GROWTH HORMONE SECRETION IN TYPE1 DIABETES:RELATION TO SOMATIC GROWTH AND DEVELOPMENT OF NEPHROPATHY

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ABSTRACT

Background : Type 1Diabetes (DM), the most common endocrine metabolic disorder of children and adolescents. It is characterized by chronic hyperglycemia is associated with microvascular complications. ***Objectives*** : to study GH / IGF–I axis and its relation to actual growth and glycemic control, as well as its relation to development of micro vascular complications, with particular stress on diabetic nephropathy(DN). ***Study design*** : This study was carried out on 50 diabetic children and adolescents . Group I included 20 newly diagnosed Patients & group II included 30 long term diabetics .In addition, 20 age – sex matched non diabetic children served as a control group. ***Study children were subjected to*** :1- history taking . 2- thorough physical examination including : a) assessment of nutrition status , b) fundus examination or detection of retinopathy changes if , present , and neurological examination to detect peripheral neuropathy . 3- Investigations, including: a) routine investigation ; urine analysis , CBC, liver & kidney function tests . b) Investigations for glycemic control:fasting blood glucose,determination of glycated hemoglobin (HbA1c) percent.c) Specific ***Investigations***: 1.Measurement of daily urinary albumin excretion rate (UAER) to decide if there is microalbuminurea (MA) as an indicator of the presence of DN, 2.measurement of human growth hormone (hGH) in serum 3.measurement of plasma & urine IGF-I. ***Results*** :this study found a significantly higher scores of the 3 emotional distress indices among diabetics more than that in non diabetics . in addition , there were significant differences between the 2 groups in some social aspects. Both diabetic and control subjects showed similar growth characteristics , recurrent infection, diabetic ketoacidosis and 2ndry enuresis , as well as oral and perianal moniliasis represented the most common symptoms of new diabetics . the overall rates of MA, neuropathy and retinopathy accounted for 18%, 14% & 12% respectively. Both serum GH & Urinary IGF-I were significantly higher in MA positive diabetics than that in MA negative diabetics . BMI, pubertal duration and HbA1c were significantly higher in diabetics positive for MA (MA+ve) than that in diabetics negative for MA (MA-ve). ***Conclusion*** : the present work, which reflect mean GH and IGF-I production, strengthen the evidence of an association between GH and MA and also implicate urinary IGF-I in MA.

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INTRODUCTION

The primary role of growth hormone (GH) is promotion of linear growth. This somatotropic effect is mediated partially through stimulation of the synthesis of Insulin-like growth factor-I (IGF-I), formerly named somatomedin C, in the liver and in the growth cartilage where it acts as a local paracrine-autocrine hormone. Somatic growth of children with type 1diabetes(T1D) depends on adequacy of insulin administration and degree of metabolic control. Under-insulinization and poor diabetes control can result growth delay. On other hand, improved insulin delivery usually `results in normalization of growth but can produce rapid deterioration of retinopathy and nephropathy, through increased concentrations of GH and IGF-I (1).

T1D, previously known as juvenile diabetes or insulin dependant DM (IDDM), is the major form of diabetes in those under 10 years old(2) In 1997 there were 11.5 million people with T1D in the world, this figure is expected to rise to 33.7 million, in the year 2010 (3).

Type 1 diabetes with chronic hyperglycemia is associated with microvascular complications (retino-pathy, neuropathy and nephropathy). However, advances in treatment permit tight glycemic control which delays and slows progression of these complications(4)

As early as 1936, Paul Kimmelstiel and Clifford Wilson described structural

changes in the kidneys and the clinical picture of diabetic nephropathy. Evidence-based knowledge has since accumulated and has highlighted the importance of strict glycemic and blood pressure control in the avoidance and treatment of diabetic nephropathy (DN). Despite all this positive development, epidemiological studies have demonstrated that during the past three decades, DN continues to occur in 15-40% of patients with T1D with a peak incidence after 15 to 20 years of diabetes (5). DN results from the interplay of metabolic and hemodynamic factors in the renal microcirculation, trigerred by hyperglycemia (6). The GH, IGF-I, IGF binding protein (GH- IGF- IGFBP-3) axis has been suggested both to maintain normal renal function and to play an important role in the development of DN (7). The aim of this work was to study GH / IGF –I axis in children and adolescents suffering type 1 diabetes and its relation to actual growth and glycemic control, as well as its relation to development of micro vascular complications, with particular stress on DN.

SUBJECTS AND METHODS

This study was carried out in the Pediatrics Endocrine OutPatient Clinic at the Children's Hospital of Zagazig University Hospitals, during the period from Jan. 2009 to Dec. 2010, on 50 children and adolescents suffering from type 1diabetes (TID). In addition, 20 age – sex matched apparently healthy subjects served as a control group.

Patients:Patients selected were either suffering newly diagnosed T1D, within one month of disease onset (Group I), or suffering T1D, with various disease durations (Group II).

Methodology

All study patients were subjected to the following:

1.History taking :

- Personal data: name, age (years), sex (boy/girl), order among siblings.
- Social aspects (8).
- Psychological aspects (9)
- Age at onset of diabetes, and duration of the disease
- Insulin dose (IU/KG/24H), frequency of adminestration and/ or history of omission OF insulin . Daily dose of insulin injection was defined as the total unit of injected insulin per kilogram of body weight per day in the past month.
- Frequency of DKA and/or hypoglycemic coma / seizure.
- History of weight loss and eating habits
- Symptoms suggestive of diabetic neuropathy.
- History of previous hospital admission(s), infectious diseases, operation, and/or trauma.
- Revision of the follow-up sheet.

2- Thorough clinical examination, including:

- Identification of patients with DKA or hypoglycemic coma.
- General and systemic physical examination.
- Assessment of the nutritional status, using body mass index (BMI).
- Weight (kg)/age and height (cm)/age were recorded, using electrical scales and wall-mounted stadiometer.
- BMI was calculated as kilograms per square meter (kg/m2). Overweight and obesity were defined by the age and sex specific cutoffs. These are international cutoff points for BMI, overweight (BMI equivalent to 25kg/m2 at age ≤ 18 years) and obesity (BMI equivalent to 30kg /m2 at age ≤ 18 years) by sex from 2 to 18 years (10).
- The retinal examination was performed by fundus photography through a dilated pupil with three fields per eye (45^{o}) nasal, temporal and central including stereo photos of the macular region (Nikon NFC 50). The different degrees of retinopathy were classified as no retinopathy, background retinopathy and potentially sight – threatening retinopathy. The latter was defined as clinically significant macular edema or severe non-proliferative

retinopathy or proliferative retinopathy (**11**).

- Neuropathy was assessed by measuring vibration perception thresholds (VPT) at the great toe of the dominant foot, using a biothesiometer (Arnold Horwell, London, UK). The mean of three trials was used and a z score was derived after logarithmic transformation and correction for age, height and sex. Neuropathy was classified as absent (z<2.0), mild (z = 2.0 – 3.0), moderate (z =3.0 – 4.0) and severe (z > 4.0) (**12**).

3- Investigation:

A- Routine investigations:

1) Urine analysis, with particular stress on glucosuria, ketonuria, albuminuria pyuria, hematuria, and / or casturia. Cases with urinary tract infection (UTI), glomerulonephritis and nephrotic syndrome were identified and excluded from the study.
2) Complete blood count (CBC).
3) Liver function tests and kidney function tests.

B- Investigations for glycemic control:

1) Fasting blood glucose determination, using dimension RXL auto analyzer (Siemens medical solutions diagnostic, Tarrytown, WY, USA).
2) Determination of glycated hemoglobin (HbA1c) percent:

Glycemic control was considered "good to excellent" with HbA1c less than or equal to 8.0%, "fair" control 8.1-10.0% and "poor" control if HbA1c > 10.0 % (**13**).

Specific Investigations:

1. Measurement of urinary albumin excretion rate (UAER) in 24h urine collections by an enzyme immunoassay (14). Normo-albuminuria was defined as an UAER of < 30mg/24h in at least two separate urine specimens. MA was defined as an UAER of 30-300 mg/24h (**15**).
2. Quantitative measurement of human growth hormone (hGH) in serum, using the IMMULITE and IMMULITE1000 Analyzer (16). Patient must be fasting and at complete rest 30 minutes before blood collection. The use of an ultracentrifuge is recommended to clear lipemic samples. Hemolyzed samples should not be used. To prevent erroneous results due to the presence of fibrin, ensure that complete clot formation has taken place prior to centrifugation of samples.
3. Quantitative measurement of plasma & urine IGF-I (RayBio® Human IGF-I ELISA) (17).

RESULTS

Study subjects comprised 50 children and adolescents with type 1 diabetes (TID), (23 boys and 27 girls) and 20 age and sex matched apparently normal subjects, as a control group.

The results of this study were presented in Tables (I-IX) and Figures (I-III).

There was non significant difference between the two groups(diabetics &control) with respect to some social aspects (number of close friends, frequency of meeting friends, number of hours spent on recreational activities) (**Table I**).

Table II shows that the mean scores of total emotional distress, anxiety and depression were significantly higher in children with diabetes than that in controls. Both groups were significantly different in child's image in the eyes of friends (P<0.01), and in the eyes of parents (P =0.028), with non significant difference in the child's need for emotional support.

There was no significant difference in age between the two groups after correction by gender. In addition, body weight, body height, and BMI were not significantly different among groups after correction by age and gender. The level of HbA1c (glylated hemoglobin) was significantly higher in diabetic children than in healthy children. The statistical results showed that gender has a significant impact on body weight, and age has a significant impact on body weight, height, BMI, and HbA1c%, **Table III**.

The mean duration of common symptoms of hyperglycemia was significantly higher in long-term diabetics

than in newly diagnosed children, p<0.05. weight loss & enuresis / nocturia are more significantly encountered in the newly diagnosed diabetics .Fifty percent of newly diagnosed diabetic versus 10% of long-term diabetics had infections prior to entry to the study, with significant difference; the common cold was the most common infection, followed by sore throat, febrile illness and gastroenteritis. Forty-five percent of newly diagnosed diabetics presented with enuresis/nocturia versus 10% in long-term diabetics with significant difference p<0.05.The pubertal duration was significantly higher in the long-term diabetics than that in the newly diagnosed diabetics, p<0.01. Forty percent of newly diagnosed diabetics presented in DKA versus 10% in long-term diabetics, with significant difference. Meanwhile, hypoglycemic coma was reported in 3 (10%) of long-term diabetics, with significant difference, **Table IV**.

The mean blood glucose level before starting insulin therapy (in Group I) was significantly higher than that in diabetics kept on insulin therapy (Group II). The mean HbA1c value, at diagnosis (in Group I) was 8.6 ± 0.7, is significantly lower than that in long-term diabetics (8.6±0.7vs 10.4±1.9. Sixty-five percent of children with newly diagnosed diabetes (Group I) had ketonuria at onset (+, ++ or +++) which was significantly more prevalent than that in long-term diabetics, p<0.01. There was non-significant difference in the mean value of BUN in both groups of patients, (**Table V**).

Table VI and Figure I illustrates the microvascular complications of T1D in 50 children and adolescent. Diabetic retinopathy was detected in 12% (6/50), with significantly higher frequency among long-term diabetics than newly-diagnosed cases (16.7% Vs 5%). Neuropathy was identified by VPT. VPT was elevated in 14% of diabetics (7/50), with significant rise among long-term diabetics(20% vs 5%). MA was diagnosed in 16% (8/50) of diabetics, with significantly higher frequency among long-term diabetics than among newly diagnosed patients (20% Vs 10%). No cases were detected with macroalbuminuria (UAER > 300mg/24 hours).

The mean UAER/day and urinary IGF-I/day were significantly higher among long-term diabetics than that among newly-diagnosed diabetics, with nonsignificant change of plasma IGF-I, nor serum GH, **Table VII and Figure II**.

The mean body weight, body height, BMI, pubertal duration and HbA1c were significantly higher in diabetics positive for MA (MA+ve) than that in diabetics negative for MA (MA-ve) **Table VIII**.

Mean serum GH and urinary IGF-I excretion rates were significantly higher in MA+ve subjects than in normoalbuminuric subjects (22.4 ± 2.6 vs 11.1 ± 0.9 ng/ml [p<0.01] and 645 ±110 vs 293 ±18 ng/day [p<0.05]), respectively, with nonsignificant difference for plasma IGF-I, **Table IX & Fig. III.**

Table I: Social characteristics of 50 diabetic children and adolescents versus 20 control non-diabetic subjects.

	Control n = 20	Diabetics n = 50	p-value
Number of close friends, X±SD	4±2	5±1	0.382
Frequency of meeting friends, n & (%)			
Once a week	5(25%)	10(20%)	
Every other day	3(15%)	9(18%)	0.211
Daily	12(60%)	31(62%)	
Number of hours spent on recreational and social activities per week, X±SD	13±2.3	14±1.6	0.235

n: number %: percent X±SD: mean ± standard deviation

Table II: Psychological characteristics of 50 diabetic children and adolescents versus 20 non-diabetic subjects.

	Control n = 20	Diabetics n = 50	p-value
Child's image in the eyes of friends, n & %(%)			
Poor	4(20%)	13(26%)	<0.01(S)
Average	5(25%)	16(32%)	
Good	11(55%)	21(42%)	
How do parents look at the child, n & (%)			
Poor	4(20%)	12(24%)	
Average	4(20%)	13(26%)	0.028(S)
Good	12(60%)	25(50%)	
Child's need for emotional Support, n & (%)			
Not at all	5(25%)	12(24%)	
Sometimes	9(45%)	25(50%)	0.437
A great deal	6(30%)	13(26%)	
- Total emotional distress, score, X±SD	1.57±0.6	1.79±0.7	<0.01(S)
- Anxiety score, X±SD	1.5±0.8	1.8±0.7	<0.01(S)
- Depression score, X±SD	1.6±0.7	1.68±0.8	0.003 (S)

n : number %: percent X ± SD: mean ± standard deviation S : significant

Table III: Growth response {body mass index (BMI)} and degree of glycemic control (HbA1c%) of 30 long-term diabetic children and adolescents versus 20 non-diabetic subjects.

Variable X±SD	Control N = 20	Long-term Diabetics N = 30	P-values		
			Group	Gender	Age
Age (years)	10.1±4.9	10.98±4.61	0.387	0.955	
Gender (Male/Female)	8/12	23/27			
BMI (Kg/m^2)	18.27±3.66	19.13±2.81	0.512	0.13	<0.001(s)
HbA1c (%)	4.76±0.51	8.93±1.58	<0.001	0.510	<0.001(s)

n : number %: percent X ± SD: mean ± standard deviation S : significant

Table IV: Clinical presentation of 20 newly diagnosed diabetics (Group I) versus 30 long-term diabetics (Group II), at entry to the study.

	Group I n = 20	Group II n = 30	p-value
Age (years),			
X±SD	8.61±2.7	12.2±4.1	<0.05(S)
Range	6-10	9-15	
Duration of symptoms (days)			
X±SD	19 ±8.3	456.6±96.4	0.001(S)
Range	11-29	380-715	
Infection, n & (%)	10(50%)	3(10%)	<0.05 (S)
Enuresis or nocturia, n & (%)	9(45%)	3(10%)	<0.05 (S)
Diabetic ketoacidosis, n & (%)	8(40%)	3(10%)	<0.05 (S)
Weight loss, n & (%)	4(20%)	2(6.7%)	<0.05 (S)
Candidiasis, n & (%)	2(10%)	4(13.3%)	>0.05(NS)
Hypoglycemic seizure/coma, n & (%)	0.0(0%)	3(10%)	<0.05(S)
Pubertal duration (years), X±SD	0.9±0.6	5.1±3.2	0.01(S)

%: percent n: number S: significant X±SD: mean ± standard deviation

Table V: The mean blood glucose, glycated hemoglobin (HbA1c) percent, BUN and ketonuria of 20 newly diagnosed diabetics (Group I) versus 30 long-term diabetics (Group II) at entery to the study.

	Group I n = 20	Group II n = 30	p-value
Blood glucose (mg/dl)			
X ±SD	218±97.2	193±44.7	<0.05(S)
Range	189-465	171-305	
HbA1C (%)			
X ±SD	8.6±0.7	10.4±1.9	<0.05(S)
Range	7-9	9-12	
BUN (mg/dl),			
X ±SD	19.3±10.8	16.4±6.8	0.09 (NS)
Ketonuria, n & (%)	13(65%)	4(13.3%)	<0.01(S)

BUN: blood urea nitrogen n: number %: percent
X±SD: mean ± standard deviation. S: significant NS: nonsignificant

Table VI: Frequency of microvascular complications of type 1 diabetes in 20 newly diagnosed diabetics (Group I) and 30 long-term diabetics (Group II), at entry to the study.

Complication, no (%)	All patients n =50	Group I n = 20	Group II n= 30
Retinopathy (All levels)	6(12%)	1(5%)	5(16.7%)*
Background retinopathy	5(10%)	1(5%)	4 (13.7%)
Potentially sight-threatening retinopathy#	1(2%)	---	1(3.3%)
Neuropathy## (All levels)	7(14%)	1(5%)	6(20%)*
Mild (Z=2-3)	4(8%)	1(5%)	3(10%)
Moderate (Z=3-4)	3(6%)	---	3(10%)
Severe (Z>4)	---	---	
Microalbuminuria (MA) $	8(16%)	2(10%)	6(20%)*

*n: number %: percent * Significant*

#:defined as clinically significant macular edema or severe non-proliferative or proliferative retinopathy.

$: defined as a urinary albumin excretion rate (UAER) of 30-300mg/24 hours.

##: assessed by measuring vibration perception thresholds (VPT) at the great toe of the dominant foot, using biothesiometer. Neuropathy was classified as absent-Z-score <2, mild (Z=2-3), moderate (Z=3-4), and severe (Z>4).

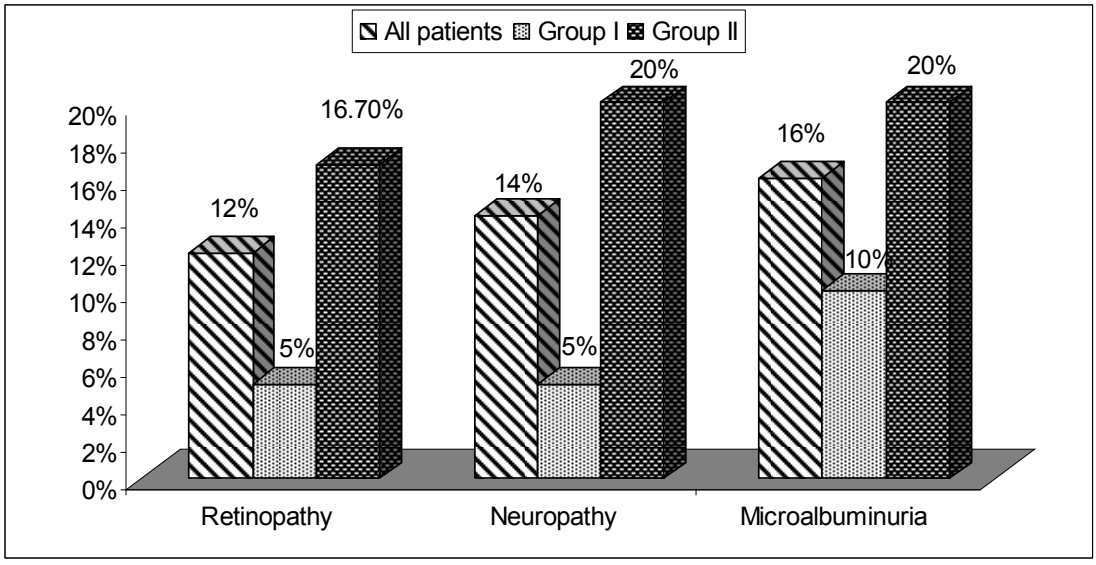

Figure I: Frequency of micro vascular complications in 50 diabetic children and adolescents, in newly diagnosed diabetics (Group I) and in long-term diabetics (Group II).

Table VIII: Urinary albumin excretion rate (UAER), serum growth hormone (GH), urinary insulin growth factor-I (IGF-I) and plasma IGF-I, in 20 newly-diagnosed diabetics (Group I) versus 30 long-term diabetics (Group II), presented as mean ± standard deviation (X ± SD).

	Group I n = 20	Group II n = 30	p-value
UAER (mg/24h)	26 ±1.5	168±87.3	<0.01(S)
serum GH (ng/ml)	13.4±1.6	12.5±2.3	>0.05(NS)
Urinary IGF-I (ng/day)	143±18	395±32	<0.01(S)
Plasma IGF-I (ng/ml)	301±14	308±21	>0.05(NS)

n: number S: Significant NS: nonsignificant mg: milligram ng: nanogram

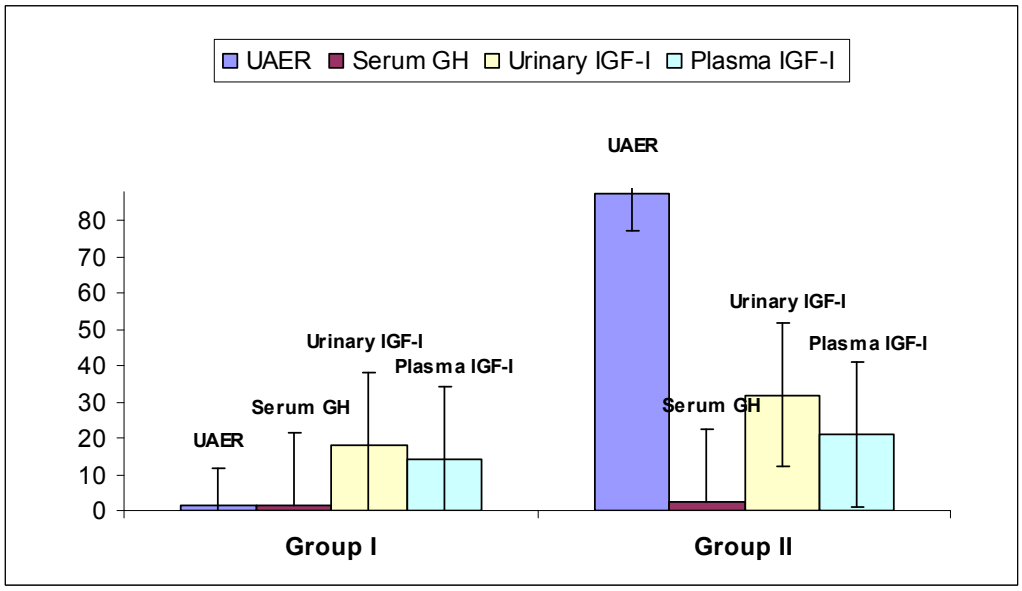

Figure II: UAER/day, serum GH (ng/mL), urinary IGF-I/ day and plasma IGF-I/mL, in newly-diagnosed diabetics (Group I) and in long-term diabetics (Group II).

Table IX: Body weight, body height and body mass index (BMI), pubertal duration and glycated hemoglobin (HbA1c) in diabetic children and adolescents with microalbuminuria (MA) and children without MA, presented as mean ± standard deviation (X±SD).

	MA -ve n=42	MA +ve n = 8	P- Value
BMI (Kg/m^2)	19.1±1.2	22.2 ±2.3	<0.05(S)
Pubertal duration (year)	1.6±0.8	4.4±1.7	<0.05(S)
HbA1c (%)	6.8±1.2	11.0±1.8	<0.01(S)

n: number %: percent S: significant -ve: negative +ve: positive

Table IX: Mean serum growth hormone (GH), urinary insulin growth factor-I (IGF-I) and plasma IGF-I in diabetic children with microalbuminuria (MA+ve) and in children without MA (MA-ve), presented as mean ± standard deviation (X ± SD).

	MA -ve n=42	MA +ve n = 8	P Value
serum GH (ng/ml)	11.1± 0.9	22.4±2.6	<0.01 (S)
Urinary IGF-I (ng/day)	293±18	645±110	<0.05 (S)
Plasma IGF-I (ng/ml)	213±17	228±16	>0.05 (NS)

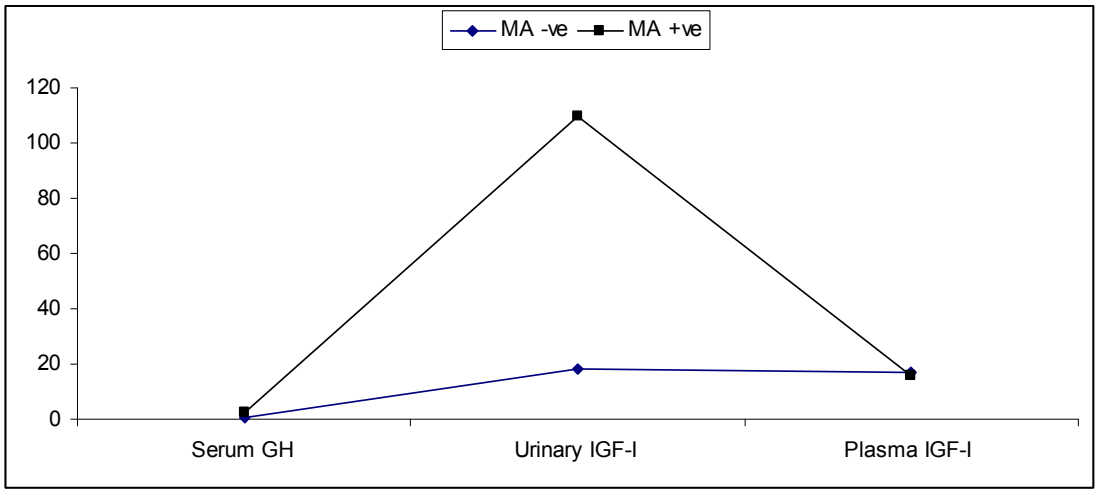

Figure III: Serum GH, urinary IGF-1 and plasma IGF-1excretion rate in MA –ve and MA +ve diabetic children and adolescents.

DISCUSSION

Type 1 diabetes is a disease that results from autoimmune destruction of the insulin-producing beta-cells (β-cells)in the pancreatic islets of langerhans. The pathophysiological mechanism initiating this autoimmune response remains to be determined (**18**). It is associated with accelerated atherosclerosis and predisposes to certain specific microvascular complications, including retinopathy, neuropathy and nephropathy (**15**). Classically, the development of diabetic microangiopathy depends mostly on the

duration of diabetes and on the degree of glycemic control. However, the development and progression of DN shows a significant variation between individuals and, consecutively, develops only in fraction of diabetic subjects despite the inadequately controlled diabetes, while nearly all of them develop the other microangiopathies. (**19**).

Upon study of the psychosocial characteristics, this study found significantly higher scores of the three emotional distress indices (anxiety, depression and total distress) in children and adolescents with T1D than in those without diabetes. Higher proportion of children with diabetes reported poor or average image in friends' eyes. These findings are in keeping with earlier studies which concluded that children with T1D were worse than healthy children without diabetes in psychosocial adjustment (**8, 20**).

However, this study did not find significant differences between diabetics and controls in other social aspects (number of close friends and frequency of meeting them and number of hours spent on recreational activities), and need for emotional support, indicating adaptation to their diabetes. On other hand, **Moussa et al** (**2005**)(8) reported that children with poor glycemic control (Hb A1c >10.0%) had significantly higher distress than children with good glycemic control (HbA1c ≤ 8.0%). Another study (**21**) concluded that metabolic control was related to compliance to treatment, and the latter may have been influenced by psychological functioning. However, **Kovacs et al** (**1996**)(22) found no relation between depression and metabolic control.

In this study, diabetic children had similar growth response as the healthy non-diabetic children, evidenced by the similar body weight, body height, and BMI after being corrected for age and gender. **Lo et al** (**2004**) stated that the increased insulin dosage and disease duration may be the reasons, at least partly, that BMI was significantly increased with age in diabetic children because insulin is a well-known anabolic hormone with lipogenic action-increased leptin production through the effect of insulin on adipocytes.(18). However, many factors influence glycemic control in children. In general, metabolic control tends to deteriorate in teenagers with diabetes (particularly girls), in those with a longer duration of disease or difficult psychosocial circumstances, and in those who have had repeated hospitalizations or poor clinic attendance . In addition, diabetes control may deteriorate during intercurrent illness. In some illnesses, poor food intake may predispose the child to hypoglycemia; in others, the stress of the illness may lead to a vigorous counter-regulatory hormone response with hyperglycemia and ketosis (**23**).

There is a close relationship between degree of glycemic control and onset &/or progression of microvascular complications in adolescents and adults with t1d . however, intensification of of therapy is associated with increased risk of hypoglycemia and this can be a limiting factor in achieving good metabolic control as severe hypoglycemia in young children has been associated with cognitive deficits later in life (23).

In this study, the most prevalent clinical presentations among early-onset diabetics included history of infections (50%), enuresis/nocturia (45%), DKA (40%), followed by weight loss and oral/ perineal candidiasis. On other hand, the most common clinical presentations among long-term diabetics included infections, candidiasis, DKA, nocturnal enuresis, hypoglycemic seizure/ coma and later weight loss. Similar results were reported by other studies (**23,24,25**), who stated that younger children are more likely to present in DKA and that HbA1c and the loss of β-cell function is insidious, even in children under age 6 years.

Although it is well known that *Candida albicans* thrives in adolescents with uncontrolled diabetes and frequently causes vulvo-vaginitis, our observations highlight the association of oral and perineal candidiasis in young children with new-onset T1D. Furthermore, **Quinn et al (2006)(25)** identified a significant association between the duration of candidal infection to HbA1c at diagnosis and underscored the importance of early recognition of candidiasis to detect the onset of T1D before it progresses to DKA. The significantly longer duration of candidiasis in young children who present in DKA (p=0.004) justifies the inclusion of yeast infections as a sign of new-onset diabetes in this susceptible age group.

In the present study, the mean glucose level and ketonuria at onset among newly-diagnosed children were significantly higher than that in long-term diabetics. On other hand the mean value of HbA1c at diagnosis and entry to the study was higher in long term diabetics than that in newly diagnosed cases. Similar results were obtained by other studies (**26,27,28).**

Microvascular complications in kidneys, eyes, and nerves are usually diagnosed after puberty and relate to the quality of blood glucose control in the preceding years (**15**). When examining the development of retinopathy, diabetes duration after initiation of puberty contributed two times more than the diabetes duration before puberty (**29**).

Persistent microalbuminuria (UAER 30-300mg/day) is a strong predictor for overt DN (macroalbuminuria) and is diagnosed in 30-40% of adults and 15-25% of children and adolescents with T1D. The prevalence of elevated UAER increases after 10-15 years of diabetes duration. In children and adolescents, the role of diabetes duration is, however, more controversial. Some pediatric and adolescent studies have shown a possible association (**10,30**).

In this study, the overall rate of microalbuminurea (MA), neuropathy and retinopathy accounted for 16%, 14% and 12%, respectively, being more detected in patients with long-term diabetes. Similar rates of microvascular complications were reported in other studies (**10,15, 29**). There is considerable evidence that multidisciplinary care, including psychosocial support and intensive therapy, reduces the risk and progression of microvascular complications (**4**).

Puberty is characterized by significant changes in the hormonal milieu, particularly in GH, insulin growth factor-1 (IGF-1) and sex steroid secretion. These hormonal factors may contribute to the renal growth and emergence of early DN, in diabetics.

MA is a strong risk marker for progression to overt DN (macroalbuminuria) in patients with T1D (**15**).

In this study, daily urinary excretion of albumin (UAER), and IGF-1, and serum GH (ng/ml) in addition to plasma IGF-I (ng/ml) were determined in newly-diagnosed children and adolescents and in long-term diabetics. Long-term diabetic children and adolescents had significantly higher UAER and urinary IGF-I than that in newly diagnosed cases. These findings are consistent with Cummings et al.,1998 (**31**). Meanwhile, plasma, IGF-1 and serum GH levels were non significantly different in both groups.

In this study, out of 50 diabetics, 8 patients were identified to have MA, accounting for a prevalence of 16% in children and adolescents with T1D. The mean body weight, body height, and BMI, pubertal duration and HbA1c percent were significantly higher in diabetics positive for MA than that in diabetics negative for MA.

Both serum GH and urinary IGF-1 were significantly higher in MA +ve diabetics than that in MA-ve diabetics, associated with the presence of MA, in this study. A similar result was reported by **Cummings et al (1998)(31)**.

Plasma IGF-1 levels tended to be lower in diabetic adolescents with MA compared with subjects without MA (**32**). However, we did not find a significant relationship between plasma IGF-1 and MA. Our data, which reflect mean GH and IGF-1 production, strengthen the evidence of an association between GH and MA and also implicate urinary IGF-1 in MA.

Although the association between serum GH and MA that we report is consistent with animal studies that implicate GH in glomerulosclerosis and DN, there is less support for a role for IGF-1 in this process. GH-deficient rats with diabetes are relatively protected from the typical renal effects of diabetes seen in GH-sufficient rats, while transgenic mice expressing excess GH develop glomerular hypertrophy, albuminuria, and glomerulosclerosis, a sequence of events similar to the evolution of DN. Similarly, transgenic mice expressing excess IGF-1 binding protein have elevated GH levels and develop mesangial hypertrophy and glomerulosclerosis, despite a decrease in plasma IGF-1 levels (**7**).

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الملخص العربي

المقدمة:

مرض البول السكري من النوع الأول (المعتمد علي الأنسولين) هو مرض يصيب الجهاز المناعي وذلك بسبب عوامل وراثية أو بيئية أو مناعية مما يؤدي إلي تدمير خلالا البنكرياس (بيتا) مما يؤدي إلي مضاعفات مثل زيادة السكر بالدم وحدوث اعتلال كلوي واعتلال في شبكية العين واعتلال عصبي.

النمو الطبيعي للجسم في مرض البول السكري يعتمد علي جرعة الأنسولين الصحيحة وإذا لم يتم التحكم في معدلات السكر بالدم يحدث تأخر في النمو الجسمي وعلي النقيض خذ جرعت الأنسولين بانتظام يؤدي إلي النمو السليم للجسم ولكن يمكن حدوث اعتلال كلوي لزيادة أفراز هرمون النمو ومعامل النمو الأنسوليني -1.

الهدف من الدراسة:

أجرى هذا البحث لدراسة هرمون النمو في الدم ومعامل النمو الأنسوليني -1 في البول والدم وارتباطهم بالنمو ونسبة السكر بالدم وحدوث الاعتلال الكلوي.

خطة الدراسة:

أجرى هذا البحث في الفترة من يناير 2009 إلي ديسمبر 2010 علي 50 طفل مصاب بمرض البول السكري النوع الأول (23 ذكور – 27 إناث) كان متوسط أعمارهم. 4.61 ± 10.98 والذين يترددون علي العيادة الخارجية التخصصية لمرض البول السكري للعلاج والمتابعة بمستشفيات جامعة الزقازيق، وتم تقسيمهم إلي مجموعتين، المجموعة الأولى 30 طفل (متوسط مدة المرض أكثر من سنة)، والمجموعة الثانية 20 طفل حديث العهد بالمرض (متوسط مدة المرض أقل من شهر).

بالإضافة إلي 20 طفلا من الأطفال الطبيعيين في سن وجنس مماثل للمرض كمجموعة ضابطة متوسط أعمارهم 4.9± 10.1 سنة (8 ذكور – 12 أنثي)، وقد أجرى لهم فحص طبي شامل متضمنا التاريخ المرضي ويشمل مدة المرض ونوع وجرعة الأنسولين وحدوث غيبوبة سكرية ووجود مضاعفات لمرض السكر وتأثيره اجتماعياً ونفسيا علي الطفل.

الكشف الإكلينيكي:

ويشمل قياس الوزن والطول وفحص قاع العين وفحص الجهاز العصبي.

الفحوصات المعملية:

والتي تضمنت: (تحليل البول – صورة دم كاملة – وظائف كبد وكلى – نسبة سكر صائم الدم – نسبة الهيموجلوبين السكري بالدم – مستوى الاخراج البولي للزلال المجهري – نسبة هرمون النمو في الدم – نسبة معامل النمو الأنسوليني -1 في الدم والبول).

النتائج:

أثبتت الدراسة علي مجموعة المصابين والمجموعة الضابطة:

1- وجود نسبة عالية للاختلال النفسي في الأطفال المصابين بالمرض.
2- حدوث مضاعفات مثل غيبوبة سكرية سلسل بولي ثانوي وزيادة نسبة العدوى البكتيرية والفطرية يشمل نسبة عالية في المجموعة حديثة العهد بالمرض.
3- إرتفاع نسبة السكر بالدم ووجود أجسام كيتونية في مجموعة حديثي العهد بالمرض.
4- نسبة الاخراج الولي للزلال المجهري وحدوث اعتلال عصبي واعتلال بشبكية العين كمضاعفات للمرض هي 18%، 14% ، 12% علي التوالي.
5- وجد أن نسبة هرمون النمو في الدم ومعامل النمو الأنسوليني -1 في الدم عالية في المرضى المصابين بالاخراج البولي للزلال المجهري.
6- وجدت علاقة إيجابية بين وزن الجسم والطول ومؤشرة كتلة الجسم وفترة البلوغ والهيموجلوبين السكري مع نسبة الاخراج البولي للزلال المجهري.

المستخلص من البحث :

من هذه الدراسة نستخلص :

1- إرتفاع هرمون النمو ومعامل النمو الأنسوليني -1 في الأطفال المصابين بمرض البول السكري النوع الأول عنه في أطفال المجموعة الضابطة.
2- إن حدوث المضاعفات يزداد مع طول مدة مرض السكري وعدم السيطرة علي المرض.

التوصيات:

1- اخضاع أطفال المرض السكري لكشف سنوى كامل شامل لأمراض المناعة الذاتية.
2- الدعم النفسي للطفل.
3- خطورة ظهور عدوى بكتيرية وفطرية سلسل بولي ثانوي كدليل لحدوث المرض السكري.
4- السيطرة علي نسبة السكر بالدم لمنع حدوث الاعتلال الكلوي نتيجة لزيادة نسبة هرمون ومعامل النمو الانسوليني -1.
5- كشف دوري لاكتشاف الاعتلال الكلوي والاعتلال الشبكي والاعتلال العصبي وخاصة في فترة البلوغ.