Symbiosis

www.symbiosisonlinepublishing.com
ISSN Online: 2374-6890

Research Article | Journal of Endocrinology and Diabetes | Open Access

Examining the Frequency of Insulin Resistance in Children with Chronic Hepatic Disease

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Received: February 21,2019; Accepted: March 05,2019; Published: March 25, 2019

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Abstract

Background: Liver is one of the most important insulin target organs and insulin resistance (IR) accompanies chronic hepatic disease. IR is one of the main pathophysiological features characteristic of chronic hepatic diseases. As a result, early diagnosis of IR is very important in patients with chronic hepatic disease.

Methods: After recording demographic properties of the patients and calculating the rate of IR (HOMA-IR) and severity of hepatic disease (PELD/MELD Scores), statistical analysis of the obtained data was performed to compute the frequency and relationship of IR based on age, sex, body mass index (BMI), the type of background disease, and severity of hepatic disease. Statistical analyses were performed using SPSS Software.

Results: The results obtained showed that the frequency of males, under 12 years old, with BMI values under 18.5 kg/m2were higher. However, IR rate was higher in female gender, age group of above 12 years old, and normal BMI. The effect of age and BMI parameters on IR was also statistically significant ($p<0.001$), while sex and disease severity had no significant effect on IR.

Conclusion: The diagnosis and treatment of the affected children at lower ages and administration of proper dietary regimens could assist in preventing disease progression and also in more effective treatment.

Keywords: Insulin Resistance; Chronic Hepatic Disease; HOMA-IR; PELD Score; MELD Score.

Introduction

Liver is the biggest internal organ and gland of the human body with the main functions of detoxification and regulation of carbohydrate, fat and cholesterol metabolism [1]. Now, there is no doubt about the importance of glucose absorption by hepatocytes [2]. Glucose metabolism disorders are common in hepatic damages; among them, the most usual disorders are hyperglycemia and glucose intolerance [2].

The serum insulin level in diabetic patients suffering from chronic hepatic diseases is higher than other diabetic patients [3]. The insulin resistance (IR) is common among children and is associated with the risk of cardiac, hepatic, and metabolic diseases and therefore, is of special importance [4]. For decades, IR has been well-known as one of major characteristics in development of type 2 diabetes mellitus in adults and is associated with obesity, metabolic syndrome, hypertension, and cardiac diseases [5]. Liver has been known as a major target of damage in patients with IR or metabolic syndrome [6]. IR is among important metabolic parameters, particularly in children, which along with factors such as hepatic disorders [7], age [8] and body mass index (BMI) [8, 9], is in association with chronic and background hepatic diseases [10-11].

Considering the role of IR in the emergence of a wide spectrum of clinical risks (particularly chronic hepatic diseases), it is extremely necessary to identify the factors leading to hepatic diseases and to diagnose them at early stages.

Methods and Materials

The present study is a non-interventional cross-sectional study conducted on 65 children under 18 years old who were suffering from chronic hepatic diseases, referred to Specialized Pediatric Liver Clinic affiliated to Shiraz University of Medical Sciences during 2017. The diagnosis of chronic hepatic disease was based on sonography and histopathologic findings of liver biopsy specimens. Patients with the history of diabetes mellitus and endocrine disease of their own or their families were excluded. Demographic and clinical data of the patients such as age, sex, weight and height, and background diseases were recorded. After the consent forms were obtained, 5-cc blood samples were taken and transported to the laboratory to determine the serum glucose concentration and serum insulin level (by the aid of Cobase411 Apparatus, Roche, Germany) after an eight-hour fasting period. Hematologic factors were also examined to determine the severity of hepatic disease using standard criterion of PELD/MELD Scores [12]. The rate of IR was calculated by using HOMA-IR Model with the standard formula as follows [13]: HOMA-IR = fasting insulin (µu/mL) x fasting glucose (mmol/L)/22.5. The value of HOMA-IR

was considered by calculating two thresholds of above 1.7 and 2.1 as the presence of abnormal IR [14, 15]. Statistical analysis of the data obtained was performed using SPSS Software at the significance levels (p-values) under 0.05, alpha = 0.05, p = 62.5%, and d = 7.5%.

Results

Of 65 children studied with chronic hepatic diseases, most of cases were males (34 individuals, 52.3%) and the age range of all cases varied from 3 months to 18 years, with the mean age of 92 months (7.5 years). The mean BMI value in the studied individuals was 16.95 kg/m^2 with a minimum value of 11.45 kg/m^2 and maximum value of 27.78 kg/m2. 54% of the girls and 75% of the boys were in the normal range (Normal or Healthy Weight; the 5th percentile to less than the 85th percentile) [16]. Of the background diseases present in the individuals studied (Table 1), the most frequent ones were progressive familial intrahepatic cholestasis (PFIC) and Cryptogenic.

The frequency of IR (HOMA-IR>1.7) was 30.7%. The average insulin resistance rate (HOMA-IR) in patients with hepatic disease was 1.73. In terms of gender, this rate was 1.58 for males and 1.9 for females. However, this difference was not statistically significant (p-value = 0.589), meaning that the sex had no effect on IR rate. In terms of age, the average insulin resistance rate was 1.14 and 2.63 for individuals under12 years of age and above 12 years of age, respectively. According to Mann-Whitney test, this difference is significant at the level of 0.05 for these two age groups (p-value = 0.001). Therefore, these results are indicative of the effect of age on IR rate. According to BMI, the average IR rate was 1.03 for the underweight group, 2.06 for normal-weight group, 1.75 for the overweight group, and 0.92 for the obese group. There was a significant direct relationship between BMI and IRIr rate (p-value = 0.001). Regarding the grouping of BMI factor, there were no significant differences between four BMI groups in terms of IR. The results of statistical analysis indicated the lack of effectiveness of hepatic disease severity on the IR rate. Analysis of hepatic disease severity and examining its relationship with IR rate based on children's age in individuals under the age of 12 years old (PELD score) and above the age of 12 years old (MELD score) showed no significant relationship (p-value = 0. 07 and p-value = 0.38, respectively). As to the distribution of average insulin resistance rate in background disease, individuals with tyrosinemia had the lowest rate of IR (0.47%) and those with hepatic fibrosis had the highest IR rate (5.19%) (Table 1).

Table 1: Frequency of background disease in the individuals studied and insulin resistance rate in each one

Background Disease	Frequency	Percent	HOMA-IR		
			Average	Maximum	Minimum
Tyrosinemia	3	0.47	0.96	0.05	4.6
Cryptogenic	10	1.72	5.61	0	15.4
PFIC	17	0.89	3.37	0.03	26.2
Wilson`s disease	7	1.47	3.19	0.61	10.8
Neonatal hepatitis	8	1.61	5.57	0.02	12.3
Biliary atresia	7	1.8	7.58	0.34	10.8
Primary sclerosing cholangitis	2	2./85	4.52	1.19	3.1
Autoimmune hepatitis	7	3.36	13.52	0.03	10.8
GSD	2	1.75	3.4	0.1	3.1
Hepatic fibrosis	2	5.19	9.34	1.01	3.1

The results of statistical analysis on ten types of common background diseases in the individuals studied showed that there was no significant difference between the average IR rate in these background diseases (Chi-square = 8.997, df = 9, p-value = 0.438). Therefore, it is concluded that the type of background disease has no effect on IR rate. The average severity of hepatic disease for HOMA-IR<1.7 patients is 10 and this value for HOMA-IR>1.7 patients is 9.45, which are not significantly different, indicating no relationship between severity of hepatic disease and IR rate in these two groups (Mann-Whitney = 384, p-value = 0.411). The average severity of hepatic disease for HOMA-IR<2.1 patients was 10.08 and this value for HOMA-IR>2.1 patients was 9, which were also not significantly different in this case (Mann-Whitney =355, p-value = 0.841).

Discussion

Analysis of data obtained from the present study with the aim of examining the frequency of IR in children with chronic hepatic diseases revealed that the frequency of IR (HOMA-IR>1.7) was 30.7%. In an investigation by Yin and coworkers, the prevalence of IR in children with obesity or metabolic syndrome was 67.2% and 86%, respectively [14]. Of the total 65 children studied suffering from chronic hepatic diseases, the frequency of boys (52.3%) was slightly more than that of the girls, and there was no significant relationship between sex and HOMA-IR (p-value = 0.58). In accordance with our results, in 2013, Wang and colleagues reported that the prevalence of IR in the boys was higher than that of the girls [17]. Similar results were reported in studies by Hainevora et al. and Bonneau et al. [18, 19]. In

2015, Van Der Aa and coworkers reported that in seven out of eighteen studies examined by them, reporting the results related to sex in terms of sex, it seemed that in comparison with boys, girls were more resistant to insulin [15]. In contrast to the studies mentioned, in comparison to boys, the rate of IR was higher in girls [20-21]. Of course, some studies such as those conducted by Yin et al. (2013) and Caserta et al. [14, 22] reported the IR prevalence to be similar between boys and girls.

The analysis of data obtained from the patients studied showed that there was a direct significant relationship between BMI and IR rate ($p<0.001$).Consequently, it could be concluded that with increasing BMI, IR rate increases, but there is no significant difference between the four BMI groups with respect to IR rate ($p = 0.1$). These results are in accordance with many studies. Compatible with our findings, Ferrannini knows IR and increased insulin secretion as features of obesity. They showed that insulin sensitivity has a linear relationship with BMI at a particular age and sex [23]. In 2013, through examination of numerical value of HOMA-IR among 3203 Chinese children aged 6-18 years, Yin found that the prevalence of IR in children with obesity and metabolic syndrome was 44.3% and 61.6%, respectively [14]. In 2015, via examination of eighteen population-based studies on epidemiology IR in children, Van Der Aa and coworkers reported that IR prevalence was 3.1-44% among them. The prevalence of IR was also higher among overweight and obese children than that in normal-weight children [15]. In 2009, Ferreira et al. investigated the relationship of BMI and IR with metabolic syndrome in 109 Brazilian children, showing that obesity and IR are connected to each other and playing the role of cardiovascular disease risk factors, these two factors are linked to metabolic syndrome [24]. During 2015, in an inter-sectional investigation on 817 healthy teenagers aged 15-16 without diabetes, Lin et al. reported that HOMA-IR was significantly related with body weight and BMI in both genders ($p<0.001$).The intermediate level of HOMA-IR had a positive and direct relationship with obesity indices in male teenagers. However, HOMA-IR values had no relationship with body fat percentage in female teenagers [25]. Ibáñez et al. in 2006 reported that noticing the increased weight of children between the birth time and 2 years of age, there have been remarkable changes regarding central obesity and IR from 2 to 4 years of age [26].

In terms of the significance level, variance analyses are indicative of a strong relationship between age and IR so that the average HOMA-IR rate of individuals above 12 was higher than those under12 and the age influenced IR rate ($p<0.001$). This was in accordance with the results of Lin et al. in 2015, who reported that HOMA-IR had a significant relationship with body weight and BMI in both genders ($p<0.001$) [25].

The results of the present investigation showed that the severity of hepatic disease in individuals below12 years old (based on PELD score) was remarkably higher than those above 12 years (based on MELD score) (78.5%). However, there was no significant relationship ($p>0.05$) between the severity of hepatic disease in the individuals studied in total, and in the age groups under12 and above 12. Statistical analyses also showed no significant effect of background disease on average IR rate totally, and with limits of 2.1 and 1.7 for IR ($p>0.05$). Although there were few data available, in accordance with our results, Saki and Karamizadeh (2014), in their investigation on 102 obese Iranian children, reported that the severity of hepatic disease had a positive relationship with HOMA index. They also found that the grade of fatty liver had a significant relationship with body weight and BMI [27]. Using histological data of 458 Italian patients, Francanzani et al. (2008) discovered that the patients with hepatic disorders were significantly older and had lower HOMA-IR [28]. Marchesini et al. indicated that NAFLD accompanies IR and hyper insulinemia, even in lean persons with normal glucose tolerance [29]. The findings of Angelico and coworkers showed that individuals with higher IR had higher prevalence of severe steatosis [30].

Conclusion

In conclusion, according to the analysis of the results obtained from the present investigation, it can be concluded that the frequency of males aged under 12 years with normal BMI was higher among 65 patients studied, whereas IR rate was higher in females with chronic hepatic diseases above 12 years old with normal BMI. It was also found that the two factors of age and BMI had statistically significant effects on insulin resistance ($p<0.001$). However, sex and severity of hepatic disease had no significant effect on IR, which could originate from small population size included in the present study. From the results obtained, it can be inferred that diagnosis and treatment of children at lower ages and administration of proper diets controlling their weights can assist in prevention from disease progression and its more successful treatment.

Acknowledgements

This study was entirely financed by Shiraz University of Medical Sciences (project no. 95-01-49-13430). The authors would like to thank Center for Development of Clinical Research of Nemazee Hospital and Dr. Nasrin Shokrpour for editorial assistance.

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