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Original Article

Insulin resistance in nonobese, euglycemic and normotensive first-degree relatives of individuals with obesity

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Abstract

Insulin resistance (IR) is reportedly high in individuals with obesity and relatives of patients with diabetes. However, there is a paucity of data on its prevalence in first-degree relatives of obese individuals. The study aimed to determine whether non-obese, normotensive and euglycemic first-degree relatives of obese individuals differ in IR from controls. This cross-sectional study compared 35 first-degree, nonobese, normotensive, euglycemic relatives of obese individuals with 35 age, gender, and body mass index (BMI) matched first-degree relatives of normotensive, euglycemic, nonobese individuals. More than 1/3rd of subjects in the study group had IR as compared to the control group [34% (95% CI: 21–51) *vs.* 14% (6–9); p=0.05]. It highlights an important trend of higher IR in first-degree relatives of the at-risk populations. Hyperinsulinemia was also higher in the study group (37% *vs.* 17%). Impaired fasting glucose (IFG) and serum insulin levels were higher in the group with IR [47% *vs.* 9.4%; p=0.001 (IFG) and 184 *vs.* 114 (serum insulin); p<0.0001). We observed a high proportion of healthy relatives of individuals with obesity to have IR. There is a need to closely monitor these apparently healthy individuals for the development of diabetes mellitus. Our findings are exploratory and provide novel information that needs further confirmation.

Keywords: obesity, insulin resistance, diabetes mellitus, relative.

Introduction

The association of obesity with Diabetes Mellitus (DM) has been well described, and insulin resistance (IR) is an important risk factor for its development in this population [1]. Ineffective utilization of insulin, despite its adequate production, characterizes the clinical entity of Insulin resistance. The prevalence of insulin resistance is reported to range between 3.1–44% in various population-based studies of children and adolescents [2]. Over time, IR progresses to the development of prediabetes and diabetes mellitus due to the inability of beta cells to respond to the increasing demands of the body for insulin [3]. There is also evidence to suggest that IR and hyperinsulinemia are not only associated with obesity but can contribute to its development [4].

While IR is mostly documented in individuals with obesity when they present with complications such as hypertension or diabetes as part of their workup, it is also observed in lean individuals. Most people with IR are unaware of this condition until they develop type 2 diabetes, a serious lifelong disease. Since IR has been shown to cause various cardiometabolic diseases independent of other risk factors, it becomes important to identify apparently normal individuals with IR [4]. Early recognition of IR can also help closely monitor the individual for the development of DM, and necessary lifestyle changes may be implemented. While it is important to identify such individuals, there is a dearth of studies targeting the normal population or even the first-degree relatives of the affected population [5–8]. There are no studies that have estimated the IR prevalence in healthy first-degree relatives of individuals

with obesity. Our study aimed to determine the prevalence of IR in first-degree, nonobese, normotensive and euglycemic relatives of obese individuals.

Material and methods

Study design and setting

The study had a cross-sectional design and was conducted at a referral Academic hospital in India after obtaining Institutional ethical clearance. It was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association after having obtained informed consent from all the participants.

Participants, inclusion, and exclusion criteria

The "study group" comprised previously healthy individuals who were not obese, had normal blood glucose levels, were non-hypertensive and were first-degree relatives of nondiabetic, normotensive and obese individuals aged >18 years. The "control group" comprised of gender, age, and body mass index (BMI) matched previously healthy, euglycemic, normotensive, nonobese, first-degree relatives of nondiabetic, normotensive nonobese individuals.

We excluded those with a known history of diabetes, hypertension, polycystic ovarian disease, hyperlipidemia, stroke, myocardial infarction, severe sepsis, on steroids and other drugs influencing levels of glucose in blood. Those with a known history of hypertension or diabetes in the family and those refusing to participate in the study were also excluded.

Objectives

Our objective was to determine the prevalence of IR, and the definition used was the value of the homeostasis model assessment-estimated insulin resistance (HOMA IR), which exceeded the 75th percentile for our study population.

Study definitions

The definitions used in the current study were:

1. First-degree relative: A parent, brother, sister, or child of the patient [9];
2. Body Mass Index (BMI): obtained by dividing the weight of the person (kilograms) by the square of height (meters);
3. Obesity: BMI ≥30 kg/m^2 [10];
4. Insulin resistance: Insulin resistance was defined as HOMA IR values that exceeded the 75th percentile of our study population [11];
5. Hypertension: On anti-hypertension medications or blood pressure ≥140/90 mm Hg [12];
6. Diabetes: Fasting blood glucose ≥126 mg/dL (7.0 mmol/L) or 02-hour plasma glucose >200 mg/dL (11.1 mmol/L) or HbA1C ≥6.5% or random plasma glucose >200 mg/dL (11.1 mmol/L) with symptoms of hyperglycemia [13];
7. Impaired fasting glucose (IFG): Fasting blood glucose level between 100–126 mg/dl [13];
8. Impaired glucose tolerance (IGT): Two-hour postprandial blood glucose level between 140–200 mg/dl [13];
9. Physical inactivity: Less than ten minutes of activity at a stretch, during work, leisure, or transport.

Study methods

Enrolment

All first-degree relatives accompanying obese individuals to the outpatient department were eligible for participation. They were screened for insulin resistance as per protocol. As for the control group, similar age, gender, and BMI-matched first-degree relatives accompanying the individuals without obesity to the outpatient department were invited.

Data collection

Baseline variables, including age, gender and anthropometric variables, were collected. Blood pressure was measured on two separate occasions, and both values were averaged. After an overnight fast of >8h, blood samples were collected to estimate serum insulin, blood glucose, and serum lipid levels. Seventy-five-gram glucose was given to all those enrolled, and blood glucose levels were obtained after 2 hours post glucose plasma. The hexokinase enzymatic method was used to estimate plasma glucose levels, whereas radioimmunoassay (RIA) was used to measure serum insulin levels. In each patient, the degree of IR was estimated at the baseline by HOMA. The insulin resistance score (HOMA-IR) was computed using the HOMA-2 calculator. The HOMA IR values that exceeded the 75th percentile of our study participants were considered to have insulin resistance. This value was considered

because of the lack of any definitive cut-off value of HOMA-IR for defining IR. Individuals found to have insulin resistance were counseled individually about the need to follow up regularly, and necessary dietary and lifestyle modifications were advised.

Sample size estimation

Various population-based studies have reported a 3–46% prevalence for insulin resistance [14, 15]. Assuming a prevalence of 30% in first-degree relatives of obese individuals, a precision of 10% and 80% statistical power, 35 individuals were needed to be enrolled in each group.

Statistical analysis

Data was entered into Microsoft Excel 2013 and analyzed using Stata 11 (Stata Corp, College Station, TX). Categorical data was presented as number (%) while continuous variables were presented as mean (SD) if normally distributed and median (interquartile range) if skewed. Statistical analysis was performed using the Student's t-test/Wilcoxon rank sum test and Chi-square test for continuous and categorical variables. P-values of <0.05 were considered significant.

Results

A total of 35 subjects were enrolled in the study group, and an equal number of age, sex and BMI-matched subjects were enrolled in the control group. Table 1 shows the baseline characteristics, which were comparable in both groups. Males comprised 57% of the enrolled subjects in both groups with a mean (SD) age of 31±10 years. The mean (SD) BMI was 22.7±3 in both groups, and the percentage of overweight and underweight individuals was similar in both (Table 1).

The prevalence of insulin resistance was higher in the study group as compared to the control group [34% (95% CI: 21 to 51) *vs.* 14% (6 to 9); p=0.05]. The levels of HOMA IR levels were 2.5±0.7 and 2.2±0.6 in the study and control groups, respectively. The "study group" had a higher percentage of individuals with impaired GTT in comparison to the "control group" [23% *vs.* 9%; OR: 2.67 (0.77 to 9.23)] (Table 2). Increased insulin levels were also seen in more subjects in the "study group" compared to the "control group", although it was not found to be statistically significant (37% *vs.* 17%; p=0.06). The lipid profile parameters were similar in both groups (Table 2).

A total of 17 subjects belonging to both groups had insulin resistance. Table 3 compares the laboratory and demographic profiles of those with and without IR. Males constituted 71% of subjects with insulin resistance where, whereas it was 53% of subjects without insulin resistance. There were no differences in other demographic characteristics, such as age and BMI. The mean fasting blood glucose was higher in the group with insulin resistance compared to those without insulin resistance (98 *vs.* 88 gm/dL, p=0.002).

Similarly, the postprandial blood glucose levels were also higher in those with IR than those without IR (128 *vs.* 121 gm/dL, p=0.05). A similar trend was observed for serum insulin levels, which was found to be higher in the group with IR in comparison to those without IR (184 pmol/L *vs.* 114 pmol/L, p<0.0001). The difference in HDL levels (lower in those with IR), LDL levels (higher in those with IR), triglyceride or total cholesterol between the groups did not reach the level of statistical significance (Table 3).

Discussion

In this study comparing nonobese, nondiabetic, non-hypertensive first-degree relatives of individuals with and without obesity, we observed more than 1/3rd (34%; 95% CI: 21 to 51) of the first-degree relatives of

Table 1: Baseline characteristics of the study population.

Variables	Relatives of obese individuals (n=35)	Relatives of nonobese individuals (n=35)	P-value
Age in years[Mean (SD)]	31 (10)	31 (10)	0.9
Gender (male) (n, %)	20 (57%)	20 (57%)	1.00
BMI [Mean (SD)]	22.7 (3)	22.7 (3)	0.6
Overweight (n, %)	10 (29%)	10 (29%)	1.00
Underweight (n, %)	7 (20%)	7 (20%)	

Note: BMI – Body Mass Index; RR – Relative Risk; CI – Confidence Interval; SD – Standard Deviation.

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Table 2: Comparison of insulin resistance and other biochemical parameters in the study groups.

Variables	Relatives of obese individuals (n=35)	Relatives of nonobese individuals (n=35)	RR (95% CI)	P-value
HOMA IR (Mean, SD)	2.5 (0.7)	2.2 (0.6)	-	0.07
Insulin resistance (n, %,)	12; 34 (21–51)	5; 14 (6–9)	2.4 (0.94–6.09)	0.05
Fasting glucose in mg/dL (Mean, SD)	92 (13)	89 (10)	-	0.51
Impaired fasting glucose (n, %)	9 (26)	4 (11)	2.25 (0.76–6.62)	0.14
PP glucose in mg/dL (Mean, SD)	124 (16)	121 (12)	-	0.12
Impaired PP glucose (n, %)	8 (23)	3 (9)	2.67 (0.77–9.23)	0.11
Serum insulin in pmol/L (Mean, SD)	139 (38)	123 (33)	-	0.12
Increased serum insulin (n, %)	13 (37%)	6 (17%)	2.17 (0.93–5.05)	0.06
HDL in mg/dL (Mean, SD)	41 (12)	41 (14)	-	0.80
Low HDL	28 (80%)	27 (77%)	1.04 (0.81–1.33)	0.78
High HDL	2 (6%)	2 (6%)	1 (0.15–6.71)	0.99
LDL in mg/dL (Mean, SD)	94 (26)	95 (21)	-	0.71
LDL high	1 (3%)	0	1 (0.27–3.69)	0.5
TG level in mg/dL (Mean, SD)	130 (28)	133 (21)	-	0.34
Cholesterol in mg/dL (Mean, SD)	160 (40)	163 (23)	-	0.27

Note: Values are expressed as n (%) unless specified otherwise; SD – Standard Deviation; HOMA – Homeostatic Model assessment; PP – Post Prandial; IR – Insulin Resistance; TG – Triglycerides; HDL – High Density Lipoproteins; LDL – Low Density Lipoproteins; RR – Relative Risk; CI – Confidence Inter.

Table 3: Comparison of demographic and biochemical parameters between those “with” and “without” insulin resistance.

Variables	Insulin resistance (n=17)	No insulin resistance (n=53)	RR (95% CI)	P-value
Age (Mean, SD)	32 (12)	32 (9)	-	0.91
Male gender	12 (71%)	28 (53%)	1.34 (0.89–1.99)	0.19
BMI (Mean, SD)	22.2 (3)	22.7 (3.8)	-	0.67
HOMA IR (Mean, SD)	3.4 (0.1)	2.1 (0.38)	-	0.07
Fasting glucose in mg/dL	98 (13)	88 (11)	-	0.002
Impaired fasting glucose	8 (47%)	5 (9.4%)	5.01 (1.88–13.22)	0.001
PP glucose in mg/dL (Mean, SD)	128 (16)	121 (14)	-	0.05
Impaired PP glucose (n, %)	5 (29%)	6 (11%)	2.6 (0.91–7.45)	0.07
Serum insulin pmol/L (Mean, SD)	184 (6)	114 (24)	-	<0.0001
Increased serum insulin (n, %)	17 (100%)	2 (4%)	26.5 (6.81–103.2)	<0.0001
HDL in mg/dL (Mean, SD)	38 (12)	42 (13)	-	0.23
Low HDL	14 (82%)	41 (77%)	1.06 (0.82–1.40)	1.00
High HDL	3 (6%)	1 (6%)	9.35 (1.04–84.1)	
LDL in mg/dL (Mean, SD)	98 (30)	94 (22)	-	0.48
LDL high	0	1 (2%)	1	0.75

Table 3: Continued.

Variables	Insulin resistance (n=17)	No insulin resistance (n=53)	RR (95% CI)	P-value
TG in mg/dL (Mean, SD)	135 (29)	131 (24)	-	0.62
Cholesterol in mg/dL (Mean, SD)	163 (38)	161 (31)	-	0.8

Note: Values are expressed as n (%) unless specified otherwise; SD – Standard Deviation; HOMA – Homeostatic Model Assessment; PP – Post Prandial; IR – Insulin Resistance; TG – Triglycerides; HDL – High Density Lipoproteins; LDL – Low Density Lipoproteins; RR – Relative Risk.

individuals "with obesity" had insulin resistance compared to 14% (95% CI: 6 to 9) of the relatives of individuals "without obesity". Ours is the first study to report the prevalence of Insulin resistance in healthy first-degree relatives of individuals with obesity who are non-diabetic through the distribution of HOMA-IR, which is a validated measure of insulin resistance.

The reported prevalence of IR varies for various ethnicities and races. Insulin resistance is found to be higher for Asian Indians than for Caucasians. The reported prevalence of IR in the Mexican population is 3%, and in the Japanese population, it is reported to be 1.6% [16, 17]. In a previous study of 1070 subjects from India, Deepa *et al.*, insulin resistance was observed in 11.2% (95% CI: 9.4 to 13) [18]. The authors reported on the prevalence of insulin resistance syndrome, which is the presence of insulin resistance in combination with at least two of the following conditions: hyperglycemia, hypertension, dyslipidemia, or central body obesity. On evaluation of various factors, higher socio-economic strata and age were found to be associated with insulin resistance syndrome in the study. We did not include those with risk factors. We wanted to evaluate the prevalence of IR only as we wanted to explore the hypothesis that first-degree healthy relatives of obese individuals may be at increased risk for insulin resistance. This is because lifestyle, environmental factors, and genetic profiles are common to these individuals, even if they are apparently healthy. Such screening is important because it may help initiate changes in their lifestyle and environment early, thereby preventing progression to insulin resistance syndrome or diabetes.

The fact that IR may progress to diabetes mellitus or may be associated with other metabolic and clinical abnormalities is well known. A higher prevalence of Insulin resistance has been reported in the first-degree relatives of patients with diabetes mellitus. Various studies have reported the prevalence of IR in first-degree relatives of type 2 diabetes patients. Volk *et al.*, in their study of healthy first-degree relatives of type-2 diabetes mellitus patients, reported a prevalence of 40% [19]. Isomaa *et al.* reported a prevalence of 25% in their study of normoglycemic relatives of type-2 diabetes mellitus patients [20]. Arvind *et al.*, in their study, also showed a higher prevalence of insulin resistance in first-degree relatives of individuals with obesity (43.8%) than in controls (15.2%). Since insulin resistance is associated with obesity and *vice-versa*, it becomes even more important to find out the prevalence of insulin resistance in the so-called healthy population, *i.e.*, the first-degree relatives of individuals with obesity who are Normotensive, nondiabetic and nonobese.

Insulin resistance has been reported to be associated with increased fasting insulin levels, as it is thought to be a physiological abnormality. Our study findings also highlight this association, as we observed that all subjects with IR in the study group had raised fasting serum insulin levels (139 pmol/L in the study group as compared to 123 pmol/L in the control group). Similar findings were reported by Arvind *et al.* in relatives of type 2 diabetes patients. The proportion of subjects with hyperinsulinemia in our study was 37% in the study group as compared to 17% in the control group.

People with IGT and IFG are at an increased risk of developing diabetes. We observed that the proportion of subjects with impaired fasting glucose and IGT was higher in the study group than in the control group, even though the difference was not statistically significant. The observed prevalence is similar to the overall crude prevalence of IGT reported (age-standardized: 10.2%) in the CURES study [21]. There was no association of IR with BMI, age or lipid profile in our study, probably because we enrolled healthy nonobese individuals.

The strengths of our study are that it is the first attempt to explore the hypothesis of higher prevalence of IR in healthy first-degree relatives of individuals "with obesity" as compared to healthy first-degree relatives of individuals "without obesity". It paves the way for future studies to evaluate the need for screening of at-risk healthy populations.

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The major limitations of our study are that it is a single-center study and that the sample size was small, as it was a hypothesis-generating study. Our findings are exploratory and provide novel information that needs further confirmation.

Conclusion

We observed a high proportion of healthy relatives of individuals with obesity to have insulin resistance. In the future, these apparently healthy individuals need to be closely monitored for the development of diabetes mellitus. Our findings are exploratory and provide novel information that needs further confirmation.

Conflict of interest

The authors declare no conflict of interest.

Ethics approval

The approval for this study was obtained from the Ethics Committee of ESIC Medical College, Faridabad (approval ID: 134/A/11/16/Academics/MC).

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