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Prevalence of insulin resistance in apparently normal population in rural Maharashtra

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Abstract
Obesity, particularly abdominal obesity, is associated with Insulin resistance. The associated hyperinsulinemia and hyperglycaemia and adipokines may also lead to vascular endothelial dysfunction, an abnormal lipid profile, hypertension, and vascular inflammation, all of which are the components of the metabolic syndrome. Metabolic syndrome is a multifactorial and insulin resistance appears to be the primary mediator of metabolic syndrome. The present study was undertaken to study the prevalence of insulin resistance in apparently healthy population.

The methods used to assess insulin resistance clinically were- 1. Insulin Sensitivity Index (ISI), 2. American Diabetes Association Score (ADA), 3. Finnish Diabetes Risk Score and 4. Indian Diabetes Risk Score (IDRS). The total number of patients studied was 150. After detailed medical history, each patient underwent laboratory investigations of urinalysis, Fasting Blood Sugar estimation, blood urea, serum creatinine levels and a fasting Lipid Profile. Metabolic syndrome was measured using ATP III revised criteria 2005. Insulin Resistance was calculated for all subjects using all four different methods and later results were compared with each other. The relationship of each risk factor with Insulin Resistance was also calculated and studied statistically. This study revealed significantly high prevalence of Insulin resistance in 40% of apparently normal individuals as measured by ISI method. It confirms the fact that high insulin resistance is the predecessor and precursor of the metabolic syndrome and can be and should be detected in normal individuals for implementing effective preventive measures.

Keywords: insulin resistance, metabolic syndrome, insulin sensitivity index, obesity

Introduction

Obesity, particularly abdominal obesity, is associated with resistance to the effects of insulin on peripheral glucose and fatty acid utilization, often leading to Type 2 Diabetes Mellitus. Insulin resistance, the associated hyperinsulinemia and hyperglycemia, and adipocyte cytokines (adipokines) may also lead to vascular endothelial dysfunction, an abnormal lipid profile, hypertension, and vascular inflammation, all of which are the components of the metabolic syndrome and promote the development of atherosclerotic cardiovascular disease (CVD) [1, 4]. A similar profile can be seen in individuals with abdominal obesity who do not have an excess of total body weight [5, 8]. Genetic predisposition, lack of exercise, and body fat distribution all affect the likelihood that a given obese subject will become overtly diabetic or develop CVD.

Metabolic syndrome is a multiplex risk factor that arises from insulin resistance accompanying abnormal adipose deposition and function. It is a risk factor for coronary heart disease, as well as for diabetes, fatty liver, and several cancers. Insulin resistance appears to be the primary mediator of metabolic syndrome [9] and therefore there is unquestioned need to identify and manage insulin resistance to decrease morbidity and mortality associated with metabolic syndrome, diabetes mellitus and cardiovascular disease [10, 11]. The present study was undertaken to study the prevalence of insulin resistance in apparently healthy population. Following methods were used to assess insulin resistance clinically-

1. Insulin Sensitivity Index (ISI)
2. American Diabetes Association Score (ADA)
3. Finnish Diabetes Risk Score
4. Indian Diabetes Risk Score (IDRS)

This study has used all these four methods for assessment of Insulin Resistance and also has compared their results. These methods are easy, effective and convenient. They provide quantitative as well as qualitative assessment of degree of Insulin Resistance in patient studied. Since all of these individuals included in the study are apparently healthy persons attending health check-up, the presence of metabolic syndrome and the estimation of insulin resistance provides them strong motivation to undertake lifestyle measures to forestall progression to overt diabetes mellitus. In other words, it provides a "*Real Value Information*" to a clinically "*Normal Individual*" about pre-clinical metabolic dysfunction. Indeed, such is the raison d'être of the preventive health check-up.

Aims and objectives

This study was conducted with aim to

1. To measure prevalence of Insulin Resistance in apparently normal population attending Medicine OPD.
2. To analyse risk factor profile of the patients with respect

to Insulin Resistance.
3. To Estimate the burden of Insulin Resistance in the population and value of application of this criteria to forestall progression of metabolic syndrome to overt cardiovascular disease and Type-2 diabetes mellitus.

Material and Methods

Study Design

- The present study was carried out at Department of Medicine, DVVPF's Medical College during Jan 2016 to July 2016. The total number of patients studied was 150.
- Inclusion Criteria: Age> 18 yrs and all of them were not previously known to have diabetes or hypertension or any significant disease or disorder.
- Exclusion Criteria: All patients, those who were found to have valvular heart disease, cardiomyopathies with pathological q - waves on ECG, Known cases of Ischemic Heart disease, Renal disease, Liver disease, Pregnancy, and women on contraceptives.

Methodology

A detailed medical history of the patient including symptomatology, details of past illnesses, occupation, illnesses in the family and other co-morbid illnesses were obtained. A complete physical and cardiovascular examination was performed including Blood pressure and anthropometrical measurements. Height was recorded to the nearest cm. without foot wear; weight was obtained on a regular weighing scale and recorded to the nearest five hundred grams with the lightest of clothing. BMI was calculated in each of them. Fundoscopic examination was performed on each patient.

Biochemical Investigations Each patient underwent laboratory investigations of urinalysis, fasting blood sugar estimation, blood urea, serum creatinine levels and a fasting Lipid Profile.

Metabolic syndrome was assessed using ATP III revised criteria 2005 (Table 1)

Calculation of Insulin Resistance Insulin Resistance was calculated for all subjects using all four methods and later results were compared with each other. The relationship of each risk factor with Insulin Resistance was also calculated and studied statistically.

The four different insulin resistance scores used were

I. Insulin Sensitivity Index (ISI)
II. American Diabetes Association Score (ADA)
III. Finnish Diabetes Risk Score
IV. Indian Diabetes Risk Score (IDRS)

I) Insulin Sensitivity Index (ISI)

This was calculated using the standard Nomographs prepared by Berglund L., Lithell H.et al. [12] It uses Subscapular skin fold thickness, waist circumference and Serum triglycerides and the standard Nomographs to calculate ISI. This method was initially studied to calculate insulin resistance in PCOS patients, later a scale and nomographs were developed using the standard Hyperinsulinemic Euglycaemic clamp method. These Nomograms can be used to calculate the insulin sensitivity index for general population. (Nomogram showing the relationship between waist girth and the insulin sensitivity index for different values of serum triglycerides).

II) American Diabetes Association (ADA) Score [13]

This score is calculated by asking a standard questionnaire to the patient (Table 2).

III) Finnish Diabetes Risk Score [14]

This was also calculated using a similar questionnaire as ADA Score (Table 3).

IV) Indian Diabetes Risk Score (IDRS) [15]

Insulin Resistance was studied using IDRS score which includes Age, Physical Activity, Abdominal Obesity and Family history (Table 4). Score is 72.5% sensitive and 60.1% specific in detecting Insulin Resistance.

Statistical Analysis

The collected data was analysed statistically and tested for significance.

Observation & Results

Age and Sex Distribution Maximum patients were in 20-39 years of age, while less number of patients are there from both extremes of age. Out of these, 95 (63%) were male patients and 55 (37%) were female (Table 5).

Prevalence of insuline resistance Insulin resistance was calculated using 4 methods.

Most important one is by measuring Insulin sensitivity index through Nomogram developed by comparing gold standard hyper-insulinemic euglycemic clamp method. According to ISI, 40 patients out of 100 having high Insulin resistance. High insulin resistance is defined as ISI < 6.3, while ISI > 6.3 suggest lower insulin resistance.

As insulin resistance measured in this study revealed higher number of patients having high insulin resistance (40%). It indicates that insulin resistance measurement by ISI is a more sensitive tool. Kristen A. McAuley also counted 41% of population with high insulin resistance by this method [16] it also proves that insulin resistance develops much earlier than the actual development of Metabolic Syndrome. It also emphasizes that moderate level of insulin resistance when found in apparently normal person should not be ignored as these patients are at major risk of developing Metabolic Syndrome in future. Insulin resistance by rest of the three methods also has been calculated and compared with the ISI method in Table 6. As is evident, Finnish score being less sensitive but more specific, while ADA score and Indian Diabetic Score results are comparable to ISI results. IDRS was found 72.5% sensitive and 60.1% specific if cut off value is $\geq$ 60, to detect undiagnosed diabetics in CURE study at Chennai in 2005 having 42.9% of patients with high insulin resistance [15].

Age Distribution and Prevalence of Insulin Resistance Bar diagram 1 shows that insulin resistance is higher in older people. NHANES III study in US population also shows increase prevalence of insulin resistance with increase in age [17].

Gender and Prevalence of Insulin Resistance Bar Diagram 2 suggest high prevalence of insulin resistance in female population (49%) than in male population (35%). Study done by Ramchandran *et al.* and P. Rastogi and R. Gupta also suggested that Indian woman have higher prevalence of metabolic syndrome and Insulin Resistance among females (39.9%) in comparison to males (22.9%) [18].

Obesity and Prevalence of Insulin Resistance There is very high prevalence of insulin resistance in obese patients (BMI > 30 kg/m^2) suggesting that obesity is an important risk factor (Bar Diagram 3). Rastogi and Gupta also showed steep rise in the prevalence of metabolic syndrome & insulin resistance in obese patients [19].

Prevalence of Insulin Resistance as per Waist Size Obesity also can be defined by high waist circumference and it is a better tool to measure central obesity. According Madras Diabetic Research Centre, 2007 the cut off value of the waist size for Indian population is > 87 cm for man and > 82 cm woman. The same criterion has been used in our study. The obese individuals with high waist circumference shows 81% prevalence of high insulin resistance as compared to 21% among non- obese group. Our results are in concordance with the study by Rastogi and Gupta.

Blood Pressure and Prevalence of Insulin Resistance JNC 8 guidelines have been used to divide patients into 2 sub-groups depending upon their blood pressure. The 2 sub-groups were - hypertensives and non-hypertensives with blood pressure level > 150 or > 90 & < 120 and < 80 mmHg respectively. The prevalence of insulin resistance was high among hypertensives patients. Insulin Resistance is now considered as one of the causative factor for development of essential hypertension and hypertension is one of the important criteria for presence of metabolic syndrome. Kotchen also shows high prevalence of insulin resistance (72%) in hypertensive group [20].

Fasting Blood Sugar: In our Study mean Fasting blood sugar of patients with Low IR is 86 and in High IR mean Fasting blood sugar is 103 mg/dl. According to ATP III criteria FBS >100 mg/dl required for metabolic syndrome. As depicted in bar diagram 5, the patients with high insulin resistance had mean FBS value 103.16 mg/dl, which is similar to revised ATP III criteria, where FBS level is decreased to 100 mg/dl for presence of metabolic syndrome. High mean value of FBS is statistically significant (P<0.01) in patient with metabolic syndrome and high insulin resistance (Bar Diagram 5).

Lipids and Insulin Resistance This study revealed direct correlation of LDL cholesterol and Triglycerides with high Insulin resistance and inverse correlation between HDL cholesterol and Insulin resistance. The role-of triglycerides had always been under estimated in causing Coronary Artery Disease and IHD, until the concept of insulin resistance and metabolic syndrome came, which gave this laboratory investigation its real value. In our Study mean Triglycerides of patients with Low IR is 125 mg/dl and in High IR mean Triglycerides is 156 mg/dl (P < 0.01) (Bar Diagram 6). The mean HDL cholesterol level of patients with Low IR is 55 mg/dl and in those with High IR mean HDL cholesterol level was 48 mg/dl (P < 0.01) (Bar Diagram 7). HDL cholesterol was found to be a negative risk factor, as has been mentioned in ATP - III guidelines as well. The mean LDL cholesterol of patients with Low IR is 134 mg/dl and in High IR mean LDL cholesterol was 148 mg/dl (P < 0.05) (Bar Diagram 8). These values indicate that role of triglycerides and HDL cholesterol is more important than LDL cholesterol in metabolic syndrome and insulin resistance.

Table 1: ATP III criteria for metabolic syndrome

ATP III Diagnostic criteria for the Metabolic Syndrome		
Risk Factor		**Defining Level**
Abdominal obesity (waist circumference)	Men	>102 cm
	Women	>88 cm
Triglycerides		>150mg/dL
HDL cholesterol	Men	<40 mg/dL
	Women	<50 mg/dL
Blood pressure		>130/80 mmHg
Fsting glucose		>100 mg/dL

Nomogram indicating the relationship between waist girth and the insulin sensitivity index for different values of serum triglycerides

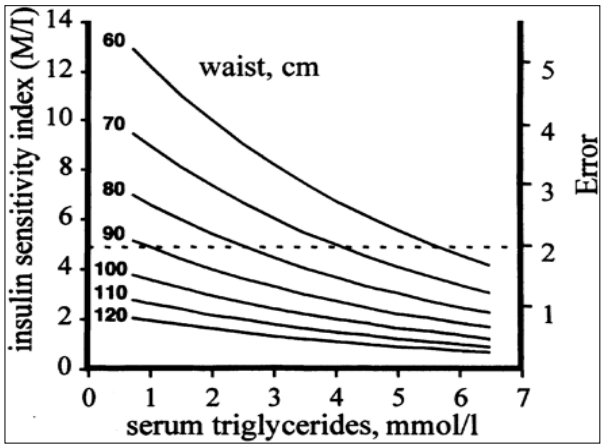

Fig 1

Table 2: ADA risk score

S. No	Question	Yes	No
1.	My weight is equal to or above that listed in the BMI chart?	5 pts.	0 pts.
2.	I am under 65 yrs. of age and I get little or no exercise during a usual day?	5 pts.	0 pts.
3.	I am between 45 and 64 yrs. of age?	5 pts.	0 pts.
4.	I am 65 yrs. old or older?	9 pts.	0 pts.
5.	I am a woman who has had a baby weighing more than nine pounds a birth?	1 pt	0 pts.
6.	I have a sister or brother with diabetes?	1 pt	0 pts.
7.	I have a parent with diabetes?	1 pt	0 pts.

Scoring 3-9 points – Low risk of having Insulin Resistance at present but follow up required.
Scoring 10 or more points – High risk of having Insulin Resistance

Table 3: Finnish diabetes risk score

Variables		Score
Age	45 – 54	2
	≥ 55	3
BMI (Kg/m^2)	>25 to ≤30	1
	>30	3
Waist circumference (cm.)	Men, 94 to <102; Women, 80 to <88	3
	Men, ≥102; Women ≥88	4
Have you ever used drugs for high blood pressure?	Yes	2
	No	0
Has a Physician ever told you have high blood sugar?	Yes	5
	No	0
Do you exercise at least 30 min. on most days?	Yes	0
	No	2
How often do you eat vegetables, fruits or berries?	Every Day	0
	Not Every Day	1

Score <9 – Signifies Low level of Insulin Resistance
Score ≥10 – Signifies High level Insulin Resistance

Table 4: Indian diabetes risk score

Particulars		Score
Age (yrs.)	<35	0
	35 – 49	20
	≥50	30
Abdominal Obesity	Waist <80 cm (Female), <90 cm (Male)	0
	Waist ≥80 – 89 cm (Female), ≥ 90 – 99 cm (Male)	10
	Waist ≥90 cm (Female), ≥100 cm (Male)	20
Physical Activity	Exercise (Regular) + strenuous work	0
	Exercise (Regular) or strenuous work	20
	No Exercise or sedentary work	30
Family History	No Family history	0
	Either Parents Diabetic	10
	Both Parents Diabetic	20

Score <60 – Low level of insulin Resistance
Score ≥60 – High level of insulin Resistance

Table 5: Age and sex distribution

Age group (in yrs)	No. of patients
< 20	12
20-39	75
40-59	33
≥ 60	30
Male	95
Female	55
Total	150

Table 6: Insulin resistance as calculated by different methods

Insulin resistance	ISI	ADA Score	Finnish Score	Indian Diabetes Score
Low resistance	90	89	114	98
High resistance	60	61	36	52
Total	150	150	150	150

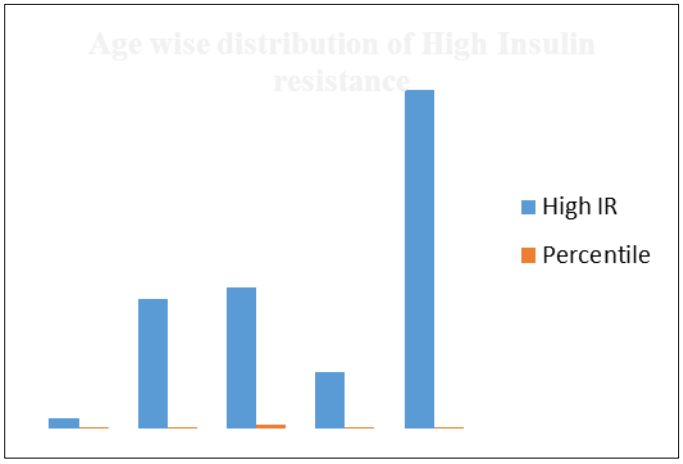

Fig 2: Age wise distribution of insulin resistance

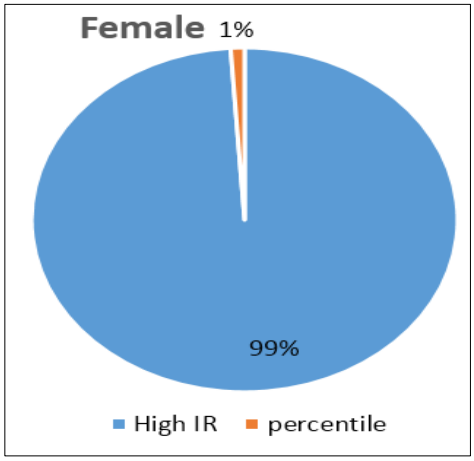

Fig 3: Gender wise prevalence of insulin resistance

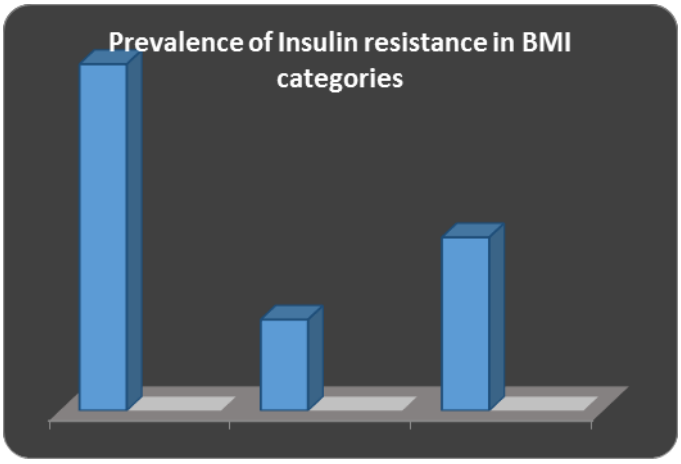

Fig 4: Prevalence of insulin resistance in BMI categories

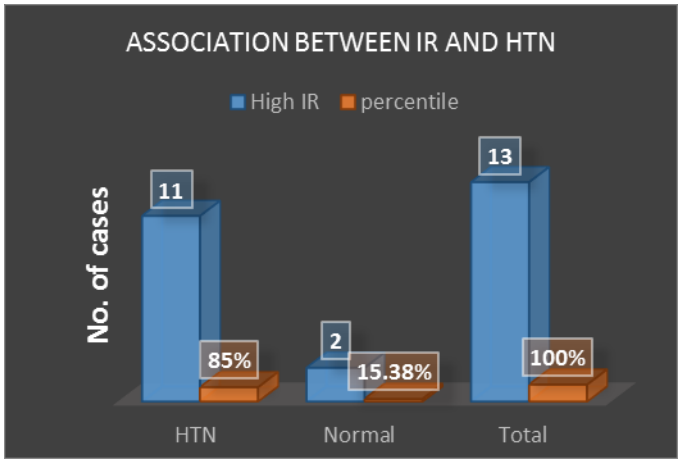

Fig 4: Association between hypertension and insulin resistance

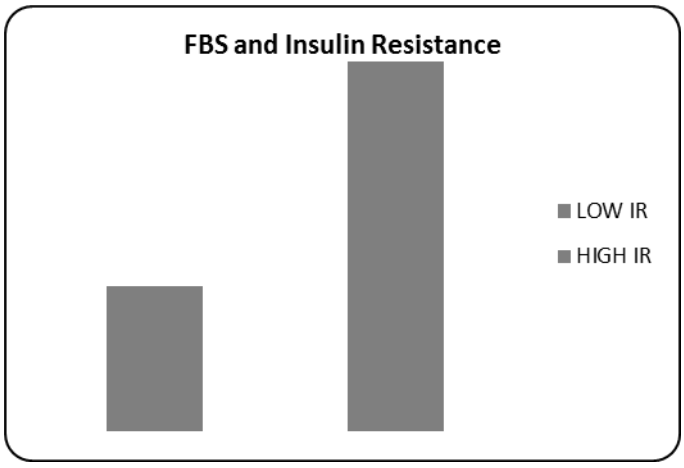

Fig 5: FBS and insulin resistance

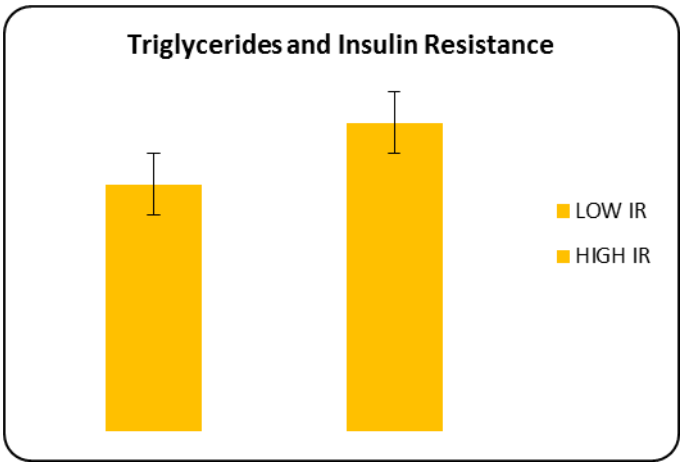

Fig 6: Triglycerides and insulin resistance

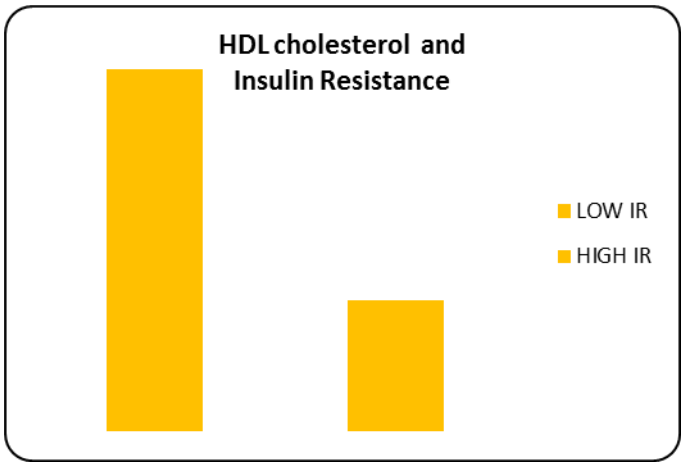

Fig 7: HDL cholesterol and insulin resistance

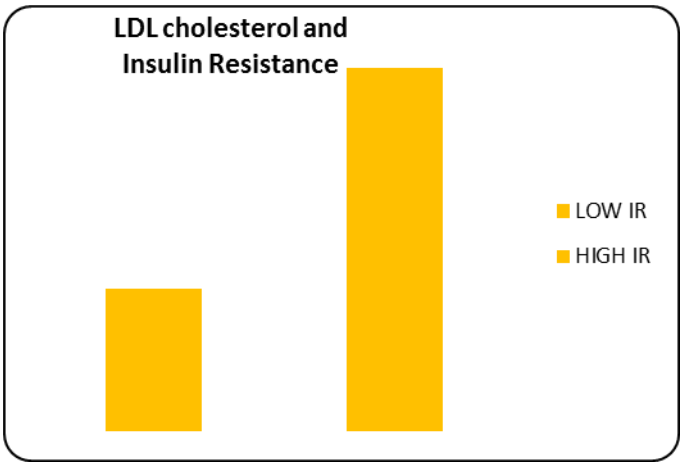

Fig 8: LDL cholesterol and insulin resistance

Conclusion

This study revealed significantly high prevalence of Insulin resistance in 40% of apparently normal individuals as measured by ISI method. It confirms the fact that high insulin resistance is the predecessor and precursor of the metabolic syndrome and can be and should be detected in normal individuals for implementing effective preventive measures. The presence of insulin resistance found higher in the hypertensive group as compare to pre- hypertensive and non-hypertensive group. Insulin resistance is highly prevalent obese individuals. The central obesity, measured by waist circumference, is specially a very important risk factor for metabolic syndrome and insulin resistance.

The scoring systems used for assessing the insulin resistance are based on clinical criteria, so can be useful for screening of general population as they do not require any costly or special investigations. They can be easily incorporated in the health check-up schemes in hospitals for healthy individuals. Investigations and anthropometric measurements required for these methods are simple and can be done anywhere. The individuals with objective documentation of high insulin resistance will further motivate them to institute lifestyle modification measures, aimed at prevention of diabetes and atherosclerosis.

The statistical analysis of the study results revealed contributing factors for the development of insulin resistance and subsequently of metabolic syndrome are aging, obesity, large waist circumference, hypertension, high fasting blood sugar, high serum triglyceride and LDL cholesterol and low HDL cholesterol level in blood.

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