HK J Paediatr (new series) 2014;**19**:22-27

The Relationship between Glycosylated Haemoglobin (HbA1c) Levels and Serum Lipid Profiles in Insulin Resistant Children

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Abstract ***Purpose:*** We aimed to evaluate the impact of glycaemic control on serum lipid profiles in children according to their insulin resistance screened by homeostasis model assessment (HOMA-IR) levels. ***Methods:*** This study included 130 children, aged between 3 and 15 years old who were admitted to our clinic with upper respiratory infection symptomps. We analysed their anthropometric measures, serum glycosylated haemoglobin (HbA1c) levels. Insulin resistance was estimated by HOMA-IR. Serum total cholesterol, high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL- C) and triglyceride levels were analysed. ***Findings:*** When serum HDL-C levels of ınsulin resistant group with HOMA-IR ≥3.5 were significantly lower, triglyceride levels were significantly higher, compared to the non-resistant group with HOMA-IR <3.5. Serum HDL-C, LDL-C, total cholesterol and triglyceride levels did not correlate with HbA1c levels among the insulin resistant group with HOMA-IR ≥3.5 and irresistant group with HOMA-IR <3.5. ***Conclusions:*** Insulin resistance status was directly associated with higher serum triglyceride and lower HDL-C levels, however HbA1c levels reflecting glycaemic status did not reveal an association with serum lipid profiles among insulin resistant children with HOMA-IR ≥3.5 levels.

Key words Child; Haemoglobin A1c protein; Insulin resistance; Lipids

Introduction

Insulin resistance is a common pathway for the development of glucose metabolism disorders, dyslipidemia and high blood pressure, all of which are components of the metabolic syndrome. In previous studies, the relationship between obesity and prevalence of metabolic syndrome has been reported, however it is not exactly known how and to what extent insulin resistance is associated with the components of metabolic syndrome.[1,2] One of the severe complications accompanying insulin resistance states is the hypertriglyceridaemia that is due to overproduction of triglyceride-rich apolipoprotein B (apo B) containing lipoproteins.[3] In previous studies, investigators reported that glycaemic control was directly related to lipid metabolism.[4]

In this study, we aimed to evaluate the insulin resistance status and the association of HbA1c levels (used as marker of glycaemic control) with the hyperlipidaemia which is the component of metabolic syndrome among insulin resistant children.

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Received March 25, 2013

Methods

This study included 130 children, who were admitted to our clinic with upper resipiratory infection symptoms.

These 70 obese and 60 normal weighed children were between 3-15 years old. When 69 children were younger than 10 years old, the remaining 61 were between 10 and 15 years old. Children who had known chronic illnesses, endocrinologic disorders and family history of dislipidemia were excluded. Body mass index (BMI) was calculated by the following formula: Body weight (kg)/height^2 (m^2). Subjects whose BMI values above 25 kg/m^2 were accepted as obese. Institution approval of Local Ethic Committe was obtained.

Fasting (12 h) venous blood samples were obtained by venipuncture into vacutainer tubes. Once centrifuged, the fractions were separated and frozen at -70°C. Plasma glucose was measured by the glucose oxidase method. Plasma cholesterol and triglycerides were measured enzymatically with an RA-1000 Autoanalyser. High density lipoprotein-cholesterol (HDL-C) was also measured in the RA-1000 after precipation of apo-B-containing lipoproteins. Low density lipoprotein-cholesterol (LDL-C) was calculated according to Freidewald's Formula (LDL-C: Total cholesterol–(VLDL-C+HDL-C), VLDL-C: Triglyceride/5).

Serum insulin concentrations were measured by radioimmunassay (RIA) using a commercial kit (Bıo-Rad). Insulin resistance was estimated using the homeostasis model assessment (HOMA; fasting insulin [mU/mL] X fasting glucose [mmol/L] / 22.5). Cut off HOMA-IR level ≥3.5 was accepted. HbA1c was measured by HPLC (high performance liquid plasma chromatography) method (BioRad Laboratories Ltd).

Statistical Methods

Analysis of distribution was carried out on all variables using the Kolmogorov-Smirnov test for normality. Statistical tests used were the independent samples. Student's t-test, chi-square test were used.

Statistical analyses were conducted using the statistical package SPSS version 20.0. P value ≤0.05 was defined as statistically significant.

Results

Thirty-nine of total 89 children with HOMA-IR <3.5 were obese, the remaining 50 were normal weight. When 73 of 89 children with HOMA-IR <3.5 had levels of HbA1c ≤5.5, the remaining 16 children had levels of HbA1c >5.5. Thirty-one of total 41 children with HOMA-IR ≥3.5 were obese, 10 of them were normal weight. When 29 of 41 children with HOMA-IR ≥3.5 had levels of HbA1c ≤5.5, the remaining 12 had levels of HbA1c >5.5.

Mean age distribution of children with HOMA-IR ≥3.5 was significantly higher than that of the group with HOMA-IR <3.5. There was no significant difference in gender distribution among the groups with HOMA-IR ≥3.5 and with HOMA-IR <3.5, respectively. When 69 children were younger than 10 years old, 61 were between 10 and 15 years old (Table 1).

HbA1c levels of insulin resistant group with HOMA-IR ≥3.5 and non-resistant group with HOMA-IR <3.5 did not reveal significant differences (p>0.05). The percentages of including patients with the ratios of levels HbA1c ≤5.5 and HbA1c >5.5 did not show significant difference in both of resistant and non-resistant groups (Table 2).

Serum LDL-C and total cholesterol levels were not significantly different among the insulin resistant and non-resistant groups. However, insulin resistant group with HOMA-IR ≥3.5 revealed significantly lower HDL and higher triglyceride levels, compared to insulin non-resistant group with HOMA-IR <3.5 (Table 3).

In the group with HOMA-IR <3.5, the HDL-C, LDL-C, total cholesterol and triglyceride levels of the groups with HbA1c ≤5.5 and with HbA1c >5.5 did not reveal significant difference (Table 4).

In the group with HOMA-IR ≥3.5, serum HDL-C, LDL-C, total cholesterol and triglyceride levels were not significantly different among the group with HbA1c ≤5.5 and the group with HbA1c >5.5 (p>0.05)(Table 5).

Discussion

Insulin resistance has been implicated to play a major role in dyslipidemia in individuals not only with normal glucose tolerance, and in those with impaired glucose tolerance and type 2 diabetes, as well.[4,5] Investigators from the Bogalusa Heart Study reported that overweight schoolchildren compared to normal weight ones, were more likely to have elevated total cholesterol, LDL-C and triglycerides and more likely to have hyperinsulinemia.[6] Glycaemic control is directly related to lipid metabolism. Researchers suggest that triglyceride-rich lipoproteins accumulate in the insulin-resistant state, causing the decreased activity of lipoprotein lipase, increased lipolysis in adipose tissue and increased output of very low density lipoprotein (VLDL) particles from the liver.[7,8]

The Search for Diabetes in Youth Study, examined 1973 children and adolescents aged 10 years and older for diabetes type, HbA1c and serum lipid levels. They detected the association between poor glycaemic control and higher levels of triglyceride, LDL-C and total cholesterol in

Table 1 Age and gender distribution according to homeostasis model assessment (HOMA-IR) levels

		HOMA-IR <3.5		HOMA-IR ≥3.5		p
Age	Mean±SD	8.29±3.09		11.38±2.43		0.0001*
	<10	59	66.3%	10	24.4%	0.0001**
	10-15	30	33.7%	31	75.6%	
Gender	Female	43	48.3%	19	46.3%	0.834**
	Male	46	51.7%	22	53.7%	

*Student t-test; **Chi Square test

Table 2 Serum HbA1c levels according to homeostasis model assessment (HOMA-IR) values

		HOMA-IR <3.5 Mean±SD		HOMA-IR ≥3.5 Mean±SD		p
HbA1c (%)		5.40±0.19		5.42±0.29		0.647*
HbA1c (%)	HbA1c ≤5.5	72	80.9%	29	70.7%	0.196**
	HbA1c >5.5	17	19.1%	12	29.3%	

*Student t test; **Chi-square test

Table 3 The relationship between serum lipid profiles and homeostasis model assessment (HOMA-IR) levels

	HOMA-IR <3.5 Mean±SD	HOMA-IR ≥3.5 Mean±SD	p
HDL (mg/dl)	48.03±11.02	43.32±9.33	0.019*
LDL (mg/dl)	91.21±25.84	91.71±30.38	0.924*
Triglyceride (mg/dl)	69.22±29.22	111.98±55.63	0.000*
Total cholesterol (mg/dl)	153±30.77	160.34±30.50	0.268*

HDL: High density lipoprotein; LDL: Low density lipoprotein

*Student t-test

Table 4 Serum lipid profiles according to HbA1c levels among the group with homeostasis model assessment (HOMA-IR) <3.5

HOMA-IR< 3.5	HbA1c ≤5.5 Mean±SD	HbA1c >5.5 Mean±SD	p
HDL (mg/dl)	47.69±10.71	49.47±12.49	0.785*
LDL (mg/dl)	93.04±24.26	83.47±31.36	0.553*
Triglyceride (mg/dl)	69.64±26.06	67.47±40.94	0.171*
Total cholesterol (mg/dl)	154.69±29.41	150.53±36.79	0.618*

HDL: High density lipoprotein; LDL: Low density lipoprotein

*Student t-test

Table 5 Serum lipid profiles according to HbA1c levels among group with homeostasis model assessment (HOMA-IR) ≥3.5

HOMA-IR ≥3.5	HbA1c ≤5.5 Mean±SD	HbA1c >5.5 Mean±SD	p
HDL (mg/dl)	41.90±9.94	46.75±6.88	0.972*
LDL (mg/dl)	92.62±27.65	89.50±37.45	0.131*
Triglyceride (mg/dl)	112.17±55.79	11.50±57.72	0.769*
Total cholesterol (mg/dl)	157.59±28.54	167.00±35.22	0.375*

HDL: High density lipoprotein; LDL: Low density lipoprotein

*Student t-test

diabetic patients between 10 and 22 years old. The correlation between higher HbA1c levels and higher lipid levels were independent of BMI for age, gender, duration of both types of diabetes. They analysed that, poor glycaemic control group correlated with higher total and LDL-C levels, compared to both control and optimical glycaemic control group. Poor glycaemic control group included a high percentage of children having higher total cholesterol, LDL-C and triglyceride levels increased with elevating values of HbA1c.[9]

Borai et al assessed the correlation between HbA1c and insulin resistance accross a range of glucose tolerance. They analysed the subjects with normal glucose tolerance, impaired fasting glucose, impaired glucose tolerance and type 2 diabetes. They found a strong correlation between HbA1c and indices of insulin sensitivity in the normal glucose tolerance group. They suggested that HbA1c could be evaluated as a simple marker to determine insulin sensitivity in adults with normal glucose tolerance and relatively high insulin sensitivity.[10] In a previous study by Sung et al, similar outcomes were analysed between HbA1c and HOMA-IR levels in non-diabetic Korean adults.[11] But our study revealed significant differences between HbA1c levels among the groups with HOMA-IR <3.5 and with HOMA-IR ≥3.5, respectively. The percentage of children with HbA1c ≥5.5 to HbA1c <5.5 was similar in both of insulin resistant and non-resistant groups according to HOMA-IR levels. Our study demonstrated that, HbA1c screening did not reflect insulin resistance status.

Data from The Diabetes Control and Complications Trial (DCCT) showed that glycaemic control affected the levels of total cholesterol, LDL-C and triglycerides. Their data indicated that intensive glucose control significantly decreased the concentrations of total cholesterol, LDL-C and triglyceride in patients aged 13 to 40 years with type 1 diabetes.[12] Our study did not show significant correlation between HbA1c and HDL-C, LDL-C and triglyceride levels in insulin resistant group with HOMA-IR ≥3.5. However serum HDL-C levels of insulin resistant group with HOMA-IR ≥3.5 were significantly lower, their triglyceride levels were significantly higher than the group with HOMA-IR <3.5. Insulin resistance status was directly associated with higher serum triglyceride and lower HDL-C levels, but HbA1c screening did not correlate with serum triglyceride or HDL-C levels.

Abraha et al investigated the effect of poor metabolic control and genetic factors influencing abnormal lipid levels in 141 children (7.7-19 years aged range) with type 1 diabetes. They estimated non-fasting lipid and glycosylated haemoglobin levels. They also analysed serum lipid levels of their parents. Their data showed that HbA1c was positively associated with total cholesterol, VLDL-C and triglyceride levels, but not with HDL-C. The potential impact of genetic variation (familial tendency) on plasma levels of total cholesterol and lipoprotein has been also demonstrated.[13]

Kobbah et al in their 2 year follow-up study, included thirty 3-15 years old diabetic children. They found a significant correlation between HbA1c and serum lipid levels. However, they observed no further association between glycaemic state and lipid profiles following 2 years of insulin treatment (good management of diabetes) and decreasing HbA1c levels.[14] In our study, we did not measure parental lipid profiles so could not determine familial genetic tendency. We did not reveal any association between HbA1c and serum lipid profiles in insulin resistant children.

In previous studies, the degree of impaired glycaemic control was defined by different HbA1c cut off values. Selvin et al defined good and poor glycaemic control, according to the HbA1c levels <6% and >7.5%, respectively.[15] They found a linear association between cardiovascular heart disease and HbA1c levels, the risk was increasing with the elevating levels of HbA1c even lower than 7.0%.[16] Khan et al reported that HbA1c screening not only reflected glycaemic control, but predicted serum lipid profiles in diabetic patients as well. They demonstrated comparatively stronger association of HbA1c levels with serum lipid profiles than fasting blood glucose.[17]

We have to recognise genetic factors as important determinants of lipid levels. Previous reports have suggested that alterations of sex steroids during puberty period affected serum lipid levels.[18] Azad et al, in their study reported that there was no significant effect of age or sex on total cholesterol and triglyceride levels in children in the age range of 11-17 years.[19] The weak point of our data is not to classify the children according to distribution of gender and pubertal status which could be as risk factors for higher lipid levels. We only analysed the impact of glycaemic status with screening HbA1c on serum lipid levels.

Shalitin et al analysed 256 patients, 109 males and 147 females aged 5-22 years for BMI, HOMA-IR, fasting insulin, fasting glucose, serum lipid levels, age and gender. They concluded that HOMA-IR correlated significantly with triglyceride levels but not with total cholesterol, LDL-C, HDL-C or HbA1c levels.[20] Our findings were similar to this study because we also determined that serum triglyceride values revealed higher levels in the group with HOMA-IR ≥3.5, compared to the group with HOMA-IR <3.5, but lower HDL-C levels in insulin resistant group.

The result of reflecting no correlation between HOMA-IR and HbA1c levels was similar to Shalitin's study data.

Caceres et al, analysed the association between insulin resistance and components of the matabolic syndrome in a group of 61 Bolivian obese children aged between 5 and 18 years old. The prevalence of high triglyceride level was 42.6%, low level of HDL was 55.7%. Insulin resistance (HOMA-IR >3.5) was found in 39.4% of the children, with a higher rate in males (50%) than females (29%). They reported that there was a strong correlation between insulin resistance and high triglyceride levels. They determined insulin resistance commonly among obese children, accompanying high blood pressures and high triglyceride presence. [21] Our data was similar to this study since insulin resistance correlated with high triglyceride levels. However the limitation of our study is that we did not analyse the impact of pubertal status on lipid levels and insulin resistance.

Osei et al examined the impact of HbA1c in first degree 219 non-diabetic relatives of African-American patients with type 2 diabetes. HbA1c was divided into tertiles (normal range: 3.3-6.4%). The mean HbA1c was 4.7% (range 3.3-4.8%) for tertile 1, 5.4% (range 4.9-5.6%) for tertile 2, and 5.8% (range 5.7-6.4%) for tertile 3. They found that mean HOMA-IR was significantly higher in tertile 3, compared to tertile 1 and tertile 2. Higher HOMA-IR levels directly correlated with higher HbA1c levels. However, they found no significant relationships between serum lipid levels and HbA1c values in tertiles in their cohort. They determined that higher levels of HbA1c could be used as a screening tool in order to examine metabolic syndrome components (insulin resistance and blood pressure) for high-risk individuals who had tendency to type 2 diabetes.[22]

Our study data revealed difference from this study since our subjects showed no correlation between HbA1c values and insulin resistance screened by HOMA-IR levels. Our data determined no significant difference between serum lipid profiles and HbA1c levels among the insulin resistant groups. Insulin resistant group with HOMA-IR ≥3.5 revealed significantly lower HDL-C, higher triglyceride levels compared to the group with HOMA-IR <3.5. We reported the dyslipidemia of higher triglyceride and lower HDL levels in insulin resistant group so the dyslipidemia correlated with the degree of insulin resistance. However, HbA1c screening did not correlate with this dyslipidemic pattern in insulin resistant children. We believe that, larger comprehensive studies can highlight the impact of glycaemic control on lipid profiles that play major role in long-term cardiovascular complications of insulin resistance.

Declaration of Interest

We declare that we have no conflict of interests.

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