Original Article

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Biochemistry Section

Evaluation of Usefulness of Serum Insulin as Sensitive Predictor of Cardiovascular Dysfunction in Obese Individuals with Normal Lipid Profile

AMRUTA A. BAKSHI[1], JAYASHREE S. BAVIKAR[2], SHILPA B. ASEGAONKAR[3], JAYASHREE S. BARDAPURKAR[4], VIJAY DOMPLE[5], POOJA SK RAI[6], SMITA PAWAR[7]

ABSTRACT

Background: Prevalence of obesity and its subsequent cardiometabolic complications is on exponential rise. Hyperinsulinemia develops in obese individuals long before other metabolic derangements of obesity take place and may be a common pathophysiological factor tying together various components of cardiometabolic dysfunction.

Aim: Present study was aimed at evaluating the role of insulin as a sensitive and independent cardiovascular risk marker in apparently healthy overweight and obese individuals with normal lipid profile.

Settings and design: This was an opd based case Control study including 100 overweight and obese individuals with normal lipid profile & 100 age and sex matched normal weight healthy controls.

Materials and Methods: Participants were evaluated based on detailed history, clinical examination and laboratory investigations. Blood samples were collected after overnight fast. Serum insulin was estimated by chemiluminescence method, glucose and lipid profile (CHOLESTEROL, HDL, TG, LDL) by chemical assays on a fully automated analyser system.

Statistical analysis: Results were analyzed by unpaired t-test, p-value was determined & Correlation coefficient was calculated amongst various parameters.

Results: Significant difference was noted in mean values of BMI (29.69±1.28 VS 23.47±1.09), waist / hip ratio (0.91±0.07 VS 0.79±0.05) and serum insulin (10.54±2.5 VS 5.94±1.53) ($p<0.01$) in cases as compared to controls respectively. Glucose levels were high in cases (89.58±8.0 mg/dl) as compared to controls (88.8±7.56 mg/dl) but the difference was statistically insignificant ($p=0.11$). Hyperinsulinemia was observed in 41 cases & 4 controls. Serum insulin highly correlated with Waist/ hip ratio (R=0.53) than BMI (R=0.26).

Conclusion: Study suggests Insulin; a simple, sensitive & independent cardiovascular risk predictor in obesity even with normal lipid profile with a potential to reveal hidden burden of metabolic dysfunction and offers a hope that, cardiovascular event can be well prevented with appropriate interventions.

Keywords: Cardiovascular disease, Obesity, Insulin resistance, Lipid profile, Serum insulin, Waist/ hip ratio

INTRODUCTION

Prevalence of obesity is increasing globally at an alarming rate, setting the scene for major epidemic of non communicable diseases like Cardio vascular disease (CVD), Type 2 Diabetes Mellitus (T2DM), Stroke and Hypertension worldwide [1]. Prevalence of obesity is on tremendous increase in Indians subsequent to the wave of industrialization and modernization. Asian Indians are at high risk of cardiovascular disease and have an insulin-resistant phenotype, characterized by low muscle mass, upper body adiposity and high percentage of body fat [2]. In the context of the rising prevalence of overweight and obesity in India, especially at a younger age, it is likely, that the burden of cardio metabolic complications developing in obese will create a major impact on subsequent morbidity and mortality.

Therefore screening of this group to evaluate the status of metabolic dysfunction so as to identify those at risk of further cardiovascular events becomes an important issue. Routine investigations like blood glucose level, lipid profile, blood pressure are often unaltered in the initial stage; they are deranged when cardiovascular dysfunction is already apparent and very little can be done in the benefit of patient. This necessitates the genuine need of some marker which is simple to incorporate as well as sensitive enough to recognize the high risk obese individuals for possible cardiac complications even before dyslipidaemia, hyperglycemia or hypertension are evident. Serum insulin has gained some attention in this respect. Because insulin resistance usually develops long before metabolic complications of obesity like dyslipidaemia, hyperglycemia, hypertension establish [3] identification of insulin resistance in apparently healthy population with normal lipid profile, normal glucose level & normal blood pressure offers a hope that some or the entire sequel of obesity and possible cardiovascular event can be prevented.

So the proposed study was designed to evaluate whether serum insulin can be an independent and sensitive predictor of future cardiovascular risk in apparently healthy overweight and obese population despite of normal lipid profile, normal blood pressure and normoglycemia. If effective interventions including lifestyle changes, moderate exercise and low calorie fiber rich diet are incorporated to these hyperinsulinemic but otherwise healthy population, when metabolic abnormalities are not yet apparent, it will definitely be useful to improve quality of life.

MATERIALS AND METHODS

This case control study was conducted in Department of Biochemistry during January 2010 to July 2011. Research protocol was approved by institutional ethical committee. Patients attending outpatient clinics for minor nonspecific ailments were selected in random manner. They were divided on the basis of body mass index as cases and controls. Hundred individuals having BMI > 25 with normal lipid profile (Total Cholesterol < 200 mg%, LDL < 100mg%, HDL > 60 mg % and TG < 150 mg % as per NCEP ATP III guidelines) were grouped as cases and 100 individuals with BMI = 18.5 – 24.99 were grouped as controls. All participants

	Cases: (n= 100) BMI > 25.0	Controls: (n= 100) BMI 18.5- 24.99	p-value
Age (Years)	25.59 ± 5.25	25.04 ± 6.22	0.77
Sex (M/F)	48 / 52	55 / 45	-
Weight (Kg)	78.24 ± 4.82	61.08 ± 6.00	< 0.01*
Height (M)	1.60 ± 0.05	1.61 ± 0.06	0.20
BMI (Kg/M^2)	29.69 ± 1.28	23.47 ± 1.09	< 0.01*
WC (Cm)	94.59± 5.82	76.48 ± 3.29	< 0.01*
HC (Cm)	100.85 ± 5.18	96.72 ± 7.4	< 0.01*
W/H Ratio	0.91 ± 0.07	0.79 ± 0.05	< 0.01*
SBP (mm Hg)	120.7± 5.76	118.18 ± 6.18	0.11
DBP (mm Hg)	79.22 ± 4.1	78.32 ± 4.25	0.20

[Table/Fig-1]: Comparison of demographic Characters in studied Groups., *: highly significant p-value

	Cases:(n=100) BMI > 25.0	Controls: (n=100) BMI =18.5- 24.99	p-value
Glucose (mg/ dl) (70 – 110)	89.58± 8.0	88.8± 7.56	0.11
Insulin (µU/ml) (0.7 – 9.0)	10.54± 2.52	5.94 ± 1.53	< 0.01*
Hyperinsulinemia	41	4	--

[Table/Fig-2]: Glucose, Insulin & Number of hyperinsulinemic individuals., *highly significant p value

	BMI	W/ H	INSULIN
Age	r = 0.33	r = 0.3	r = 0.325
BMI	-	r =0.21	r =0.26
W/ H		-	r =0.53*

[Table/Fig-3]: Correlation coefficients (r value) in cases: (BMI > 25.00)., ** : strong positive correlation*

were in the age group of 15 to 40 y. Written and informed consent was obtained from all participants. Those with history of smoking, alcoholism, medications that increase body weight (contraceptive pills, steroids), CHD, chronic renal disease, hypertension, T2DM, existing cardiovascular disease were excluded from the study.

Participants were asked to answer the Standard questionnaire which included detailed history, clinical examination and laboratory investigations. History of participants including age, sex, marital status, history of any medications, addictions was taken. Clinical examination consisted of Blood pressure (mm of Hg), weight (Kg), Height (meters), Body Mass Index (BMI), Waist circumference (WC), Hip circumference (HC) and Waist/Hip ratio.

Twelve hour fasting venous blood samples were collected from all participants in Fluoride and plane bulbs. Serum was separated after 1 h by centrifugation at 3000 rpm for 10 min, and was tested for following parameters. Serum Insulin was estimated by chemiluminescence's assay using Acculite master kit. Serum cholesterol, HDL and TG were estimated by kits from Reckon Diagnostics. Serum cholesterol estimated by using cholesterol oxidase peroxidase method. Serum HDL cholesterol estimated by using Phosphotungstic acid method. Triglycerides estimated by using lipase/Glycerokinase/G-P oxidase method. LDL calculated by Friedewalds formula. LDL= TC-(HDL± TG/5). Blood glucose level was estimated by glucose oxidase peroxidase method using kits from Erba Mannheim.

STATISTICAL ANALYSIS

The results were analyzed by appropriate statistical software, (OPEN EPI version 2.3). The results were interpreted as mean ± S.D., unpaired t test was applied for comparison between two groups and correlation coefficients were calculated (r value). p-value was obtained from t test and p< 0.05 was considered statistically significant. Positive and negative r-values were estimated to find out strength of correlation.

RESULTS

[Table/Fig-1] Comparison of demographic characters in studied Groups:

[Table/Fig-1] presents demographic characters of studied groups. MEAN age of participants does not differ significantly among the studied groups (p= 0.77). There is a highly significant difference in mean values of weight, BMI, waist circumference, hip circumference and waist/ hip ratios (p< 0.01).

[Table/Fig-2] Comparison of Glucose, Insulin & Number of hyperinsulinemic individuals:

Mean levels of Insulin are significantly increased in cases as compared to controls (p < 0.01). Still mean Glucose levels do not differ significantly (p= 0.11). Hyperinsulinemia was observed in 41 cases & 4 controls.

[Table/Fig-3] Correlation coefficients (r value) in cases: (BMI > 25.00) Age of participants is positively correlated with BMI, waist/ hip ratio & insulin. BMI is also positively correlated with W/H ratio & Insulin though the correlation is not significant. Waist/ Hip ratio shows significant positive correlation with Insulin. Thus Insulin shows stronger correlation with Waist/ Hip ratio than its corresponding correlation coefficient with BMI.

DISCUSSION

Exponential rise in prevalence of overweight and obesity in developed as well as developing countries drives a growing menace on health care systems. The traditional risk factors for CVD in obese individuals like dyslipidemia, hypertension, T2DM are well recognized and modifiable but significant proportion of cardiovascular events cannot be explained by these standard risk factors. As about half of MI patients are found to be having normal lipid profile status [4], the researchers are looking for the new markers to alert the patients for prevention of cardio vascular disease. Early detection and routine screening in an apparently healthy but obese population with simple tool becomes important and desirable. Insulin resistance developing in obesity is said to be common pathophysiological factor tying together a "syndrome" of cardio metabolic disturbances.

Insulin resistance in turn increases the risk of dyslipidemia, elevates blood pressure by enhancing sympathetic nervous system activity as well as increases the prevalance of T2DM [5]. It is insulin resistance that is the culprit in mediating serious metabolic derangements of obesity and chronic hyperinsulinemia per se is, at worst, an innocent bystander [6].

Because insulin resistance usually develops long before metabolic complications of obesity establish, identifying people with insulin resistance at this stage, offers the hope that some or the entire sequel of obesity can be prevented. Therefore, screening of apparently healthy obese population, with normal lipid profile, normal glucose and normal blood pressure with more sensitive marker is an important issue from preventive objective.

The findings of our study are in accordance with previous studies. In a study by Ele Ferrannini et al, W/H ratio increased with increasing BMI. Insulin sensitivity declined linearly with increasing BMI. WC and Waist/Hip ratio correlated well with insulin hyper secretion (P< 0.001). Insulin resistance was present in 26 % of obese individuals [7]. Ross Lazarus et al., in their study found positive correlation between weight, serum insulin, BMI and W/H ratio [8]. Fahim Abbasi concluded that, there is a strong positive correlation between BMI and insulin resistance (r= 0.465) and insulin resistance at given degree of obesity accentuates the risk of CHD and T2DM [9]. Insulin resistance statistically significantly increases the risk for type 2 diabetes and CVD in normal glucose tolerant individuals. For a given level of obesity, these metabolic abnormalities are clearly

accentuated in the most insulin-resistant tertile [10]. According to one study, mean plasma concentrations of lipids were not significantly associated with overweight, obesity, WHR or body fat. So it can be said that, such obese normolipidemic group presents an apparently silent but potentially high risk group often missed in clinical practice.

CONCLUSION

Overweight individuals with normal lipid profile, normal glucose levels and normal blood pressure represent a high risk group often missed in clinical practice. The addition of serum insulin to standard investigation panel may provide an earliest possible diagnosis of insulin resistance and thus subsequent cardiometabolic burden in apparently healthy but potentially high risk population and can be a simple, inexpensive, sensitive and independent marker to improve global risk prediction. Targeting these high risk individuals for primary preventive measures like lifestyle modifications may lead to favorable changes in subsequent outcomes with considerable input from health care professionals and total commitment from the patients.

Abbreviations used in the manuscript:

- T2DM:Type 2 Diabetes mellitus
- CVD: cardio vascular disease
- HDL: high density lipoprotein
- LDL: low density lipoprotein
- VLDL: very low density lipoprotein
- BMI: body mass index
- M.I.: myocardial infarction
- OCP: oral contraceptive pills
- HRT: hormone replacement therapy
- G- P oxidase: glycerol phosphate oxidase
- IR : Insulin Resistance

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PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Biochemistry, Terna medical college, Nerul, Navi Mumbai, Maharashtra, India.
2. Associate Professor, Department of Biochemistry, Government medical college, Aurangabad, Maharashtra, India.
3. Assistant Professor, Department of Biochemistry, Government medical college, Aurangabad, Maharashtra, India.
4. Ex Professor and Head, Department of Biochemistry, Govt Medical college, Aurangabad, India.
5. Assistant Professor, Department of Community Medicine, Government medical college, Nanded, Maharashtra, India.
6. Associate Professor, Department of Biochemistry, Lokmanya Tilak med college, Mumbai, Maharashtra, India.
7. Assistant Professor, Department of Biochemistry, Lokmanya Tilak med college, Mumbai, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Amruta A. Bakshi,
804, Orient Plaza, Sector 34/C, Plot Number:2, Kharghar, Navi Mumbai, Maharashtra, India.
Phone : +918879308141 / +918879308144, E-mail : dramrutabakshi@rediffmail.com

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