million is expected to rise to 69.9 million by 2025 unless urgent preventive steps are taken. India & china contribute to 75% of total diabetic patient load of world. Diabetes is an iceberg disease. India faces a grave health care burden due to the high prevalence of type- 2diabetes and its complication like cardiovascular disease, retinopathy, nephropathy, and neuropathy.[1,2].

This study is concentrated around the insulin resistance, metabolic syndrome & visceral fat. Insulin resistance occurs when cells in the body (liver, skeletal muscle and adipose/tissue) become less sensitive and eventually resistant to insulin, the hormone which is produced by the beta cells inthe pancreas to facilitate glucoseabsorption. Glucose can no longer be taken by the cells butremains in the

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blood, triggering hyperinsulinemia;this over burdens the pancreatic beta cell of pancreas &eventually wears out the beta cells. This is the point where clinical diabetes develops [2].

Other names used for metabolic syndrome are insulin resistance syndrome, syndrome X, Reavan's syndrome, Beer belly syndrome. The IDF consensus worldwide definition ofthe metabolic syndrome (2006) contains Central obesity (defined as waist circumference > 90cm for male, > 80 cm for female, with ethnicity specific values) plus any two of the following four factors:1.Raised triglycerides ≥ 150 mg/dL (1.7 mmol/L)or specific treatment for this lipid abnormality2.Reduced HDL cholesterol<40 mg/dL (1.03 mmol/L) in males< 50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality. 3.Systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hgor treatment of previously diagnosed hypertension (FPG) ≥ 100mmHg 4.Raised fasting plasma glucose (mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes[2]. This 'clustering' of metabolic abnormalities that occur in the same individual appear to confer a substantial additional cardiovascular risk over and above the sum of the risk associated with each abnormality [3].

Visceral fat or abdominal fat[17] also known as organ fat or intra-abdominal fat, is located inside the abdominal cavity, packed between the organs (stomach, liver, intestines, kidneys, etc. Visceral fat is composed of several adipose depots, including mesenteric, epididymalwhite adipose tissue, and peri renal depots.An excess of visceral fat is known as central obesity. The association between central obesity and cardiovascular disease & diabetes is strong. There are studies reporting that visceral fat is associated with diabetes and the metabolic syndrome[4, 5, 17-21]. Insulin resistance, inflammatory diseases, and other obesity-related diseases.[17-21].

Body fat measurement can be done by several methods. Near-infrared interactance[22], Dual energy X-ray absorptiometry, or DXA (formerly DEXA)[23], Body average density measurement by Brozek formula[24] & Siri formula, skinfold estimation methods, Ultrasound, Bioelectrical impedance analysis (BIA) method.

Principle behind BIA: two or more conductors are attached to a person's body and a small electric current is sent through the body. The resistance between the conductors will provide a measure of body fat between a pair of electrodes, since the resistance to electricity varies between adipose, muscular and skeletal tissue. Fat-free mass (muscle) is a good conductor as it contains a large amount of water (approximately 73%) and electrolytes, while fat is anhydrous and a poor conductor of electric current[25].

Diabetes is multifactorial disease. there are so many factors like genetic traits , life style, environment, ethnicity that affect the outcome of metabolic syndrome .There are lots of studies done in western countries regarding metabolic syndrome. Gujrat which is considered diabetic capital of India needed to be explored in direction of insulin resistance & metabolic syndrome. With this background we decided to start a pilot project to find out the relation between insulin resistance, visceral fat & lipid profile. One of the important factors contributing to increased Type 2 diabetes in Asian Indians is the fact that they have a greater degree of insulin resistance compare to Caucasians. Mohan et al[28]first demonstrated that Asian Indians have higher insulin levels to a glucose load than Europeans (hyperinsulinemia). It was later demonstrated by euglycaemic clamp studies that insulin resistance is greater among Asian Indians compared to age, sex and body mass index matched Europeans[29].

2. Material and Methods

This study was started with the permission of IRB committee & conducted in physiology department of government medical college Bhavnagar. 70 study subjects were chosen randomly from Bhavnagar city, 38 male & 32 female. We have decided the sample size using software Raosoft with the help of prevalence rate of previous studies done in insulin resistance.

The major criterion for selection of subject was central obesity.(Waist Circumference (WC)>/= 80Cm for female and WC>/=90Cm for male which is ethnic specific value for Indians). This criterion was based on international diabetes federation's definition of metabolic syndrome. Exclusion criteria for participation in the study will be those who had unstable weight over the past 12 weeks, a significant chronic disease or were taking medications (anti-obesity medications, steroids, thyroid hormone, antipsychotics, antidepressants, anxiolytics, laxatives, oral contraceptives, beta-blockers, diuretics, oral hypoglycaemic agents, insulin, or hormone replacement therapy) that could affect body weight and body water content.

Informed consent was taken from every participant before enrolling them for study. We had proper approach towards the subjects & given them all information regarding advantages & disadvantages of participating in study. We had established Proper history taking & examination for assessing all the cardiovascular risk factor like past history of smoking, alcoholism or family history of diabetes & hypertension etc. The measurement of fasting serum insulin & fasting serum lipid is essential for the study. The fasting blood sample was taken in the morning after an overnight fast of at least 12 hour measurement of fasting insulin, fasting glucose, Total cholesterol, serum triglycerides, serum HDL, serum LDL & serum VLDL. All the biochemical parameters were assessed in biochemistry laboratory of sir takhtasinhaji hospital of Bhavnagar which is NABL accredited. Insulin resistance will be assessed using the homeostasis model assessment (HOMA-IR).[6-8]. HOMA - IR was calculated using the following formula: HOMA-IR (mmol/L _ _U/ml) is equal to fasting glucose (mmol/L) multiplied by fasting insulin (IU/ml)/22.5. Based on the number of insulin resistance, subjects were divided in 2 groups insulin resistant (greater than 3.04) & insulin

sensitive(less than or equal to 3.04).All the blood samples are collected from the individual in fasting blood samples without anticoagulant and centrifuge at 1500 rpm for 5 min and serum is collected in fresh vial for biochemical studies by using standard methods as follows.

Serum magnesium :Calmagite method (Gindler et al., 1971)

Serum total cholesterol: Cholesterol oxidase Method (Richmond,1973)

Triglycerides: Glycerolkinase, Peroxidase, method (Foosati et al., 1982)

HDL: Precipitation method

LDL: LDL-C (MG/DL) = Total cholesterol-(HDL-C+ VLDL-C)

VLDL: VLDL-C (mg/dl) = triglycerides/5

Fasting plasma insulin level (Ins)was determined using an immunoenzymatic method(analyzer AXSYM, Abbott) and fasting glucoseconcentration by the glucose oxidase method. FastingInsulin, the fasting Glucose /Insulin ratio and the homeostasisassessment model for insulin resistance (HOMA-IRZfasting Ins (mU/l) fasting Glucose (mmol/l)/ 22.5) were chosen as measures of insulin sensitivity[26-27]

Complete body composition analysis was done by instrument named Omron HBF-514C Full Body Composition Monitor with Scale provided by company Omron pvt. Ltd. Company from Japan. The visceral fat measurement is dome on principal of electrical impedance as we have discussed above.

3. Results

Statistical tools: Data were entered and analysed with the Graph Pad.com. Statistical tests used for comparison is Student's t-test. Results are presented as mean (SD) and number (%) of cases as appropriate. The level of significance was set at $P < 0.05$, and 95% confidence intervals were calculated for the main outcome measures.

Table 1 is showing the distribution of subjects according to insulin sensitivity index. Persons with insulin resistance are considered as cases. Persons with better insulin sensitivity are included in control groups.

Table 1. distribution of subjects

Insulin sensitivity index	No. of subjects
Insulin sensitive(≤ 3.04)	33 controls
Insulin resistant(> 3.04)	37 cases

Table 2. comparison of visceral fat in case & controls(unpaired t test)

Groups	Mean ± SD	t	P
case	10.58±3.69	7.24	<0.05
control	4.84±2.76		

Table 2 is showing that the mean value of visceral fat component in insulin resistant people is higher than insulin sensitive people. P value is < 0.05 which shows that the difference in mean value is significant.

Table 3. comparison of Total cholesterol(mg/dl) in case & controls (unpaired t test)

Groups	Mean ± SD	t	P
case	178.31±40.18	0.42	>0.05
control	174.73±28.68		

Table 3 is showing that the mean value of total cholesterol in insulin resistant people is higher than insulin sensitive people.

Table 4. comparison of serum triglycerides(mg/dl) in case & controls (unpaired t test)

Groups	Mean ± SD	t	P
case	155.08±78.15	1.856	>0.05
control	123.91±59.07		

Table 4 is showing that the mean value of serum triglycerides in insulin resistant people is higher than insulin sensitive people.

Table 5. comparison of HDL(mg/dl) in case & controls (unpaired t test)

Groups	Mean ± SD	t	P
case	38.63±12.13	3.507	<0.05
control	48.18±10.29		

Table 5 is showing that the mean value of HDL in insulin resistant people is higher than insulin sensitive people. P value is < 0.05 which shows that the difference in mean value is significant.

Table 6. comparison of LDL(mg/dl) in case & controls (unpaired t test)

Groups	Mean ± SD	t	P
case	96.317±39.715	0.3586	>0.05
control	93.404±25.574		

Table 6 is showing that the mean value of LDL in insulin resistant people is higher than insulin sensitive people.

Table 7. comparison of VLDL(mg/dl) in case & controls (unpaired t test)

Groups	Mean ± SD	t	P
case	34.311±40.18	2.007	<0.05
control	26.212±12.628		

Table 7 is showing that the mean value of VLDL in insulin resistant people is higher than insulin sensitive people. P value is < 0.05 which shows that the difference in mean value is significant.

4. Discussion

The findings of the current study are consistent with the findings of earlier studies that visceral component of abdominal fat is strongly related to cardiovascular risk factors in other ethnic groups.[4,5] The results of Framingham Heart Study also support the hypothesis that visceral fat is more strongly associated with an adverse metabolic risk profile[9].

Although the exact molecular mechanisms behind the association of visceral fat with increased cardiovascular risk are unknown, the effect could be due to either anatomical location of the fat within the abdomen or due to the differences in the metabolic properties. The anatomical proximity to the portal venous system leads to the direct drainage of metabolites and secretory products like free fatty acids to the liver resulting in hepatic insulin resistance which in turn may lead to increased hepatic gluconeogenesis 10. The other hypothesis states that the active lipolytic feature of visceral adipocytes which make visceral fat deposition more deleterious[11, 12].

There are studies indicating that abnormal lipid profile is associated with increased incidence of IHD & there are at risk subjects with cardiovascular morbidities[13]. In present study total cholesterol & triglycerides are not significantly elevated in insulin resistant subjects even though the mean value is more. HDL is considered good lipoprotein, protective lipoprotein[13, 14]. The mean value of HDL is significantly higher in insulin sensitive people than insulin resistant. From this point of view it seems like insulin sensitive people are at safer side. LDL & VLDL are known to be playing deleterious role in ischemic heart disease (IHD).[13, 14, 15]. The mean values of LDL & VLDL are significantly elevated in insulin resistant people. There are studies which indicate that lipid disorder & hyperinsulinemia is highly significant independent risk factor for coronary heart disease along with diabetes mellitus, hypertension and smoking[16]. From this angle appears that insulin resistant peoples are at risk of cardiovascular disease.

While discussing metabolic syndrome we can't ignore the factors like ethnicity, genetic factors, life style modification. Mohan et al.[30] has indicated why Indians are more prone to diabetes. According to author, Type 2 diabetes is increasing in migrant Indians& prevalence of diabetes in the urban metros of India is approaching the figures reported in the affluent migrant Indians. Environmental and lifestyle changes resulting from industrialization and migration to urban environment from rural settings may be responsible to a large extent, for this epidemic of Type 2 diabetes in Indians. Obesity, especially central obesity and increased visceral fat due to physical inactivity, and consumption of a high - calorie/high-fat and high sugar diets are major contributing factors. Strategies to achieve healthy fetal and infant growth and encouraging the use of traditional diets rich in fibre are also important steps. Such interventions should be attempted in those who are genetically predisposed to diabetes in order to tackle the explosion of, and thereby reduce the burden due to, diabetes within the Indian subcontinent. Also the Indians have high body fat percentage even with normal BMI, according to a study done by Deurenberg et al. in immigrants of Singapore who are from different ethnic groups the Indians have highest body fat percentage in comparison to muscle mass.[31]. There is another study done by Chandrasekharan N et al in Indian people which mention that Indian subjects showed higher body fat percentage and risk factors like hypertension and type 2 diabetes at normal BMI range proposed by the WHO.[32]

Diet also plays important role in development of metabolic syndrome.Trans fatty acids in the Indian diets are mostly derived from hydrogenated vegetable oil, a type of cooking medium frequently used to prepare snacks and sweets. With widespread and increasing use of this vegetable oil increases intake of trans fatty acid in the Asian Indian population. Trans fatty acids elevate the level of Lipoprotein A, which is an independent risk factor for CHD[33]. This fact is critically important in Asian Indians.

From all of above views & angles it seems like Asian Indians are high risk subject for metabolic syndrome world-wide. To decrease the global burden of syndrome X, with our limited resource we must focus our preventive guideline to high risk group which is insulin resistant group. Limitation: insulin resistance & other lipid profiles are invasive tests which lead 2 subject discomforts. Sample size was small but enough to make this study relevant.

5. Conclusions

Outcome: present study shows that there is significant higher level of visceral fat in insulin resistant subject. Evaluation of lipid profile indicates that HDL is decreased and LDL & VLDL is increased insulin resistant people. Insulin resistant people are at risk of cardiovascular morbidities. Implication: As, insulin resistance is reversible at this phase we can take preventive step. So, the insulin resistant people are subjects of prime importance because they are high risk subject & by giving priority this group we may reduce the global burden of diabetes. We may think of insulin sensitivity test not only as diagnostic but also as screening & prognostic test.

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