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MARKERS OF INSULIN RESISTANCE AND METABOLIC SYNDROME IN NORMAL WEIGHT ADOLESCENTS

Clinical Research

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ABSTRACT

The prevalence of insulin resistance (IR) is rising rapidly in adolescents. However, the risk predictors of IR are less established in adolescents, and the studies reporting the prevalence of IR in normal-weight adolescents are scanty in the literature. Therefore, a cross-sectional observational study was carried out, including eighty apparently healthy normal, weight adolescents aged 10-19 years, to investigate the markers of IR and estimate the prevalence of IR. The study demonstrated the prevalence of insulin resistance and metabolic syndrome in normal-weight adolescents. Cutaneous markers, waist circumference, waist-to-hip ratio, plasma insulin, serum triglycerides, HDL, and ALT levels were identified as markers of IR. To conclude, normal BMI and euglycemia do not overrule insulin resistance. All adolescents should be screened thoroughly for the presence of markers of Insulin resistance. The risk predictors of IR can also be employed to predict cardiovascular risk in adolescents. Therefore, all insulin-resistant individuals and those at risk should be further screened for the components of metabolic syndrome.

KEYWORDS

Insulin resistance; Adolescents; Non-obese; Insulin; HOMA IR; Metabolic syndrome.

INTRODUCTION

Insulin resistance (IR) is diminished tissue responsiveness to insulin-mediated cellular actions (Tagi et al., 2019). It is a state in which plasma insulin at normal levels has an impaired ability to promote peripheral glucose utilization, suppress hepatic glycogenolysis, and inhibit VLDL release by hepatocytes (Eyzaguirre & Mericq, 2009). Studies have reported the association of IR with obesity, type 2 diabetes (T2D), dyslipidemia, atherosclerosis, polycystic ovarian syndrome (PCOS), and non-alcoholic fatty liver disease (NAFLD). IR has also been recognized as an independent risk factor for the development of cardiovascular diseases (Yvette E. Lentferink, Marieke A. J. Elst, Catherijne A. J. Knibbe & Vorst, 2017). A strong positive association of IR with the prevalence of components of metabolic syndrome in obese children and adolescents has been reported in the literature (Kostovski et al., 2018; Tagi et al., 2019; Tobisch et al., 2015). Although IR is often related to obesity, some studies have reported the prevalence of IR in non-obese individuals implying that increased adiposity is not the sole determinant of IR (Córdoba-Rodríguez et al., 2022). An association of IR with puberty has also been reported (Cardenas-Vargas et al., 2018; Tobisch et al., 2015; Urakami & Morimoto, 2011). During puberty, insulin sensitivity declines to around 25–50% and improves when puberty ends (Tagi et al., 2019). Adolescents have been demonstrated to have higher insulin levels than pre-pubertal children (Urakami & Morimoto, 2011). Although hyperinsulinemia compensates for IR in maintaining glucose homeostasis, it increases the susceptibility for early atherosclerosis, hypertension, acanthosis nigricans, hypercoagulation, polycystic-ovary syndrome, dyslipidemia, fatty liver infiltration, and some types of cancers (Eyzaguirre & Mericq, 2009). Considering the multiple risks involved, careful and timely screening of adolescents for the determinants of IR is crucial.

The essential biochemical markers to assess Insulin resistance include plasma insulin levels, the homeostasis model assessment for IR(HOMA-IR), hyperglycemic euglycemic clamp, C-peptide measurement (Pulungan et al., 2013), and the quantitative insulin sensitivity check index (QUICKI) assessment(Tagi et al., 2019). The hyperinsulinemic-euglycemic clamp is a gold standard method to evaluate IR; however, owing to its invasive, expensive, and complicated procedure, it is less common in clinical practice, instead surrogate markers of IR are used (Pulungan et al., 2013; Tagi et al., 2019). Studies report that lifestyle indices, anthropometric assessments, and biochemical estimations can assess IR(Aguilar et al., 2013; de Morais et al., 2016; Eyzaguirre & Mericq, 2009). However, these associations have been established in adults; the reports of these markers in adolescents are either incomplete or conflicting. Moreover, studies reporting the prevalence of IR in normal-weight adolescents are scanty in the literature. The present study, therefore, aimed to investigate the prevalence of IR by identifying the markers of insulin resistance and determining their prospective associations with puberty, lifestyle indices, anthropometric assessments, and biochemical estimations in normal-weight North Indian adolescents.

MATERIAL AND METHODS

A cross-sectional observational study was carried out at Sri Guru Das University of Health Sciences, Amritsar, Punjab, India, including eighty apparently healthy non-obese adolescents aged 10-19 years. The study was approved by the Research and Ethics Committee of the University. Participants with BMI ranging between 18.5 to ≤24.9 kg/m2 and pubertal stage T2-T5 were included in the study. Obesity was defined by the Childhood Working Group of the International Obesity Task Force (Afshin et al., 2017). The pubertal staging was assessed according to Tanner criteria (breast and pubic hair stages for girls; genitalia and pubic hair stages for boys). Subjects were assigned to one of three categories based on pubertal stages: pre-pubertal (T1), pubertal (T2–T4), and post-pubertal (T5). Pre-pubertal (T1stage), overweight (BMI >25.0- 29.9 kg/m2) and obese participants (BMI >30 kg/m2) or those suffering from Type 1 diabetes mellitus, chronic, hereditary, endocrine, infectious, inflammatory, and systemic diseases were excluded from the study.

Participation in the study was voluntary, and written informed consent was obtained from the parents or legal guardians of each of the study participants. In addition, a formal letter explaining the aim of the study and the details of the procedures that would be followed before and during data collection was given to parents, teachers, and participants. A questionnaire was completed for each participant, which included information on demographics, family history, dietary habits, physical activities, sleeping patterns, home environment, anthropometric assessments, and biochemical estimations. The anthropometric assessments included height, weight, BMI, waist circumference, hip circumference, waist-to-hip ratio, and blood pressure measurements. Additionally, the general physical examination was carried out to determine pubertal staging and the presence of physical markers such

as acanthosis nigricans, striae, acne, and hirsutism in females and gynecomastia in male participants. Acanthosis was graded based on the standard scale of 0-4, as described by Burke et al. (1999).

Physical activity details were recorded on a modified Paffenbarger activity questionnaire (Sadanshiv et al., 2020). Biochemical estimations included plasma glucose, insulin, HOMA IR, lipid profile, and transaminases (ALT and AST) estimations. Homeostatic model assessment [HOMA index] was used to assess Insulin resistance (Guzzetti et al., 2019). HOMA-IR = Glucose (mg/dL) × insulin (μU/L)/405].

Statistical Analysis

Continuous data as mean ± SD and the categorical data were expressed as frequencies and percentages. All continuous variables were first tested for distribution normality using Kolmogorov- Smirnov and Shapiro-Wilk normality tests. Then, parametric and non-parametric statistical tests were conducted depending on the distribution's normality. An independent t-test and one-way ANOVA test were performed to analyze normally distributed data, and Pearson correlation coefficients were calculated. When data were not normally distributed, the Man-Whitney U test was conducted, and Spearman correlation coefficients were calculated for non-ordinal variables. The Pearson Chi-square was used to analyze differences in categorical variables. Data were analyzed by using the statistical package STATISTICA 14.0. P values < 0.05 was considered statistically significant.

RESULTS

Demographics, anthropometric assessments, and biochemical estimations of the study participants are shown in Table 1. The mean HOMA IR in study participants was 2.7±1.88. Variations of HOMA IR in different groups are shown in Table 2 and Figure 1.

Parameter	Mean	Standard deviation (SD)	Parameter	Mean	Standard deviation (SD)
Age (years)	15.77	2.15	Plasma Glucose (mg/dL)	77.18	11.27
Weight (kg)	48.28	6.64	Plasma Insulin (μI U/L)	9.5	7.63
Height (meters)	152.68	27.44	HOMA IR	2.7	1.88
BMI (kg/m2)	19.51	1.94	Total Cholesterol (mg/dl)	158.28	33.93
WC (cm)	76.65	6.31	Triglycerides (mg/dl)	107.71	30.87
Hip circum ference (cm)	86.86	6.38	LDL(mg/dl)	83.42	32.00
WtHR	.87	.060	HDL(mg/dl)	55.03	10.04
Systolic BP (mmHg)	112.56	1.65	S. Uric acid (mg/dL)	4.59	1.15
Diastolic BP (mmHg)	77.12	15.35	ALT(U/L)	29.59	7.91

Anthropometric Assessments

Gender and pubertal stage-specific variations in anthropometric assessments are shown in Table 2. The age variations in the male and female groups were statistically insignificant (p=.085); however, in the pubertal and post-pubertal groups, age variations were highly significant (p=.000). Males and post-pubertal participants had higher body weight and were taller than their counterparts.

The pubertal stage-specific weight variations were highly significant (p=.000), but the gender-specific variations were insignificant (p=.703). However, height variations in both the groups, gender-specific (p=.021) and pubertal stage-specific (p=.005), were statistically significant.

BMI was significantly higher in females (p=.022). The post-pubertal participants had higher BMI, but the differences were statistically insignificant (p=.159). Additionally, statistically significant variations in waist circumference (WC), hip circumference (HC), and waist-to-hip ratio (WtHR) were observed in pubertal and post-pubertal groups. However, gender-specific variations in these parameters were insignificant statistically. Furthermore, the systolic and diastolic blood pressure variations in both study groups were insignificant (Table 2).

Table 2- Gender and pubertal variations in Age and Anthropometric Assessments

Parameters	Males (n=42) (Mean ±S. D)	Females (n=38) (Mean ±S. D)	P value	Pubertal (n=41) (Mean ±S. D)	Post-pubertal (n=39)(Mean ± S. D)	P value
Age (years)	15.3 ±1.89	16.23 ±2.5	.085	14.21±1.33	18.10±1.04	.000
Weight (kg)	49.80 ± 9.35	49.10 ± 5.78	.703	46.67± 5.87	53.41± 8.13	.000
Height (meters)	160.88 ± 11.97	155.33 ±7.68	.021	155.13± 9.93	161.92± 9.4	.005
BMI (kg/m2)	19.14 ±2.13	20.29 ±2.01	.022	19.46 ± 2.09	20.19±2.15	.159
Waist circumference (cm)	77.78 ±7.53	77.18± 6.71	.722	74.36±13.24	79.16±8.0	.004
Hip circumference (cm)	87.18± 7.03	87.76± 6.33	.715	85.02±6.15	91.07±5.63	.000
Waist-to-hip ratio	.88±.05	.87±.069	.425	.89±.057	.85±.066	.025
Systolic blood pressure (mmHg)	113.78 ±1.12	111.31± 1.34	.718	111.66± .93	113.96±1.08	.087
Diastolic blood pressure (mmHg)	73.9±1.03	72.89±1.11	.412	72.61±1.05	74.13±1.13	.056

Biochemical Estimations

Gender and pubertal stage-specific variations are shown in Table 3. The mean plasma glucose levels were higher in females and post-pubertal participants compared to their counterparts. The differences were statistically highly significant (males v/s females p=.016 and pubertal v/s post-pubertal p=.001). On the other hand, the mean plasma insulin levels were higher in males (p=.004) and pubertal participants (p=.046). Similarly, HOMA IR levels were also higher in males and pubertal participants. The gender-specific (p=.001) and pubertal stage (p=.002) specific variations in mean HOMA IR levels were statistically significant. Similarly, highly significant variations in serum cholesterol (p=.001), LDL (p=.000), uric acid (p=.000), and transaminase levels (ALT p=.001 and AST p=.049) were observed amongst males and females. In the pubertal and post-pubertal groups, except AST (p=.042), the variations were insignificant statistically.

Table 3- Gender and pubertal variations in Biochemical parameters

Parameters	Males (n=42) (Mean ±S. D)	Females (n=38) (Mean ±S. D)	P value	Pubertal (n=41) (Mean ±S. D)	Post-pubertal (n=39)(Mean ±S. D)	P value
Plasma Glucose (mg/dL)	73.62±8.62	80.72±11.8	.016	73.80±7.6	82.65±12.96	.001
Plasma Insulin (μI U/L)	11.89±8.76	7.01±5.06	.004	9.96±7.24	8.29±7.57	.046
HOMA IR	3.31±1.71	2.17±1.94	.001	3.13±1.76	2.08±1.99	.002
Total Cholesterol (mg/dl)	145.80± 25.41	169.17± 37.05	.001	157±32.97	160.21±36.06	.531
Triglycerides (mg/dl)	115.31± 29.90	103.03± 30.77	.094	105±30.91	104.68±30.66	.359
LDL(mg/dl)	68.62± 6.39	95.92±33.01	.000	80.52±31.19	87.16±34.16	.399
HDL(mg/dl)	55.65± 7.11	54.68±12.20	.690	55.0±8.26	55.3±12.46	.648
S. Uric acid(mg/dL)	5.10±1.02	4.16±1.10	.000	4.7±1.1	4.44±1.23	.531
ALT(U/L)	33.95±10.06	26.95±5.6	.001	27.6±6.24	31.36±11.9	.725
AST	24.73±6.84	29.23±6.84	.049	29.4±8.12	25.67±8.29	.042

Prevalence of IR

IR was found in 27 percent of our normal-weight participants. Variations of HOMA IR levels in different groups, such as males, females, pubertal, post-pubertal, rural, urban, vegetarian, and non-vegetarian, are shown in Figure 1. Mean plasma HOMA IR fell from 2.7 to 1.8 after excluding IR-positive participants. The variations in all the groups mentioned above, except vegetarians and non-vegetarians,

were statistically significant.

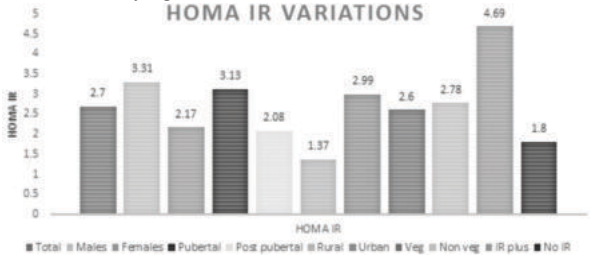

Figure 1- Comparison of HOMA IR levels in different groups

IR markers

IR was associated with waist circumference, waist-to-hip ratio, plasma insulin, serum triglycerides, HDL, and ALT (Table 5). In Insulin resistant participants, acanthosis nigricans, acne, and striae were observed in 46, 35, and 38 percent. However, all three markers were seen in 27 percent of IR positive group. In anthropometric assessments, the variations in waist circumference (p=.024) and waist-to-hip ratios were highly significant (p=.018). Similarly, the variations in mean plasma insulin (p= .000), HOMA IR (p=.000), and serum triglyceride levels (p=.023) were statistically significant.

Table 4- Variations in anthropometric assessments and biochemical estimations in insulin-resistant and non-insulin-resistant participants.

Parameter	Participants with IR Mean±S.D	Participants with no IR Mean±S.D	Significance P Value
Waist circumference (cm)	84.77±6.99	76.46±5.12	.024
Waist-to-hip ratio	.88±.060	.82±.061	.018
Plasma insulin	15.31±9.25	5.98±3.13	.000
HOMA IR	4.69±1.51	1.8 ±.70	.000
S. Triglycerides	121.40±24.58	105.47±43.19	.042
HDL	52.26±11.57	55.76±6.97	.346
ALT	30.27±5.33	26.64±9.18	.048

Prevalence of metabolic syndrome

Fourteen percent of IR individuals were identified as having two components of metabolic syndrome, mainly high triglycerides and waist circumference. Only two participants were diagnosed with metabolic syndrome who had high waist circumference, hypertension, and high triglyceride levels.

Table 5- Correlation of HOMA IR with anthropometric measurements

Parameter	Correlation	P value
Age	0.307	.009
Waist	0.565	0.000
Waist-to-hip ratio	0.419	0.006
Height	0.228	0.005

DISCUSSION

Our study demonstrated the prevalence of insulin resistance in normal-weight adolescents. Twenty-seven percent of our participants had higher HOMA IR levels. These results are consistent with results reported by several studies (de Morais et al., 2016; Singh et al., 2013). The mean HOMA IR levels (2.7± 1.88) of our study participants were consistent with the mean levels of Indian adolescents reported in the literature (Ramesh et al., 2022; Singh et al., 2013).

In our study, pubertal participants had higher HOMA IR levels than post-pubertal participants, and the differences were statistically significant (p= .002). Higher HOMA IR levels in pubertal stage T2-T4 have been reported by several authors (Kurtoglu S et al., 2010; Urakami & Morimoto, 2011). A physiological decrease in insulin sensitivity and compensatory hyperinsulinemia occurs during puberty, which reverts to normal as puberty ends (Urakami & Morimoto, 2011). The mean HOMA IR levels of males were higher compared to females in our study. The levels in males and females were 3.31±1.71 and 2.17±1.94, respectively. Literature shows conflicting reports; some studies have reported higher HOMA IR levels in females (Singh et al., 2013), some have reported no variations (Lopez-Sandoval et al., 2018), and some have reported higher HOMA IR levels in males (de Morais et al., 2016; Singh et al., 2013) similar to our study. Our study's higher HOMA IR levels might be due to the higher number of males (25) compared to females (16) in the pubertal group with relatively higher HOMA IR levels. During puberty, there is a normal elevation of growth hormone/IGF-1 and sex steroids that contribute to developing a physiological IR state (Eyzaguirre & Mericq, 2009).

Besides gender and pubertal stage variations, our study also investigated the effect of lifestyle indices on IR. Non-vegetarian and urban participants had higher HOMA IR levels than their counterparts (Figure 1). These results are reinforced by the findings of a meta-analysis which states that vegetarian and vegan diets improve HOMA-IR levels and can prevent the development of T2DM irrespective of the BMI status of an individual (Chen et al., 2022; Martins & Conde, 2022). Literature shows that dietary habits with animal protein consumption and low vegetable food intake promote insulin resistance in healthy subjects and in patients with diabetes (Adeva-Andany et al., 2019). Higher HOMA IR levels in urban Indians have been reported in the literature and are attributed to energy-dense foods, low physical activity, higher stress, and exposure to air pollutants (Thanikachalam et al., 2019).

In anthropometric assessments, highly significant variations in waist circumference and waist-to-hip ratios were observed amongst our insulin-resistant and non-insulin-resistant participants (Table 4). Insulin-resistant participants had higher waist circumference and waist-to-hip ratios than non-insulin-resistant participants. Several authors have reported similar results Barseem & Helwa, 2015; de Morais et al., 2016; Singh et al., 2013). Furthermore, except for BMI, all other anthropometric parameters were found to be associated with HOMA IR and plasma insulin levels (Table5), implying thereby that BMI is not an ideal tool and a normal BMI does not preclude obesity-related diseases; instead, waist circumference and waist-to-hip ratios are better risk predictors of insulin resistance and cardiovascular diseases. Studies report that waist circumference is a marker of visceral adiposity and an independent risk factor for CHD (Lopez-Sandoval et al., 2018). Visceral adiposity has been associated with IR, dyslipidemia, hypertension, atherosclerosis, and nonalcoholic fatty liver disease(Lopez-Sandoval et al., 2018). In our study, a state of borderline dyslipidemia manifested as relatively higher triglycerides and lower HDL levels was observed in insulin-resistant participants. Studies have shown that elevation in serum triglycerides and fall in HDL levels occur secondary to IR in insulin-resistant individuals (Tagi et al., 2019).

On close inspection, our study identified cutaneous markers, waist circumference, waist-to-hip ratio, plasma insulin, serum triglycerides, HDL, and ALT levels as markers of IR. Hyperinsulinemia in our insulin-resistant participants could be due to a compensatory response to utilize glucose which was why euglycemia was observed in this group. This implies that a normal BMI and euglycemia in adolescents do not preclude risk for IR and associated diseases, especially in the pubertal stage, and this population should be screened thoroughly for other markers, such as cutaneous markers and tools to measure visceral adiposity. The prevalence of cutaneous markers in our study, especially acanthosis nigricans in insulin-resistant participants, is in close agreement with several studies (Eyzaguirre & Mericq, 2009; Patidar et al., 2012). In addition, authors have reported that acanthosis nigericans can serve as a valuable tool for health screening and prevention (Pulungan et al., 2013).

IR markers of our study identified the metabolic syndrome in two participants. Not only are these results in close agreement with other studies (Barseem & Helwa, 2015; Ramesh et al., 2022), but they also confirm that IR markers can be used as tools to detect components of metabolic syndrome in susceptible adolescents.

CONCLUSION

Normal BMI and euglycemia do not overrule insulin resistance. Therefore, all adolescents should be screened thoroughly for the presence of markers of Insulin resistance. The cutaneous markers, waist circumference, waist-to-hip ratio, plasma insulin, serum triglycerides, HDL, and ALT levels can serve as useful screening tools to predict the risk of insulin resistance. In addition, all insulin-resistant individuals and those at risk should be further screened for the presence of components of metabolic syndrome. The risk predictors of IR can also be employed to predict cardiovascular risk.

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Conflicts Of Interest: No

Limitations Of The Study

Small sample size, non-inclusion of body composition parameters, and birth history are limitations of the current study.

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