Cardiac Autonomic Function Tests in Type 1 Diabetic Patients (Four Years Follow up Study)

[1]Ahmed A. Battah , [2]Soha M. Abd El Dayem and [1]Randa A. Soliman

[1]Critical Care Department, Kasr El Ani Hospital , Cairo University ,[2]Pediatrics Department, National Research Center, Cairo, Egypt.
s_eldayem@yahoo.com

Abstract: Objective : to undertaken in a group of type 1 diabetic patients who were followed for 4 years to shed further light on the natural progression of cardiac autonomic neuropathy. Patients and methods : The study consisted of 57 patients who were originally studied using a battery of five cardiovascular autonomic tests . Two years later , 46 patients were reevaluated, again 2 years later, 55 patients from the original study were reevaluated for the 3rd time using the same protocol. The control group comprised 30 age and sex matched healthy volunters. Results: The prevalence of established cardiac autonomic neuropathy (CAN) at the beginning is 14%. Q-Tc intervals were found to be significantly higher in patients with abnormal cardiovascular reflex (CVRs) in 2nd examination. Eighteen patients of the original studied group showed deterioration of their CVRs test between 1st and 3rd examination , there is deterioration of their glycemic control guided by glycosylated hemoglobin and albumin / creatinine ratio. On the other hand, 12 patients of the original studied group showed regression of their CVRs test. Only their insulin dose showed significant decrease. Conclusion: The prevalence of CAN in diabetic patients is high. Our data suggest that valsalva – stimulated heart rate response is highly susceptible to the presence of autonomic dysfunction over time. Proper glycemic control is mandatory to prevent development of diabetic complications or ameliorate the pre- existing complication [Journal of American Science. 2010;6(10):252-259]. (ISSN: 1545-1003).

Keywords: Cardiac Autonomic Function Tests; Type 1 Diabetic Patients

1. Introduction

Most studies concerning cardiovascular autonomic neuropathy (CAN) in type 1 diabetes mellitus (DM) begin by stating that CAN , although common, is a neglected complication, which often asymptomatic and therefore dangerous. The danger lies in increased morbidity and mortality. Ewing et al .,[(1)] and Rathman et al., [(2)] demonstrated up to 50 % mortality within 5 – 10 years from CAN diagnosis. Nonetheless, the mortality study from 2006 showed that the cause of death in type 1 DM is not represented by chronic complications of diabetes, among which belongs also CAN but cardiovascular diseases [(3,4).]

The pathological alteration of the nervous system in diabetic patients is extensive and frequently severe. The prevalence of the diabetic neuropathy reach high levels with the evolution of the diabetes, often showing frequencies higher than 50% in several groups of patients. The neurological lesion in this pathological situation is extensive in the diabetic patient, including widely the peripheral nervous system with its components sensory, motor and autonomic: with typical symptoms and in accordance with the pathogenesis of metabolic origin and/or microvascular disease. The autonomic nervous system is a main regulator of many systems in the human body. Then its lesion can promote significant alterations in the function of the cardiovascular, respiratory, gastrointestinal, urogenital system, that can be related to increased mortality [(5).]

CAN is a severe complication of diabetes, causing death and morbidity and large costs to the welfare system. The mechanisms by which CAN exerts negative influence on quality and length of life are controversial, but many relationships have been found, e.g., to exercise intolerance [(6)], silent myocardial ischemia[(7)], and prolongation of the QT interval causing lethal arrhythmias [(8)]. CAN results from damage to the autonomic nerve fibers to the heart, and the earliest indicator of CAN is a decrease in heart rate variation (HRV) during deep breathing, which is easily assessed by a simple bedside test [(9)].

The CAN probably contributes to the bad prognosis of the coronary heart disease and of the heart failure in type 1 and type 2 diabetic patients. For diabetologists, the nervous complications of diabetes are the result of an increase influx of glucose to the neuronal and endothelial cells. Evidences show that, with the aim of preventing these complications, the diabetic patients should receive a precocious diagnosis and be instructed for having a good metabolic and blood pressure control. Use of angiotensin converting enzyme inhibitors and beta adrenergic blockers are probably of impact in the prevention of the cardiac autonomic complications of diabetes [(10)].

We are aiming to undertaken in a cohort of type 1 diabetic patients who were followed for 4 years to shed further light on the natural progression of cardiac autonomic neuropathy with repeated , every 2 years measurements of standard cardiovascular reflex (CVR) tests (for three times) and to correlate its presence , progression or regression with glycemic control , microalbuminuria , insulin dose , duration of disease and other clinical data.

2. Patients and Methods

An informed written consent was obtained from the patients and their parents and an approval from the Ethical commite of the National Research Center was taken.

The study consisted of 57 patients with type 1 diabetes. among those attending to the endocrine clinic in the National Reaearch Centre. The control group consisted of 30 age and sex matched healthy normal volunters.

The exclusion criteria were as follows :

1) patients during acute diabetic complications e.g. diabetic ketoacidosis (DKA) or hypoglycemia.

2) Patients suffering from cardiac diseases e.g. congenital or rheumatic heart.

3) Patients younger than six years (in order to be able to perform CVR tests).

The 57 patients were originally studied using a battery of five cardiovascular autonomic tests

Two years later , 46 patients were reevaluated using the same protocol . Nine patients from the original study could not be located.

Again 2 years later, 55 patients from the original study were reevaluated for the 2nd time using the same protocol .

For the diagnosis of CAN we used the standard tests proposed by Ewing and Clarke [11] and the Consensus Statement of the members of the American Diabetes Association and the American Neurological Academy [12]. Diagnosis of CAN was made when at least two tests were pathological [11] .

Long lead II (on ECG) was done to calculate basal heart rate and correlated Q-T (QTc) interval by Bazett's formula :

$$Q\text{-}Tc = Q\text{-}T / \sqrt{R\text{-}R}$$

The following CVR tests were done in the same sequence :

1) Heart rate response to valsalva maneuver.
2) Heart rate variation during deep breathing .
3) Immediate heart rate response to standing.
4) Blood pressure response to standing.
5)Blood pressure response to sustained hand grip.

Simultaneously all patients underwent the following tests :

Glycosylate hemoglobin (HbA1c) was done every 3 months , the method used is cation exchange chromatography using kits provided by Helena [13]. A morning urine sample was taken for assessment of albumin / creatinine ratio every year by enzyme linked immunosorbent assay (ELISA).

Patients in our study were considered to have good glycemic control if their HbA1c < 8 %, moderate if their HbA1c > 8 - < 10 % and bad if their HbA1c ≥ 10 %. Also patients were considered to have microalbuminuria if they showed albumin / creatinine ratio > 30 µg/mg creatinine.

Statistical method:

SPSS program version 9 was used for analysis of data. McNemar test was done for analysis of qualitative data in a follow up study. T-test for dependent and independent variables was done. One way ANOVA was also done followed by Post HOCC test for significance.

3. Results

The study included 57 patients with type 1 diabetes , 27 male and 30 female , their mean age was 12.3 ± 4.1 yr (8 –20 yr) and mean duration of disease was 5.9 ± 3.7 yr (4 – 15 yr). Frequencies of abnormal CVRs in type 1 diabetics included in the study on 3 successive examinations with 2 years timely intervals are shown on tables 1,2, fig 1 . In the original studied group (57 patients), we found that , 21 (36.8) %) of our patients showed abnormalities in CVR tests, 13 (22.8%) with one abnormal test (early involvement), 6 (10.5 %) with two abnormal tests (definite involvement) and 2 (3.5 %) with three or more abnormal tests (severe involvement). The frequency of abnormal response between 1st and 2nd examination showed regression in heart rate response to standing, blood pressure response to hand grip and Q-Tc intervals and stationary in heart rate response to deep breathing and heart rate response to valsalva, but it is statistically insignificant. Also the frequencies of abnormal response between 1st and 3rd examination showed regression in all five CVRs and Q-Tc intervals and it is statistically insignificant. The patient is considered to have early involvement if he has one abnormal test , definite involvement if he has two abnormal tests and severe involvement if he has three or more abnormal tests. Q- Tc intervals was found to be statistically significant higher in patients with abnormal CVRs than those with normal CVRs in 2nd examination (0.4 ± 0.04 Vs 0.5 ± 0.05 , P =0.006*). The mean values of each CVRs tests on the three 2- years timely interval examinations compared to control group is shown in table 3. Patients included in the study are classified into 3 groups according to their glycemic control (table 4), no significant difference was observed between the 3 groups in their delta changes of CVR tests between 1st and 3rd examination. Eighteen patients of the original studied

group showed progression (deterioration) of their CVR test between 1st and 3rd examination. Their Characteristic are shown in table 5. As it is shown in the table, there is deterioration of their glycemic control guided by HbA1c (8.5 + 1.4 Vs 9.9 + 1.5, P= 0.05*). On the other hand, 12 patients of the original studied group showed regression of their CVR test. However, their HbA1c showed inconsistent pattern, only their insulin dose showed significant decrease as shown in table 5.

Table 1: Comparison of cardiovascular reflexes (parasympathetic and sympathetic parameter) in patients with type 1 diabetes in first and second examination (two years interval)

First examination	Second examination						
Variables	**Normal**		**Abnormal**		Borderline		
	no.	**%**	**no.**	**%**	**no.**	**%**	P- value
QT interval:							
Normal (n = 39)	31	79.5	8	20.5	0	0	0.6
Abnormal (n = 7)	5	71.4	2	28.6	0	0	
Heart rate response to deep breathing (E/I ratio):							
Normal (n = 41)	35	85.3	2	4.9	4	9.8	0.5
Abnormal (n = 3)	1	33.3	2	66.7	0	0	
Borderline (n = 2)	2	100	0	0	0	0	
Heart rate response to standing up (30/15 ratio):							
Normal (n = 37)	35	94.6	1	2.7	1	2.7	0.07
Abnormal (n = 5)	5	100	0	0	0	0	
Borderline (n = 4)	4	100	0	0	0	0	
Heart rate response to valsalva maneuver:							
Normal (n = 40)	33	82.5	7	17.5	0	0	0.07
Abnormal (n = 6)	1	16.7	5	83.3	0	0	
Systolic blood pressure decrease with standing (mmHg):							
Normal (n = 46)	46	100	0	0	0	0	
Abnormal (n = 0)	0	0	0	0	0	0	
Diastolic blood pressure increase with sustained hand grip (mmHg):							
Normal (n = 33)	26	78.8	4	12.1	3	9.1	0.5
Abnormal (n = 7)	6	85.7	1	14.3	0	0	
Borderline (n = 6)	5	83.3	0	0	1	16.7	

Table 2: Comparison of cardiovascular reflexes (parasympathetic and sympathetic parameter) in patients with type 1 diabetes in first and third examination (four years interval)

First examination	Third examination						
Variables	**Normal**		**Abnormal**		Borderline		
	no.	**%**	**no.**	**%**	**no.**	**%**	**P- value**
QT interval:							
Normal (n = 46)	42	91.3	4	8.7	0	0	0.3
Abnormal (n = 9)	9	100	0	0	0	0	
Heart rate response to deep breathing (E/I ratio):							
Normal (n = 48)	37	77.1	7	14.6	4	8.3	0.2
Abnormal (n = 4)	3	75	1	25	0	0	
Borderline (n = 3)	1	33.3	1	33.3	1	33.3	
Heart rate response to standing up (30/15 ratio):							
Normal (n = 45)	36	80	9	20	0	0	0.6
Abnormal (n = 6)	4	66.7	2	33.3	0	0	
Borderline (n = 4)	2	50	0	0	2	50	
Heart rate response to valsalva maneuver:							
Normal (n = 48)	35	72.9	13	27.1	0	0	0.1
Abnormal (n = 7)	5	71.4	2	28.6	0	0	
Systolic blood pressure decrease with standing (mmHg):							
Normal (n = 55)	55	100	0	0	0	0	
Abnormal (n = 0)	0	0	0	0	0	0	
Diastolic blood pressure increase with sustained hand grip (mmHg):							
Normal (n = 42)	37	88.1	5	11.9	0	0	
Abnormal (n = 8)	7	87.5	1	12.5	0	0	
Borderline(n = 5)	5	100	0	0	0	0	

Table 3: The mean value of parasympathetic and sympathetic parameter in both cohort and control group

Variables	First examination Mean ± SD N = 57	Second examination Mean ± SD N = 46	Third examination Mean ± SD N = 57	Controls Mean ± SD N = 30	**P-value**
Heart rate response to deep breathing (E/I ratio)	23.9 ± 9.8	23.7 ± 10.8	21.8 ± 12.6	31.1 ± 8.9	0.07
Heart rate response to standing up (30/15 ratio)	1.1± 0.1[ac]	1.2 ± 0.2[b]	1.1 ± 0.1[c]	1.2 ± 0.2[abc]	0.03*
Heart rate response to valsalva maneuver	1.6 ± 0.4	1.5 ± 0.3	1.5 ± 0.4	1.6 ± 0.3	0.2
Systolic blood pressure decrease with standing (mmHg)	- 2.5 ± 5.8	- 1.3 ± 7.5	- 3.1 ± 8.8	- 0.5 ± 3.9	0.5
Diastolic blood pressure increase with sustained hand grip (mmHg)	23.6 ± 10.8	25.8 ±10.1	26.2 ± 11.9	23.3 ± 10.1	0.5

` P-value is significant if < 0.05* Different symbols is consider significant

Table 4: Delta change of the mean value of parasympathetic and sympathetic parameter in first and third year follow up in patients with type 1 diabetes in relation to glycosylated hemoglobin

Variables	HbA1 < 8 % Mean ± SD N = 9	HbA1 ≥ 8 - < 10 Mean ± SD N = 35	HbA1 ≥ 10 Mean ± SD N = 13	**P-value**
QT intervals	- 0.02 ± 0.06	- 0.01 ± 0.04	- 0.01 ± 0.03	0.9
Heart rate response to deep breathing (E/I ratio)	- 6.7 ± 6.0	0.01 ± 10.5	7.0 ± 16.6	0.1
Heart rate response to standing up (30/15 ratio)	0.05 ± 0.1	0.01 ± 0.2	- 0.01 ± 0.1	0.9
Heart rate response to valsalva maneuver	- 0.2 ± 0.2	- 0.1 ± 0.5	0.2 ± 0.2	0.2
Systolic blood pressure decrease with standing (mmHg)	- 1.3 ± 8.5	2.1 ± 12.6	- 0.6 ± 11.5	0.8
Diastolic blood pressure increase with sustained hand grip (mmHg)	2.5 ± 26.3	0.3 ± 13.2	7.4 ± 11.2	0.5

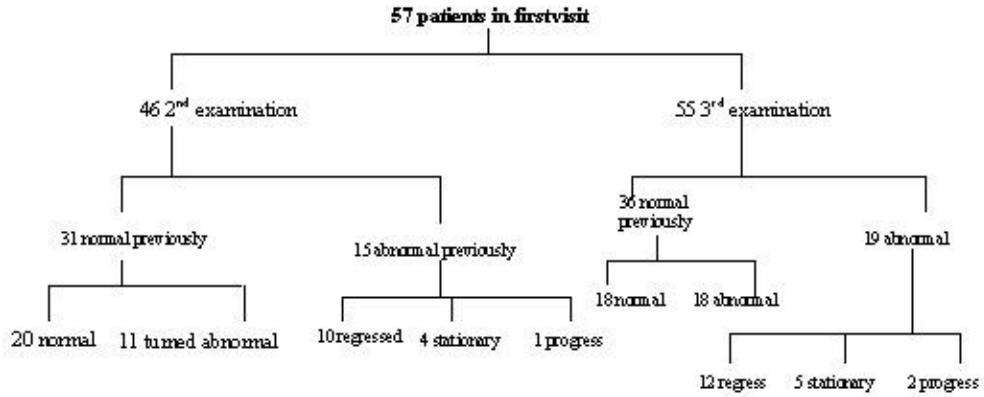
P-value is significant if < 0.05*

Table 5: Comparison of clinical and laboratory data of patients with type 1 diabetes who had progressive and regressive cardiovascular reflexes in first and third examination

Variables	First examination Mean ± SD N = 18	Third examination Mean ± SD N = 18	**P-value**
A – Patients with progressive cardiovascular reflexes			
Glycosylated hemoglobin %	8.5 ± 1.4	9.9 ± 1.5	0.05*
Insulin dose /Kg	2.5 ± 4.6	0.9 ± 0.3	0.2
Systolic blood pressure (mmHg)	106.5 ± 16.4	115.0 ± 12.1	0.01*
Diastolic blood pressure (mmHg)	69.1 ± 10.5	78.1 ± 10.5	0.005*
B – **Patients with regressive cardiovascular reflexes**	First examination Mean ± SD N = 12	Third examination Mean ± SD N = 12	**P-value**
Glycosylated hemoglobin %	8.9 ± 1.5	9.4 ± 1.4	0.4
Insulin dose /Kg	1.8 ± 1.3	1.1 ± 0.3	0.02*
Systolic blood pressure (mmHg)	104.6 ± 19.4	115.8 ± 20.2	0.1
Diastolic blood pressure (mmHg)	75.8 ± 14.1	83.3 ± 10.7	0.08

P-value is significant if ≤ 0.05*

Fig 1 : Data of cardiovascular reflexes in patients with type 1 diabetes during the period of follow up study



4. Discussion:

In the absence of a computerized system for HRV spectral analysis, the four Ewing tests should be performed for evaluatin of CAN. These tests are widely used because they are easily performed, are reliable provided the results are compared with an age-matched control group. The diagnosis of established CAN requires at least two abnormal tests. When only one of them is abnormal (usually the deep breathing test or the orthostatic one), the diagnosis of early or incipient CAN is made. Later, with the progression of CAN, the Valsalva maneuver also becomes abnormal, characterizing the diagnosis of intermediate CAN. Finally, when orthostatic hypertension is present, severe CAN is diagnosed [7, 14, 15].

In the original studied group (57 patients), we found that , 21 (36.8 %) of our patients showed abnormalities in CVR tests , 13 (22.8%) with one abnormal test (early involvement), 6 (10.5%) with two abnormal tests (definite involvement) and 2 (3.5%) with three or more abnormal tests (sever involvement). The prevalence of established CAN is 14 %.

The over all prevalence of abnormal CVR in our study is nearly similar to that of Paries et al ., [16], Who found that prevelance of CAN is 20% to 70% of diabetic subjects.

In contrast , Aman et al ., [17] reported 0% prevalence of abnormal CVR tests, O' Brien et al ., [18] reported 16% prevalence , Ringel et al ., [19] reported 29% , Veglio et al ., [20] reported 28% prevalence of abnormal CVR tests. On the other hand , Navarro et al ., [21] reported 75% prevalence .

The discordance between different investigators may be related to the different criteria used to diagnose and classify neuropathy and because the prevalence of neuropathy may be influenced by age , duration of diabetes and type of diabetes.

Several clinical studies [22, 23], suggest an important participation of CAN in the etiopathogenesis of asymptomatic myocardial ischemia (AMI) found in diabetic individuals. In a large prospective study [24], 434877 patients with MI were evaluated, and 33% of them did not present chest pain.

In the current study, although heart rate response to standing and blood pressure response to hand grip showed regression in diabetics studied over time , the others (heart rate response to deep breathing and heart rate response to valsalva) showed stationary response but it is statistically insignificant (table 1,2) . Our findings regarding stationary response of valsalva consistently overtime was the same as Ducher et al ., [25], valsalva ratio is highly susceptible to changes of autonomic function overtime and is evidently rofust against longitudinal measurement effects inspite of being difficult to perform in young children and requires considerable efforts and cooperation .

Valsalva is a complex test, it encompasses a complex reflex arch involving both sympathetic and parasympathetic pathways to the heart, sympathetic pathways to the vascular tone and baroreceptors in the chest and lungs . It is reasonable that the valsalva index is affected after total and significant autonomic nervous system damage , which occurred over the 6 years period in the study [25].

The Valsalva and sustained handgrip test depend on patient effort and compliance. The postural fall of blood pressure may be unreliable as in people with diabetes it varies throughout the day, being linked to the timing of insulin injections and patients with fluid retention may have extensive autonomic damage but without postural hypotension. Assessment of heart rate associated with deep breathing requires special equipment that indicates depth and cycle of breathing. In addition it has been recommended by diabetologists that the use of lying to standing heart rate change is clinically acceptable [26, 27].

New methods that are non-invasive and independent of patient cooperation are preferable in the diagnosis of CAN but still require further research to understand their sensitivity and specificity in risk stratification for CAN [27].

Postural dizziness, like in previous reports, was far less frequent (10.3%) and did not correlate with a greater postural drop in blood pressure, which suggests that severe sympathetic dysfunction is a rare complication in comparison to parasympathetic dysfunction [16].

Karamitsos et al., [28] demonstrated progression of CAN significantly during the 2 years subsequent to its diagnosis . However, Scaramuzza et al ., [29], did not find any significant abnormality in CVR test either at 1st examination or at 18 months follow up.

Based on our finding of the impaired heart rate response to deep breathing and to valsalva maneuver, we can report our observation that cardiac parasympathetic damage occurs earlier, in the course of diabetes, than the extracardiac sympathetic one, or it may be because the heart rate tests are rather more sensitive than the blood pressure tests.

In the current study , heart rate response to standing up was significantly higher in the

second examination than in the first and third examination , but it is insignificant with the control group . No significant difference was found between the remaining four CVR tests in either the three examination or with the control group.

In the present work , we investigated the effect of glycemic control on CVR tests. Different observations were noticed , however, a final conclusion can not be drawn . Table(4) showed no significant difference in delta changes of CVR tests (in 1st and 3rd examination) between the 3 groups of diabetics with different glycemic control (good – moderate – bad).

Moreover, no significant difference in HbA1c in the group of diabetics with improvement of their CVRs (Table 5), but it is of interest to note that those diabetics with deterioration of their CVR tests showed also deterioration of their glycemic control (Table 5). Our findings are consistent with those of Vinik and Ziegler., [14] , who found that the prevalence of CAN progressively increases in a direct proportion to age, duration of DM and poor glycemic control .

Cardiac autonomic function was preserved with HbA1c < 8.4 %, whereas cardiac autonomic dysfunction was impaired in the group with HbA1c > 8.4 % [30]. Optimized glycemic control seems to slow down the impairment in CAN function tests in type 1 diabetic patients [16].

Also it is worthy to note that the insulin dose was significantly decreasing in group of diabetics with regression of their CAN which may be related to better glycemic control.

On trying to correlate other clinical and laboratory data to progression or regression of abnormality of CVRs , table (5) showed that systolic and diastolic blood pressure were significantly higher in group of diabetics with deterioration of their CAN . However , table (5) showed no significant difference in group of diabetic with regression of their CAN but the dose of insulin was significantly lower as mentioned before.

In the current study, Q- T intervals was found to be statistically significant higher in patients with abnormal CVRs than those with normal CVRs in 2nd examination (0.4 ± 0.04 Vs 0.5 ± 0.05, P =0.006*).

The main finding of 23-year follow-up was in subjects with type 1 diabetes QTc, but not resting HR was associated with an increased risk of all-cause mortality and mortality due to cardiovascular and cardiac disease [31].

Pappachan et al .,[32], reported that, higher CAN scores correlated with longer QTc intervals (coefficient of correlation 0.73; p<0.001).

CAN is common in long standing type-1 diabetics. CAN resulted in prolonged QTc interval that may result in cardiac arrhythmias and even death. Intensive glycemic control improves the cardiac autonomic nerve functions [18]. However, measurements of QTc interval are easily obtained without the need for patient compliance, and QTc analysis is a simple, inexpensive, and noninvasive test that could be used to stratify the death risk in diabetic patients [33].

These data , given the poor prognosis of CAN , suggest urgent steps should be taken to halt CAN deterioration . These steps should be additional to effective glycemic control which does not seem to play a significant role in interrupting the progression of CAN after its discovery .

CAN is a marker of poor prognosis for microangiopathy, especially nephropathy, as demonstrated by a prospective Swedish study with an eleven-year follow-up [15].

Timely identification of DM autonomic dysfunction may improve the prophylaxis of target-organ injury – both macroangiopathy (coronary artery disease (CAD), sudden cardiac death (SCD) and stroke) and microangiopathy (chronic renal failure (CRF) and retinopathy), with the use of specific drugs for the CVRF associated with CAN: hypertension and albuminuria (angotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers) and dyslipidemia (statins). A more intensive control of DM and hypertension in individuals with incipient and intermediate CAN is also currently recommended [34] .

5. Conclusion

The prevalence of CAN in IDDM patients is high. Routine assessment of CVRs is mandatory in diabetics especially over 5 years duration on yearly basis. Our data suggest that valsalva – stimulated heart rate response is highly susceptible to the presence of autonomic dysfunction over time . proper glycemic control is mandatory to prevent development of diabetic complications or ameliorate the pre- existing complication. Blood pressure measurement both supine and standing should be included in the routine follow up visits and hypertensives should be closely monitored and controlled to avoid progression of nephropathy and neuropathy

Corresponding author
Soha M. Abd El Dayem
Pediatrics Department, National research Center,
Cairo, Egypt.

5. References

1. Seidell JC, Doak CM, de Munter JS, Kuijper LD, Zonneveld C. Cross-sectional growth references and implications for the development of an international growth standard for school-aged children and adolescents. Food Nutr Bull. 2006 Dec; 27(4 Suppl Growth Standards):S189-98.
2. Ghalli, I., Salah, N., Hussien, F., Erfan, M., El-Ruby, M., Mazen, I., Sabry, M., Abd El-Razik, M., Saad, M., Hossney, L., Ismaail, S. and Abd El-Dayem, S., et al. In: Proceedings of the 1st National Congress for Egyptian Growth Curves, Cairo University, 11 December 2003. Cairo, Recently published in: Sartorio, A., Buckler, J.M.H. and Marazzi, N. Egyptian Growth Curves 2002 for Infants, Childrenand Adolescents. Crescere nel mondo, 2008, Ferring Publisher.
3. WHO Multicentre growth reference study. WHO Child Growth Standards based on length/height, weight and age Acta Paediatr Suppl. 2006 Apr; 450: 76- 85 (http://www.who.int/childgrowth/en/index.html).
4. South Sinai Environmental and Developmental Profile. Ministry of State for Environmental Affairs and South Sinai Governorate, 2003.
5. International Fund for Agricultural Development (IFAD). (http:/www. Ifad.org/)
6. Hiernau J and Tanner JM. Growth and physical studies. In: Human Biology: A guide to field methods. 1969, Eds. Weiner J.S., Lourie S.A., IBP. London, Blackwell Scientific Publications. Oxford. U.K.
7. Remontet L et al. Growth curves from birth to 6 years of age: growth in weight, height and cranial circumference according to sex. Archives of pediatrics, 1999, 6(5):520–9.
8. Forman J. Nutritional disorders of children, prevention, and screening and follow up. DHEW Publication (No. HAS) 1988: 78 – 5104.
9. National Center for Health Statistics. Growth charts, USA department of Health. Education and Welfare. Public Health Service. Health Resources Administration Rockville, MD, USA. 1976: (HRA 76 – 1120. 25. 3)
10. Sullivan K. Anthrop Software computer Package. USA, Atlanta, Ga, Nutrition Division CDC, 1990.
11. Nichols SD& Cadogan FI. Anthropometric reference values in an Afro-Caribbean adolescent population. Am J Hum Biol. 2008 Jan-Feb;20(1):51-8.
12. Malina RM, Katzmarzyk PT. Validity of the body mass index as an indicator of the risk and presence of overweight in adolescents. Am. J. Clin. Nutr. 1999, 70: (Suppl 1) 131-136S.
13. Garrow JS, Webster J. Quetelet's index ($W\tilde{t}Ht^2$) as a measure of fatness. Int. J. Obes., 1985, 9: 147-153. MEDLINE
14. Rolland-Cachera MF, SempÃ© M, Guilloud-Bataille M, Patois E, Pequignot-Guggenbuhl F, Fautrad V. Adiposity indices in children. Am. J. Clin. Nutr. 1982, 36: 178-184. MEDLINE
15. Kamal AA, Bener A, Kareem Al-Mulla AM. Growth pattern of Qatari preschool children Croat Med J. 2004 Aug; 45(4):461-5.
16. Redlefsen T, Commentz J, Meigen C, Hermanussen M. Reference values for height, weight and body mass index of German born Turkish children. Anthropol Anz. 2007 Sep;65(3):263-74.
17. Fenn B& Penny ME. Using the new World Health Organisation growth standards: differences from 3 countries. J Pediatr Gastroenterol Nutr. 2008 Mar;46(3):316-21.
18. Schwarz NG, Grobusch MP, Decker ML, Goesch J, Poetschke M, Oyakhirome S, Kombila D, Fortin J, Lell B, Issifou S, Kremsner PG, Klipstein-Grobusch K. WHO 2006 child growth standards: implications for the prevalence of stunting and underweight-for-age in a birth cohort of Gabonese children in comparison to the Centers for Disease Control and Prevention 2000 growth charts and the National Center for Health Statistics 1978 growth references. Public Health Nutr. 2008 Jul; 11(7):714-9. Epub 2008 Jan 2.
19. Del-Rio-Navarro BE, Velazquez-Monroy O, Santos-Preciado JI, Lara-Esqueda A, Berber A, Loredo-Abdala A, Violante-Ortiz R, Tapia-Conyer R. Mexican anthropometric percentiles for ages 10-18. Eur J Clin Nutr. 2009 Apr; 63(4):588.
20. Cacciari E, S Milani[3], A Balsamo[2], F Dammacco[1], F De Luca[1], F Chiarelli[1], A M Pasquino[1], G Tonini[1] and M Vanelli.[1] Italian cross-sectional growth charts for height, weight and BMI (6-20 y). February 2002, 56 (2): 171-180.

5/20/2010