Effects of low glycemic index diet on insulin resistance among obese adolescent with non-alcoholic fatty liver disease: a randomized controlled trial

Agustini Utari, Muhammad Saifulhaq Maududi, Ninung Rose Diana Kusumawati, Maria Mexitalia

ABSTRACT

BACKGROUND Obesity is strongly correlated with insulin resistance (IR) and nonalcoholic fatty liver disease (NAFLD). Some studies suggest that dietary intake with low glycemic index (GI) may prevent IR and reduce the incidences of NAFLD. This study was aimed to determine the effects of low GI diet on IR among obese adolescents with NAFLD.

METHODS This study was a randomized controlled trial conducted in two Junior High Schools in Semarang, Indonesia. The subjects were 12–14 years obese students with NAFLD, which divided into intervention and control groups according to schools using block random allocation. The intervention group received nutrition education and lunch diet (low energy, low GI, and low fat); meanwhile, the control group only received nutrition education for 12 weeks. The biochemical evaluation included fasting blood glucose (FBG) and insulin levels. IR was assessed using homeostatic model assessment-insulin resistance (HOMA-IR).

RESULTS Thirty-two subjects were enrolled in this study, 16 of which were assigned to the intervention group and the other to the control group. After 12 weeks, the energy and carbohydrate intake reduced in the intervention group ($p < 0.05$), FBG remained unchanged, and HOMA-IR increased (4.9 [3.7]–7.2 [3.5]) compared to the control group (6.4 [4.9]–5.5 [2.8]) ($p < 0.05$). Meanwhile, within the control group, there were no significant differences in the energy and carbohydrate intake as well as biochemical variables.

CONCLUSIONS Low GI modification diet alone may not reduce IR in the obese adolescents with NAFLD.

KEYWORDS adolescent, glycemic index, HOMA-IR, NAFLD

With the increase in the prevalence of obesity among children and adolescents, it has become one of the most serious public health issues of the 21st century. Obese children are about 30–50% more likely to suffer from comorbidities such as metabolic syndrome which is considered to be a cluster of at least three or more of the following clinical and metabolic abnormalities present together: abdominal obesity, low level of high-density lipoprotein, high triglyceride, high fasting blood glucose (FBG), elevated blood pressure, and non-alcoholic fatty liver disease (NAFLD). NAFLD is one of the most common liver diseases in obese children. The estimated prevalence of NAFLD in the child population is about 10%, and it can increase up to 40–70% among obese children. A study conducted in Semarang showed that the prevalence of metabolic syndrome among the obese adolescents was 31.6%. Homeostasis model
assessments—insulin resistance (HOMA-IR) is one of the easiest ways to assess insulin resistance (IR). The best possible prevention of the IR in the adolescents is the consumption of low glycemic index (GI) diet. The low GI diet was reported to have shown positive results in reducing the weight and triglyceride levels in the obese children. The weight reduction in an obese person can significantly improve the IR.

The severity of NAFLD ranges from a simple fatty liver to more severe liver diseases, such as nonalcoholic steatohepatitis and cirrhosis. The development of NAFLD has been associated with IR, hyperinsulinemia, and dyslipidemia. Hyperinsulinemia may incite hunger and tend to cause an excessive food intake in the obese person with IR. The IR of the children is associated with the cardiovascular and metabolic risk factors, including type 2 diabetes mellitus and NAFLD. The purpose of this study was to determine the effect of low GI diet on IR, which is measured with the help of HOMA-IR index, in the adolescents with obesity.

**METHODS**

This study employed the randomized controlled trial methodology and was conducted from September to December 2012 in two schools, i.e., Domenico Savio and Nasima Junior High School Semarang, Central Java, Indonesia. The inclusion criteria were the adolescent students aged 12–14 years suffering from NAFLD as shown by the abdominal ultrasonography, and having the body mass index (BMI) in ≥95 percentile area on the basis on 2,000 Centers for Disease Control and Prevention graphic. The exclusion criteria were the adolescent students with type 2 diabetes mellitus (FBG level ≥126 mg/dl). The sample size was calculated on the basis of equivalence design for dichotomous variables with minimum subjects to be 11 children for each group.

Random allocation method was applied at the school level. Students at one school, who were determined as the intervention group, received lunch box (low energy, low GI, and low fat) during the school day and nutritional education for 12 weeks. Meanwhile, the students in the control group at another school only received nutritional education. The lunch box consisted of low-fat (fat <25% of total calories, cholesterol <300 mg/day) and low-GI diet. Three-day food recall was assessed by a nutritionist every month in both schools. The laboratory examination, before and after the intervention, consisted of determining FBG (mg/dl)–which was measured by Spectrophotometer COBAS MIRA–and insulin levels (µg/ml)–which were measured by enzyme-linked immunosorbent assay (ELISA) ELx800 Universal Microplate Reader. The IR was determined by the HOMA-IR technique that was calculated by the pre-specified formula (fasting insulin [µU/ml] x fasting glucose [mg/dl]/405). The HOMA-IR value above 3.16 mg/dl was categorized as a positive indication for IR. Paired t-test or Wilcoxon test was conducted to analyze the difference within the groups and independent t-test or Mann–Whitney test was conducted for analyzing the difference between the groups. Informed consent was obtained from the parents, and the study was approved by the ethical clearance committee of the Faculty of Medicine Universitas Diponegoro/Dr. Kariadi Hospital Semarang Indonesia (No.: 302/EC/FK/RSDK/2012, date of issue: August 23, 2012).

**RESULTS**

A total of 32 students (24 boys and 8 girls) in two schools participated in the study. They were divided into the intervention group (16 subjects) and the control group (16 subjects). Recruitment of the subjects is shown in Figure 1. There were no significant differences in the anthropometric data and laboratory results between the groups. The energy intake of the control group before treatment was lower as compared to the intervention group; however, the difference in energy intake between groups was not statistically significant (Table 1). A comparison of the energy intake before and after the intervention showed a reduction in energy intake by the end of the study. However, the lowest energy intake was found in the second month, although the difference was not significant in the control group (Figure 2). In both groups, there are no difference in the FBG levels before and after the intervention, but there was an increase in the levels of insulin and the HOMA-IR in the intervention group at the end of the study (Table 1).

**DISCUSSION**

The purpose of this study was to determine whether low GI diet may decrease the HOMA-IR.
index levels, which are related to the reduction of IR. Nevertheless, these findings indicated that the subjects in the intervention group increased their insulin and HOMA-IR index levels after 12 weeks of intervention. The food recall analysis showed a significant increase in the average energy consumption during the last month of the study. Although both of the groups showed the “yoyo phenomenon,” which indicated that the intake at the third month increased as compared to the second month, but the difference was not significant in the control group (Figure 2).

A previous study inferred that about 80% of the subjects successfully decreased their weight, but they later regained the lost weight after a year. This phenomenon is known as the “yoyo phenomenon.” The decrease in weight can be immediately achieved by limiting the calorie intake and increasing the energy expenditure. Therefore, it is necessary to arrange a long-term diet plan to maintain the decrease in weight.11 Adipokines secreted by the adipose tissue and some cytokines are also known to have directly or indirectly influence insulin sensitivity by modulating insulin signal, glucose, and lipid metabolism.12 The short-term weight decrease of the subjects in the short period of time might cause the decrease in the size of fat cells size but not in its amount. Furthermore, the adipocyte cells became “depressed,” and tried to increase the uptake of the glucose in order to compensate for the fat. In that condition, the leptin level (hormone that indicates a full stomach) is significantly decreased along with a decrease in the levels of peptide YY and cholecystokinin (induction of the full sensation) and an increase in the ghrelin level (hormone of appetite induction). Notably, subjects who achieved the target weight in short time stopped the diet and had increased energy intake after the diet.12

The other hypothesis put forward by this study is the role of glycemic variability (GV), which describes as the fluctuations of blood glucose levels throughout the day. The increase in GV has been shown to have a positive correlation with the increase of oxidative stress, BMI, IR parameters (HOMA-IR and fasting insulin) in a previous study.13 These results suggest that IR increases the fluctuations in blood glucose levels during the day. We did not measure the GV, but the energy intake of our intervention subjects increased at the end of the study as compared to the measurement conducted in the middle of the study.

Leptin, adipokines, such as adiponectin, and the newest one, chemerin, might have a role in the regulation of IR of obese children with NAFLD.4,12,14 Leptin is one of the hormones which plays a significant
Table 1. Comparison of anthropometric, nutritional intake, and biochemical variables before and after the intervention

<table>
<thead>
<tr>
<th>Variables</th>
<th>Intervention group (n = 16)</th>
<th>Control group (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.1 (6.9)</td>
<td>74.3 (6.8)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>156.6 (6.1)</td>
<td>156.6 (6.1)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.2 (1.9)</td>
<td>30.3 (2.0)</td>
</tr>
<tr>
<td>Energy (kcal)</td>
<td>2086.3 (70.3)</td>
<td>1996.9 (88.9)</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>256.8 (23.9)</td>
<td>238.9 (22.4)</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>66.6 (8.9)</td>
<td>65.6 (6.9)</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>88.1 (8.6)</td>
<td>86.6 (6.8)</td>
</tr>
<tr>
<td>FBG (mg/dl)</td>
<td>90.1 (6.5)</td>
<td>90.1 (6.2)</td>
</tr>
<tr>
<td>Δ FBG (mg/dl)</td>
<td>−0.66 (6.68)</td>
<td>−3.56 (8.44)</td>
</tr>
<tr>
<td>Insulin (μU/ml)</td>
<td>1.2 (0.8)</td>
<td>1.8 (0.7)</td>
</tr>
<tr>
<td>Δ Insulin (μU/ml)</td>
<td>−0.55 (0.65)</td>
<td>−1.56 (0.61)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>4.9 (3.7)</td>
<td>7.2 (3.5)</td>
</tr>
<tr>
<td>Δ HOMA-IR</td>
<td>2.18 (3.07)</td>
<td>−0.88 (2.60)</td>
</tr>
</tbody>
</table>

SD=standard deviation; BMI=body mass index; FBG=fasting blood glucose; HOMA-IR=homeostatis model assessment-insulin resistance.

*t-Test was used for analyzed the difference within groups; †Wilcoxon test was used for analyzed the difference within groups nonparametric data; ‡Independent t-test was used for analyzed the difference between groups; §Mann–Whitney was used for analyzed the difference between groups for nonparametric data; Significant if \( p < 0.005 \).
exercise program for the subjects, which may cause the rise of the IR. The crossover designed study of Cockcroft et al.\textsuperscript{18} of nine boys revealed that high-intensity interval exercise improved both insulin sensitivity and glucose parameters as compared to moderate-intensity exercise. In the study of Botero et al.,\textsuperscript{19} overweight and obese subjects were only given diet intervention (without physical exercise). The results showed that there was no significant difference in insulin sensitivity, bad insulin response, blood pressure, cholesterol and triglyceride levels as compared to the subjects with the low GI diet and high GI diet.\textsuperscript{19} Meanwhile, the study of Solomon et al.\textsuperscript{20} showed that the IR improved after seven days of physical exercise, and it was not affected by the low GI of the consumed food. In the view of IR, low GI diet for seven days did not showed a significant difference as compared to the high GI diet.\textsuperscript{20} A meta-analysis from 17 studies found that physical training, in general, was not related to a decrease in fasting glucose levels as compared to its control, but it was related to the reductions in fasting insulin levels. However, aerobic training is associated with the reduction of fasting insulin and HOMA-IR levels in obese and overweight children and adolescents. Thus, it might prevent type 2 diabetes and metabolic syndrome.\textsuperscript{22} Based on the previous study, it can be conclude that only dietetic intervention without physical exercise had no significant effect in reducing the IR in these subjects.

In this study, the insulin level increased in the intervention group and decreased in the control group that ultimately influenced the calculation of IR using the HOMA-IR technique. The clinical impact of increasing insulin levels in obesity is related to the risk of glucose intolerance and diabetes. However, the insulin sensitivity was not assessed using the Bergman's minimal model and hyperinsulinemic-euglycemic and hyperglycemic clamp method as a gold standard for the assessment of insulin sensitivity because it was considered to be invasive in the pediatric practice. Insulin sensitivity is influenced by several factors such as age, sex, hormonal, and pubertal stages. Insulin sensitivity declines in the puberty, while insulin secretion rises in this stage due to the increase in BMI, sex steroids, the growth hormone system, and insulin-like growth factor-1.\textsuperscript{22} The hormonal system that may have explained the factors related to the IR and insulin sensitivity in both groups was not evaluated in this study.

There were some limitations in this study such as that the dietary intervention was only given during lunch time; there was no exercise intervention; and the lack of direct family participation in deciding the daily menu. Education the whole family for the dietary intervention and also enhancing the physical activity besides the food intervention are recommended. In conclusion, the low GI modification diet alone may not reduce the HOMA-IR levels among obese adolescents with NAFLD.

Conflict of Interest
The author affirm no conflict of interest in this study.

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