Risk factors predicting insulin resistance in obese adolescents

Moushira Zaki1*, Ramy Mohamed1, Sanaa Mohamed1 and Ragaa Abd-elsalam Mohamed2

1Biological Anthropology Department, Medical Research Division, National Research Centre, Cairo, Egypt. 2Pediatric Department, Faculty of Medicine (Girls), Al-Azhar University, Egypt.

*Correspondence: moushiraz@yahoo.com Accepted: 05 July 2018 Published online: 29 Sep. 2018

Obesity is a hazard mark that associated with insulin resistance (IR). This study aimed to detect which risk factors might provide the greatest predictive value for IR in obese adolescents aged thirteen to seventeen years. One hundred obese adolescents with IR and matched age and sex 100 obese healthy controls without IR were included. Anthropometry, serum lipids and metabolic biomarkers were measured. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was used to determine insulin Resistance. Significant increase in serum lipids and metabolic parameters in obese cases with IR compared to those without. Positive correlations were observed between obesity measurements and metabolic risk markers, including increase of waist to hip ratio (WHR), sum of skin folds, blood pressure, insulin, HOMA-IR, TC, TG and LDL-C levels and decrease of HDL-C in IR adolescents. WHR showed the highest correlations with biochemical markers in IR cases. WHR was able to predict IR with area under the curve = 0.82 and TG-to-HDL-C ratio with area under the curve = 0.87. WHR and lipid/lipoprotein fractions are significantly associated with IR in obese adolescents and might be used for the prediction of IR and for cases at high risk for early intervention.

Keywords: obese adolescents; insulin resistance; clinical practice; biochemical markers

INTRODUCTION

Obesity is the main risk factor for development IR and metabolic alterations in adolescents(Mieldezis et al., 2010). Obesity is a serious health problem and the prevalence of obesity increases worldwide. Metabolic syndrome (MS) includes risk factors for cardiovascular disease (CVD) and type 2 diabetes (T2D) (Alberti and Zimmet 1998). Central obesity and insulin resistance are considered the ideal features of MS; these factors are complicated by high serum insulin levels, glucose, triglycerides levels and increased blood pressure. IR and obesity are considered serious health problems(Amos et al., 1997; Vassalle et al., 2009). The etiology of IR is still unknown in where environmental, lifestyle factors and genetic susceptibility are likely to develop this disorder. MS are more likely to develop DM2 and CVD by time. The prevalence of MS in children and adolescents has been investigated by few studies , though it is very common in the obese pediatric population (Vanlancker et al., 2017).

There are serious difficulties which face the diagnosis of MS in children and adolescents,

Previous studies on the use of risk indicators for screening for IR are scarce in the literature. Previous studies reported that waist circumference WC and body mass index (BMI) are risk factors have been used in the prediction of MS and IR in obese adolescents (Wicklow et al., 2015). Moreover, it has been reported that WC
and waist-to-height ratio is a more powerful predictor than the BMI for MS in adolescents (Savva et al., 2000). Due to lipolytic effects of adipocytes IR is associated with obesity. Different risk factors are used to predict the risk of IR in the clinical field; however, there is no agreement of the best risk factors in adolescents.

Therefore, the study aimed to detect the greatest predictive risk factors associated with IR in obese Egyptian adolescents.

**MATERIALS AND METHODS**

One hundred obese individuals with IR and matched age and sex 100 obese healthy controls without IR were included. Anthropometry, serum lipids and metabolic biomarkers were measured. They aged between thirteen to seventeen years. None of the study participants had diabetes according to the criteria of American Diabetes Association (Puavilai et al., 1999). A formal consent letter from their parents was obtained after explaining to them the whole procedure. Participants were classified (BMI ≥ 95th percentile) based on age- and gender-specific pediatric BMI criteria into obese with IR and obese without IR. To quantify a measurement's distance from the mean Z-scores (or standard deviation (SD) scores) was used for anthropometric measurements (Andaki et al., 2017; Organization and Organization 2007). They were referred to the outpatient clinic of the Pediatric Department, Faculty of Medicine (Girls), Al-Azhar University. Written informed consent was obtained from all the patients' parents and all investigations followed the Helsinki.

Insulin resistance has been estimated by the Homeostasis Model Insulin Resistance (HOMA-IR); as the outcome of fasting plasma insulin level (IU/mL) and fasting plasma glucose level (mmol/L) divided by 22.5 (Matthews et al. 1985). The HOMA-IR score of ≥ 4.0 was considered as insulin resistance, while a score of less than 4.0 was considered as insulin sensitive (Reinehr and Andler 2004).

A full description of the anthropometric and biochemical measurements has been reported elsewhere (Zaki et al., 2016).

**Statistical analysis**

SPSS 16.0 software was used for statistical analysis. Quantitative variables were given as mean and standard deviation. Student's t-test for independent samples was used. A value of p < 0.05 was considered statistically significant.

To evaluate the predictive authority of anthropometric indices to predict IR the receiver operating characteristic (ROC) curve was used and areas below the ROC curves (AUC) were used to assess the discriminatory power. Correlations between normally distributed continuous variables were evaluated by the calculation of Pearson's partial r coefficient, after adjusting for various potential confounders.

**RESULTS**

Table 1 shows Clinical and metabolic characteristics of obese adolescents with and without IR. All the metabolic and biochemical variables were significantly different between them with higher levels of WHR, SBP, DBP, glucose, insulin, HOMA-IR, TRG, LDL-C levels, TG/HDL-C ratio and lower levels of HDL-C in IR obese cases as compared to those without (p <0.01).

Table 2 shows results from the partial correlation analysis that evaluated the relationships between metabolic markers and obesity indices in obese children with IR. Results show significant positive correlations between obesity indices and metabolic risk markers including, levels of BP levels, insulin, HOMA-IR, TG, TC, LDL-C and negative correlation with HDL-C. WHR showed the highest levels of correlations with metabolic markers. Figure 1 illustrates receiver operating characteristic curves for evaluating the usefulness of WHR to identify subject with IR among Egyptian obese adolescents. ROC analysis showed that the area under the ROC curve (AUC) for WHR Z-score to detect cases with IR was 0.82 (p = 0.001).

Figure 2 illustrates ROC of TG/HDL cholesterol ratio to predict IR in obese adolescents with AUC = 0.87 (p = 0.001). TG/HDL-C ratio ≥ 3 was considered as risk factor for IR (McLaughlin et al., 2003).

**Discussion**

Childhood obesity increases the risk diabetes and cardiovascular morbidities in adults. Obesity has increased the mortality rate in obese patients when compared to normal weight subjects. IR is considered one of the most concerning complications of childhood obesity; it is also considered a precursor of type 2 diabetes mellitus and MS. Clinically, the homeostasis model assessment-insulin resistance (HOMA-IR) is used to diagnose insulin resistance (Alberti et al., 2009).
Table 1 Descriptive data regarding clinical and biochemical characteristics of obese adolescents with and without IR

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Obese with IR</th>
<th>Obese without IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>15.8 ± 2.8</td>
<td>14.3 ± 2.3</td>
</tr>
<tr>
<td>Body mass index Z-score</td>
<td>4.4 ± 1.4</td>
<td>3.7 ± 0.9</td>
</tr>
<tr>
<td>Sum of SF Z-score</td>
<td>5.4 ± 1.9</td>
<td>4.8 ± 1.2</td>
</tr>
<tr>
<td>WHR Z-score</td>
<td>5.5 ± 1.3*</td>
<td>2.9 ± 0.9</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>125.8 ± 10.7*</td>
<td>113.06 ± 12.89</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>84.8 ± 7.9*</td>
<td>70.9 ± 6.5</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>6.5 ± 1.9*</td>
<td>2.5 ± 1.2</td>
</tr>
<tr>
<td>FBG (mg/dL)</td>
<td>100.2 ± 21.7*</td>
<td>80.9 ± 20.1</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>193.55 ± 22.14*</td>
<td>162.3 ± 18.92</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>145.8 ± 20.10*</td>
<td>90.8 ± 17.16</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>43.4 ± 9.9*</td>
<td>49.8 ± 13.7</td>
</tr>
<tr>
<td>TG/HDL cholesterol ratio</td>
<td>4.9 ± 1.2**</td>
<td>2.1 ± 0.9</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>115.91 ± 23.18*</td>
<td>75.82 ± 11.29</td>
</tr>
</tbody>
</table>

Sum SF: sum of skin folds; WHR: waist to hip ratio; FPG: fasting glucose; TG: triglycerides; TC: total cholesterol; HDL: high density lipoprotein; LDL: low density lipoprotein; HOMA-IR: homeostasis model assessment-insulin resistance.*p<0.01, ** p<0.001 vs. controls

Table 2 Partial correlation (r) analysis between metabolic markers and the obesity indices in obese IR cases

<table>
<thead>
<tr>
<th>Variables</th>
<th>BMI Z-score</th>
<th>WHR Z-score</th>
<th>Sum of SF Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>0.49*</td>
<td>0.64**</td>
<td>0.38*</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.34*</td>
<td>0.74**</td>
<td>0.33*</td>
</tr>
<tr>
<td>TC</td>
<td>0.34*</td>
<td>0.65**</td>
<td>0.25*</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-0.34*</td>
<td>-0.64**</td>
<td>-0.32*</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.44*</td>
<td>0.64**</td>
<td>0.22*</td>
</tr>
<tr>
<td>Insulin</td>
<td>0.57*</td>
<td>0.69**</td>
<td>0.25*</td>
</tr>
<tr>
<td>SBP</td>
<td>0.42*</td>
<td>0.57**</td>
<td>0.32*</td>
</tr>
<tr>
<td>DBP</td>
<td>0.43*</td>
<td>0.59**</td>
<td>0.31*</td>
</tr>
<tr>
<td>TG/HDL-C ratio</td>
<td>0.45*</td>
<td>0.58**</td>
<td>0.43*</td>
</tr>
</tbody>
</table>

TG: triglycerides; LDL-C: low density lipoprotein cholesterol; TC: total cholesterol; HOMA-IR: homeostasis model assessment-insulin resistance; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI Z-score: body mass index Z-score; WHR Z-score: waist to hip ratio Z-score; SF: skin folds
*p<0.05 ** p<0.001

In the current study obesity measures and high triglycerides levels were associated with high HOMA-IR levels; this result is consistent with other studies (Kurtoğlu et al., 2010; Bindler et al., 2013). Insulin resistance has the central role in metabolic dysfunction in MS.

In obese subjects a TG-to-HDL-C ratio is associated with a 1.5- to 10-fold higher risk of insulin resistance, (Di Bonito et al. 2012). The present study provides the novel findings that a high TG-to-HDL-C is associated with metabolic and biochemical risk markers in obese adolescents with IR. Insulin resistance and T2D are characterized by hypertriglyceridemia and decrease of HDL-C (Pacifico et al., 2014).

According to The European Group for the Study of Insulin Resistance and the International Diabetes Federation (IDF) the elements of MS are (glucose intolerance, central obesity, arterial hypertension and dyslipidemia (Balkau and Charles 1999; Reinehr et al., 2007; Vanlancker et al., 2017). This study estimated that there were positive correlations between waist, WHR, abdominal skin fold and metabolic risk parameters including, serum low density lipoprotein level, serum insulin level, HOMA-IR and elevated systolic and diastolic blood pressure levels.
The highest correlations were found between waist hip ratio and lipid metabolic risk markers.

BMI Z-score ≥ 2.00 was used as an indicator of obesity. Nevertheless, according to IDF, central obesity is considered the main criterion for the diagnosis of MS, since it shares in the development of insulin resistance, hyperinsulinism and is associated with cardiovascular complications (Del-Rio-Navarro et al., 2008). HOMA-IR index diagnoses insulin resistance (the cut-off points range from 2.16 to 3.43). In our study the cut-off point for IR was HOMA-IR ≥
Abdominal obesity is associated with type 2 diabetes which is always leads to development of MS. Insulin resistance starts many metabolic changes reflected by increased serum LDL level, increased serum triglyceride, increased serum cholesterol levels and lowered serum HDL level (García et al., 2007; Koyama et al., 2014). Waist circumference is highly sensitive and specific and correlates with insulin resistance in adults and suggested by other studies to identify obesity instead of z score of BMI (Ali et al., 2014; González-Jiménez et al., 2016). There was a superior correlation between waist circumference and insulin resistance in this research thus, it may be used as an important procedure for detecting risk of developing metabolic and cardiovascular complications among overweight and obese adolescents, which is further proved by researches emphasizing that children with WC higher than the 90th percentile (central obesity) are more probable to have cardiovascular complications (Maffeis et al., 2001).

Prevalence of metabolic syndrome and its components in children and adolescents has become a public health problem worldwide, thus metabolic syndrome prevalence has increased considerably in adults (Rasouli and Kern 2008). Body mass index is considered the most widely used anthropometric index to determine metabolic alteration risk (Andersen et al., 2015; Faienza et al., 2016). However, its use is not without problems as it is unable to distinguish fat and lean mass.

Abdominal obesity is a highly prevalent mark of the metabolic syndrome; however the causal mechanism is not fully understood. MRI and computed tomography studies reported the excess of visceral adipose tissue and not subcutaneous abdominal fat is the contributed parameter that correlates with the metabolic abnormalities cases (Després 2006). The recent study carried out on 1983 children and adolescents aged 6-18 years reported that visceral fat mass and BMI were the key independent detectors of metabolic syndrome (Ding et al. 2018). In agreement with our study, other recent study showed that WHR was able to predict a higher number of components of MS and WC for MS (Perona et al., 2017). On the other hand, moderate correlation of waist to height ratio with IR was observed in both sexes (de Oliveira Alvim et al., 2018). Our results also partially coincide with other studies proposed that WC and BMI as clinically relevant anthropometric indicators to predict MS (Savva et al., 2000; Wicklow et al., 2015). TG to HDL-C ratio was found to be strongly associated with IR in previous different populations studies in children (Kang et al., 2012) (Iwani et al., 2017) which is consistent with our findings.

Moreover, other study showed complex link between glucose, HOMA-IR and serum uric acid, suggesting that adiposity indices such as visceral adipose tissue, BMI, and WC are mediators of the association between insulin resistance and serum uric acid (Mazidi et al., 2017). Previous study demonstrated the accuracy anthropometric measurements in predicting metabolic syndrome in children (Andaki et al., 2017).

In conclusion this study emphasized associations between increase of WHR and TG/HDL-C ratio and metabolic dysfunction in obese IR adolescents. Thus multiple risk factors might be used in clinical practice for the prediction of IR including obesity indices and lipid measures. Combined lipid ratio showed significant better predictive power that might be used to predict cases at high risk.

CONCLUSION
Obesity indices and lipid/lipoprotein fractions are significantly associated risk factors with IR and might be used as significant indicators for metabolic complications among obese adolescents.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS
Authors’ contributions
Moushira Zaki: Conceived the idea, planned for the study, did the statistical analysis and writing the article.
Ramy Mohamed: Collected the data and did the anthropometric measurements
Sanaa Mohamed: Collected the data and did the anthropometric measurements
Ragaa Abd-elsalam Mohamed: Clinical
assessment and reviewing the study.

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