

Assessment of Acanthosis Nigricans and Its Relation with Insulin Resistance in Newly Diagnosed Young Type 2 Diabetics

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Abstract**Original Research Article**

Background: Type 2 diabetes mellitus (T2DM) is not confined only to adults but its prevalence in children and adolescents is in alarming proportion. In this context, appearance of morphological manifestations along with biochemical alteration play a crucial role in diagnosis of disease. **Aim:** The aim of present study was to ascertain the appearance of Acanthosis Nigricans (AN) and its relation with insulin resistance and body mass index (BMI) in children and adolescents with T2DM. **Methodology:** 25 patients of either sex (08-18 years age group) suffering from T2DM and 25 normal healthy individuals as controls; were included in the study. AN was checked on the skin of the intertriginous areas in T2DM patients. Homeostasis model assessment for insulin resistance (HOMA_{IR}) was calculated along with estimation of glycemic profile using standard methods and data from patients and controls were compared by using Chi square-test and student t-test. **Result:** Marked appearance of AN was observed along with significantly high ($p < 0.001$) levels of serum insulin and fasting blood glucose levels in T2DM patients as compared to healthy controls. In addition, AN was directly associated with enhanced insulin resistance and BMI in T2DM children and adolescents. **Conclusion:** Careful examination of AN along with HOMA_{IR} index calculation and regular monitoring of blood glucose level with BMI should be carried out in order to recognize the incidence of T2DM in children and adolescents.

Keywords: Acanthosis nigricans, body mass index, Insulin resistance, HOMA index, Hyperglycemia.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) affects about 150 million people worldwide and this figure is expected to double in next two decades [1]. Interestingly, the extending arm of T2DM now touches the feet of children and adolescents and is thus emerging in epidemic proportions among children [2]. In general, T2DM is asymptomatic in nature and may remain undiagnosed in children. This reflects the importance of detection of morphological / cutaneous manifestations or physical signs for early diagnosis and management. In this context, acanthosis nigricans (ANs) have received much attention in both adults and children with T2DM. ANs are brown to black velvety hyperpigmented patches present on the of intertriginous areas. These are present in the maxilla, groin, posterior and lateral folds of neck, umbilicus, fingers, toes and other areas [3].

Among various risk factors of T2DM including environmental and genetic factors, abnormal

nutritional transition in association with decreased physical activity leading to overweight and thereby predisposing the children to develop obesity followed by T2DM. Moreover the incidence of insulin resistance (IR) has been found to be associated with T2DM [4]. IR is characterized by a dysfunction of beta cell insulin secretory capacity, decrease in the ability of insulin to stimulate the use of glucose by muscles and adipose tissue and to suppress hepatic glucose production due to defect in the affinity of the receptors [5].

Previous studies have documented the appearance of AN and incidence of insulin resistance in T2DM adult patients [6], however, studies related to association of AN with insulin resistance in children and adolescents are needed. Furthermore, the study pertaining to AN prevalence and its relation with body weight, glycemic profile, fasting insulin, insulin resistance in young population are scanty to the best of our knowledge and needs more clarification. Therefore, the aim of present study was to ascertain the appearance

of Acanthosis Nigricas (AN) along with estimation of glycemic profile and serum insulin levels in children and adolescent with T2DM; and to determine the relation of AN with insulin resistance and body mass index (BMI) in children and adolescent with T2DM.

MATERIAL AND METHODS

In the present study, 25 children and adolescents of either sex with Type 2 diabetes mellitus (17 boys and 08 girls) belonging to age group 08 to 18 years and attending Diabetic clinic were recruited as patient group. 25 numbers of age and sex matched healthy children 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) [7].

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 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.

All the children were checked for the presence of brown to black velvety hyperpigmented patches (i.e. AN), on the skin of the intertriginous areas. Fasting blood sample (5 ml) was collected from the antecubital vein of the study group subjects and divided into two parts. First part was collected in fluoride vacutainers 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 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 [8].

Serum insulin levels were measured by radioimmunoassay (Diagnostic System Laboratories, Texas, 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 [9, 10].

$$\text{HOMA-IR} = \frac{\text{Fasting plasma glucose (mmol/l)} \times \text{fasting insulin } (\mu\text{U/ml})}{22.5}$$

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 \pm SD. The relation between AN and IR along with BMI was determined by using Chi square test. 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

T2DM children and adolescents recruited in the present study in Group II and healthy controls in Group I belonged to age group 08 to 18 years i.e. 13.4 ± 4.3 and 14.2 ± 3.5 years respectively. 77% of T2DM children and adolescents had positive family history of diabetes. In addition, information pertaining to BMI, appearance of AN and biochemical profile i.e. glycemic profile, serum insulin and insulin resistance, in children and adolescents with T2DM is represented in Table 1. BMI in T2DM children and adolescents was significantly high ($p < 0.05$) than control group subjects. 74% T2DM children and adolescents had acanthosis nigricans, while this presentation was not seen at all in Group I subjects. Moreover, marked alterations in glycemic profile, serum insulin and insulin resistance were observed in children and adolescents with T2DM as compared to healthy controls.

Fasting plasma glucose level was increased significantly (59.35 % high; $p < 0.001$) in Group II subjects with respect to healthy controls. HOMA-_{IR} index was increased significantly ($p < 0.001$) in Group II subjects as it was greater than 2.5 (the cut off for normal and impaired insulin sensitivity) with respect to Group I subjects. Increased HOMA index i.e. enhanced insulin resistance was observed in T2DM subjects due to abnormality in serum insulin levels. Fasting insulin levels were significantly high ($p < 0.001$; 55.56 % high)

in the patients group (Group II) as compared to healthy control group subjects (Group I).

In addition, association of AN with insulin resistance and body weight is presented in Table 2. It was observed that AN was significantly associated with insulin resistance in T2DM children and adolescent. Similarly, AN was significantly associated with body weight (BMI) in study group subjects.

DISCUSSION

It is obvious that Type 2 diabetes mellitus is a major global health problem not only in adults over forty years of age or in overweight and obese population but also in children and adolescents. In developing countries such as India, type 2 diabetes is now reaching epidemic proportions in children as well as in adults [11]. Acanthosis nigricans is observed in both children and adults with T2DM. In the present study, seventy four percent study group population had acanthosis nigricans and it was significantly associated with insulin resistance and body weight in T2DM children and adolescent which indicates the emerging role of AN as diagnostic marker at physical or morphological level in young T2DM population. Previous study in children with Type 2 diabetes also signifies the association of AN with obesity and insulin resistance [6].

Apart from AN, prevalence of obesity is an important risk factor for the development of T2DM. Obesity has been found to be associated with T2DM in the children of Asian Indian in UK.[12] In the present study, the BMI was significantly increased in T2DM patients as compared to healthy controls (as presented in Table 1) which could be explained on the basis of abnormal life style changes and over nutrition in children. Similarly, Bloomgarden in their study also reported that T2DM children and adolescents in Japan were overweight and at high risk to develop diabetes related secondary complications [13]. Conversely, data related to occurrence of T2DM in non-obese Asian Indian children is also available[4].

Moreover, assessment of glycemic profile and insulin resistance is a key factor in the detection of T2DM in children. Balanced state of hormonal, metabolic and secondary messenger levels has a significant role in the maintenance of normal glycemic profile. Interestingly, insulin resistance has been found to be associated with obesity, T2DM and its related future cardiovascular complications as well. In the present study, hyperglycemia was observed in T2DM children along with significantly increased levels of serum insulin and HOMA index (Table 1) which reflect the impaired physiological effectiveness of insulin characterized by insulin resistance in T2DM children and adolescents with respect to healthy controls. Incidence of hyperglycemia and insulin resistance in children with T2DM could be explained on the basis of beta cell dysfunction, inability of insulin molecule to bind with insulin receptors or the effect of environmental factors in imposing insulin resistance [14, 15]. Consistent findings have been documented in European and in South Indian T2DM children and adolescents with impaired glucose tolerance and high HOMA index value [11, 16].

CONCLUSION

Although T2DM is asymptomatic in nature, direct association of appearance of Acanthosis nigricans with insulin resistance and overweight in children and adolescents implicates that T2DM can be diagnosed in early stage of life. In addition, prevention of abnormal nutritional transition (intake of increased amount of food) along with reduced physical activity should be adopted to reduce the incidence of overweight in growing children, an important risk factor of obesity and insulin resistance. Therefore, on the basis of observations in the present study, it is obvious that regular screening of AN symptoms with increase in body weight and assessment of insulin resistance along with blood glucose levels are essential diagnostic steps of T2DM in children and can be managed with an appropriate prevention and treatment strategy in early stage of life in order to avoid T2DM and its chronic complications.

Table-1.0: BMI and Glycemic profile in the study group subjects (Mean \pm S.D.)

S. No.	Particulars	Control Group (n=25)	Patient Group (n=25)	P- value
1.	Body Mass Index (BMI) (Kg/m ²)	18.56 \pm 1.36	24.75 \pm 1.32	p < 0.05
2.	Fasting Blood Glucose (mg/dl)	74.89 \pm 4.56	184.25 \pm 21.18	p < 0.001
3.	Serum insulin (nmol/l)	0.12 \pm 0.02	0.27 \pm 0.05	p < 0.001
4.	HOMA _{IR}	2.97 \pm 0.45	18.05 \pm 3.88	p < 0.001
5.	Acanthosis Nigricans (%)	0	74 %	p < 0.001

where,

p<0.1 : Non-significant

p<0.05: Significant

p<0.001: Highly significant

Table-2.0: Statistical analysis of association of Insulin resistance and BMI with Acanthosis nigricans in Type 2 Diabetes

S.N	Risk factor	Acanthosis nigricans		Total	χ^2	Result (Null Hypothesis)
		Present	Absent			
1.	HOMA index				0.48	Rejected
	≥ 5	16	4	20		
≤ 5	04	1	5			
Total		20	5	25		
2.	Body Mass Index (BMI)				0.44	Rejected
	≥ 23	15	4	19		
≤ 23	3	3	6			
Total		18	7	25		

Null Hypothesis: The risk factor is not associated with severity of disease.
 χ^2 = Calculated value of chi square.

Table value of chi square for 1 Degree of freedom & at 5% level of significance = 3.84.

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