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Original Research Article

Type 2 diabetes in children and adolescents- A Study of C-peptide and insulin levels

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Abstract: Type 2 diabetes mellitus (T2DM) is a disease affecting mostly the adults but is being increasingly recognized in children and adolescents. However, the information about the glycemic profile and insulin resistance is scanty. Therefore, the objective of present study was to study the glycemic profile along with the levels of C-peptide, serum insulin and insulin resistance in children and adolescent withT2DM. 26 patients of either sex (08-18 years age group) suffering from T2DM and 26 normal healthy individuals served as control; were included in the study. In addition to estimation of above mentioned parameters, Homeostasis model assessment for insulin resistance ($HOMA_{IR}$) were also calculated using standard methods and data from patients and controls were compared by using Student's t-test. Serum insulin, C-peptide and fasting blood glucose levels were significantly high ($p<0.001$) in T2DM patients as compared to healthy controls. Marked increase in insulin resistance was also observed in T2DM children and adolescents as characterized by increased $HOMA_{IR}$ index. Therefore, regular monitoring of blood glucose level along with $HOMA_{IR}$ index calculation should be carried even at the early stage of life in order to recognize the incidence of T2DM in children and adolescents. In addition, health information and emphasis on healthy diet along with regular physical exercise may be provided to the children and adolescents in educational programs.
Keywords: Insulin resistance, HOMA index, obesity, diabetes mellitus

INTRODUCTION:

Type 2 diabetes mellitus (T2DM) is a major global health problem in which the patients are at all the time on risk of complications. Complications may be macrovascular (coronary heart disease, peripheral vascular disease and stroke), microvascular (neuropathy, retinopathy and nephropathy) and both micro- and macrovascular (diabetic foot). [1]. In general, patients of T2DM are usually over forty years of age and are often overweight or obese. However, the mortality and morbidity of Type 2 diabetes are now in alarming phase, even in the children and adolescents. Apart from environmental and genetic factors, increase in body weight, reduced physical activity, urbanization and life style modifications also play an important role in causing insulin resistance, defect in insulin secretion and predisposing the children to develop T2DM [2,3].

In T2DM, the hyperglycemia develops late; hence, the estimation of fasting plasma glucose concentration alone may not be sufficient diagnostic criteria and has its own limitations. Moreover, C-peptide and insulin are secreted in equimolar concentrations in blood, their estimation is a good indicator of pancreatic reserve and may help in early detection of T2DM development in children and adolescents as well [4].

Insulin resistance is a state in which a given amount of insulin produces a subnormal biological response [5, 6]. In particular, it is characterized by a decrease in the ability of insulin to stimulate the use of glucose by muscles and adipose tissue and to suppress hepatic glucose production and output [6]. Previous

studies have documented the incidence of insulin resistance and hyperglycemia in T2DM adult patients, however, studies related to insulin resistance in children and adolescents are scanty.[7]Furthermore, the study pertains to assessment of glycemic profile, fasting insulin, C-peptide and insulin resistance in early stage of life and not too many literature on young population is available to the best of our knowledge. Therefore, the aim of present study was to evaluate the glycemic profile and insulin resistance in children and adolescent T2DM patients and to determine its association with body weight and family history in order to suggest the possible life style changes that may be adopted to reduce the risk of future complications of diabetes in children and adolescents.

MATERIALS AND METHODS:

In the present study 26children and adolescents of either sex with Type 2 diabetes mellitus (11 males and 15 females) belonging to age group 08 to 18 years were recruited as patient group. 26 age and sex matched healthy subjects with fasting plasma glucose less than 100 mg/dl were recruited as controls. A general information or pre-experimental questionnaire regarding demographic information, detailed clinical and family history; and limited physical examination including waist-hip measurement was completed in all the subjects after taking their informed consent and approval of protocol by ethics committee of college. All patients had T2DM, defined as per revised American Diabetic Association criteria (ADA 2013) [8].

Inclusion criteria: Subjects, who gave informed consent for study, newly diagnosed, not under any medical treatment (anti-inflammatory drug) or taking antioxidant supplement for at least one month prior to blood collection were included.

Exclusion criteria: Children's and adolescents above 18 and below 08 years of age; those with acute and chronic infections, fever, malignancy, renal disease, hepatic disease, hypertension, those taking antioxidant vitamin supplements or non-steroidal anti–inflammatory drugs; those with maturity onset diabetes of the young (MODY); adolescents girls with sexual activity; and with other connective tissue disease like systemic sclerosis, were excluded.

Fasting blood sample (5 ml) was collected from the anticubital vein of the study group subjects and divided into three parts. First part was collected in fluoride vaccutainers for glucose estimation; second part was kept for half an hour for proper coagulation followed by serum separation at 3000 rpm to estimate serum insulin and C-peptide levels. Fasting blood glucose levels were measured by using enzymatic kit based on glucose oxidase method. Glucose, in presence of glucose oxidase, converted into gluconic acid along with production of Hydrogen peroxide, which later oxidatively coupled with 4-aminoantipyrine /phenol (in presence of peroxidase) and red quinoneimine dye was produced. The intensity of the color complex was directly proportional to the glucose in specimen and showed absorption maxima at 505 nm [9]. Serum insulin and Serum C-peptide levels were measured by radioimmunoassay (Diagnostic System Laboratories, Texas, and USA). Insulin resistance was estimated using homeostasis model assessment (HOMA-$_{IR}$) from fasting serum glucose and insulin using the Oxford HOMA calculator; or by using the following formula [10, 11].

$$\text{HOMA-}_{IR} = \frac{\text{(Fasting plasma glucose (mmol/l) X fasting insulin (µU/ml)}}{22.5}$$

STATISTICAL ANALYSIS:

The data collected from patients and control were entered separately in Microsoft Excel sheet of windows 2007 and values were expressed as Mean ± SD. The significance of mean difference between patient and control groups was compared by using Student's t test. The distribution of 't'- probability was calculated depending on 'n' and significance of test was obtained. P value < 0.05 and < 0.001 were considered as significant and highly significant, respectively. P value >0.05 was considered as insignificant.

RESULT:

Demographic profile and anthropometric measurements of the study group subjects are represented in Table 1. In the present study, children and adolescents belonged to age group 08to18 years i.e. 13.2 ± 4.5 and 14.5 ± 3.4years in Group I and Group II respectively, as represented in Table 1. In addition to diabetes, Group II subjects have positive family history of T2DM (79%). BMI in T2DM children and adolescents was significantly high ($p<0.05$) than control group subjects. However, waist hip ratio also increased insignificantly ($p<0.1$) in Group II subjects as compared to group I subjects.

Marked alterations in glycemic profile, serum insulin, C-peptide and insulin resistance were observed in children and adolescents with diabetes, as represented in Table 2. In the Group II subjects, fasting blood glucose level was increased significantly (P<

0.001) with respect to healthy controls. It was observed that abnormalities in serum insulin and C-peptide levels along with insulin resistance were highly prevalent in children and adolescents with diabetes. Fasting insulin and C-peptide levels were increased significantly (p< 0.001; 92.85 and 138.46% high respectively) in the patients group (Group II) as compared to healthy control group subjects (Group I). Similarly, HOMA $_{IR}$ index was greater than 2.5 (the cut off for normal and impaired insulin sensitivity) and increased significantly (P< 0.001) in Group II subjects as compared Group I subjects.

Table 1: Demographic profile of the children and adolescents with Type 2 diabetes mellitus (Group II) and controls (Group I) (Mean ± SD).

S.No.	Parameters	Group I (n=26)	Group II (n=26)
1	Age (years)	13.2 ± 4.5	14.5 ± 3.4
2	Males/Females	13/13	11/15
3	Family history	-	79%
4	Height (meter)	152.4 ± 12.8	149.72 ± 13.2
5	Weight (Kg)	41.2 ± 4.7	53.6 ± 5.2
6	BMI (Kg/m^2)	17.92 ± 1.23	24.36 ± 1.45**
7	Waist: Hip ratio	0.78 ± 0.02	0.95 ± 0.04*

Where,
*p<0.1: Non-significant
** p<0.05: Significant;
*** p<0.001: Highly Significant;

Table 2: Biochemical parameters of the study group subjects (Mean ± SD).

S.No.	Parameters	Group I (n=26)	Group II (n=26)
1	Fasting Blood Glucose (mg/dl)	72.36± 10.5	182.28± 18.65***
2	Serum insulin (nmol/L)	0.14± 0.03	0.27± 0.05***
3	C-peptide (nmol/L)	0.52± 0.10	1.24± 0.08***
4	$HOMA_{IR}$	2.88± 0.58	18.27± 3.54***

Where,
. * P<0.1: Non-significant
** P<0.05: Significant
*** P<0.001: Highly significant

DISCUSSION:

Type 2 diabetes mellitus is emerging as a new clinical problem within pediatric practice. Previous reports indicate an increasing prevalence of type 2 diabetes mellitus in children and adolescents around the world in all ethnicities [12]. In India, type 2 diabetes in children as well as in adults, is now reaching epidemic proportions [13, 14]. Children with Type 2 diabetes are found to be overweight at diagnosis and occasionally obese [15]. In the present study, the BMI was significantly increased in T2DM patients as compared to healthy controls as presented in Table 1. These T2DM children and adolescents were overweight and were at high risk to develop diabetes related secondary complications. Our findings were in agreement with the earlier report of Bernstein on T2DM in children and adolescents [16]. In addition, the presence of family history is an important criterion in the diagnosis of T2DM in children. In the present study, a high degree of positive family history of diabetes was observed in T2DM children and adolescents with respect to healthy controls. However, waist hip ratio was increased insignificantly (p<0.1) in T2DM children.

The maintenance of glucose homeostasis depends upon a balanced state of hormonal, metabolic and secondary messenger levels. In the present study, hyperglycemia was observed in T2DM children along with significantly increased levels of serum insulin and C-peptide which reflect the impaired physiological effectiveness of insulin characterized by insulin resistance in T2DM children and adolescents with respect to healthy controls. Consistent findings have been documented in T2DM children and adolescents of

South India with high HOMA index value [17]. Similarly, Levy-Marchal *et al.;* showed that as in adults, the children with T2DM may also have insulin resistance [18]. In addition, it was suggested that the peripheral insulin resistance could be due to an abnormal insulin molecule that is not able to bind to insulin receptors [19]. According to Gerich, insulin resistance evolving from environmental factors is an equally important risk factor, apart from beta cell dysfunction in the development of T2DM in children and adolescents as well [20].

CONCLUSION:

Thus, on the basis of the present study and consistent findings of previous studies it is obvious that T2DM affects not only adults and elderly but also exerts its culprit effects in children and adolescents as characterized by hyperglycemia in association with overweight, positive family history and insulin resistance. Although the studies related to the prevalence of type 2diabetesin children in most of the developing countries are not known, type 2 diabetes in children is an entity that needs to be recognized and looked for, especially in overweight children with positive family history of diabetic parents in India. Furthermore, T2DM is asymptomatic in nature and may delay the diagnosis in many as it usually does in adult type 2 diabetic subjects but regular monitoring of blood glucose level with increase in body weight of children and adolescents along with an appropriate prevention and treatment of insulin resistance are required in order to reduce the T2DM associated risk of metabolic and cardiovascular complications.

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