Symposium

DOI: http://dx.doi.org/10.18320/JIMD/201502.02118

Journal of International Medicine and Dentistry 2015; 2 (2): 118-136

JOURNAL OF INTERNATIONAL MEDICINE AND DENTISTRY

To search.....to know.....to share

JIMD

ISSN No. 2350-045X

Type 2 Diabetes Mellitus in Children

SECTION A: Pathophysiology of Type 2 Diabetes mellitus in children

Dr. Jyoti Kini, Associate Professor, Department of Pathology, Kasturba Medical College (Manipal University), Mangalore- 575001, India;
E-mail: kinijyoti@gmail.com

SECTION B: Clinical scenario of Type 2 Diabetes mellitus in children

Dr. Mallikarjungowda S Patil, Senior Resident, Department of Pediatrics, Shridevi Institute of Medical Sciences and Research Hospital, Tumakuru- 572106, India;
E-mail: iammspatil@gmail.com

SECTION C: Epidemiology and Prevention of Type 2 Diabetes mellitus in children

Dr. Savindika Nawarathna [1], Dr. Animesh Jain [2]

[1] M.B.B.S., Colombo, Sri Lanka; Former medical student, Kasturba Medical College, (Manipal University), Mangalore- 575001, India;
E-mail: savindin1@hotmail.com

[2] Professor and Head, Department of Community Medicine, Kasturba Medical College (Manipal University), Mangalore- 575001, India.

E-mail: animesh_j@yahoo.com

SECTION A

Pathophysiology of Type 2 Diabetes mellitus in children

Jyoti Kini

Abstract:
While Type 2 diabetes mellitus (T2DM) continues to be a disease of the elderly and the middle aged, currently there has been an upsurge in the incidence of T2DM in the adolescents and the young. Family history, maternal gestational diabetes, low birth weight have contributory role to play in the pathophysiology of T2DM.
The pathophysiology underlying the development of alterations in glucose metabolism ranging from abnormal fasting glucose (AFG) to impaired glucose intolerance (IGT) is multifactorial. The early onset of diabetes in childhood or adolescence heralds a long disease interval with resultant escalation of the probability of development of co-morbidities and the entire range of macro- and microvascular complications.
Key words: Pathophysiology, type 2 diabetes mellitus, multifactorial

Introduction:

While Type 2 diabetes mellitus (T2DM) continues to be a disease of the elderly and the middle aged, currently there has been an upsurge in the incidence of T2DM in the adolescents and the young. This is especially true in high prevalence populations and is a consequence of the steady increase in the global prevalence of T2DM. [1-3]

Worldwide, in children, type1 diabetes is still the predominant type of the disease, however within ten years it will be outnumbered by those with T2DM. Until a decade ago, T2DM accounted for less than 3% of all newly diagnosed cases of diabetes in the young, though currently about 45% are credited to be T2DM.[3] Moreover the early onset of diabetes in childhood or adolescence heralds a long disease interval with resultant escalation of the probability of development of co-morbidities and the entire range of macro- and microvascular complications. [1, 2]

Pathophysiology:

There is limited data available on the pathophysiology of T2DM in the young. The rise of incidence of overweight and obesity is mirrored by a rise in T2DM indicating cause and effect. This holds good particularly when the obesity is central and there is a decrease in physical activity. Family history, maternal gestational diabetes, low birth weight have contributory role to play. These conditions are associated with insulin resistance and fall in insulin secretion secondary to β cell failure is the crucial step.[1, 2, 4]

The pathophysiology underlying the development of alterations in glucose metabolism ranging from abnormal fasting glucose (AFG) to impaired glucose intolerance (IGT) is multifactorial.[1] Owing to the paucity of information on the pathophysiology of T2DM in children and adolescents, an extrapolation with that available from adults is done. Identification of genes involved in type 2 diabetes has proved difficult as a result of the complex inheritance patterns and interaction with the environment.[1, 2, 4] Quite a few of the major predisposing genes have been located on chromosome 1q, 12q, 20q and 17q.[5] Minor genes include the Pro12Ala polymorphisms in peroxisome proliferator activated receptor (PPAR)-γ and the kir 6.2 E23K variant.[6]

Studies have revealed a strong family history of T2DM in the parents and first

degree relatives of the young affected by T2DM.[1,2] Members of these families tend to be overweight or inactive with an increased tendency to high fat intake and binge eating. Economic development and urbanization has ushered in lifestyle changes along with a rise in childhood/ adolescent overweight and obesity with consequent increase in T2DM. Even in India the age adjusted prevalence of overweight among 13- to 18- year olds was 18% in boys and 16% in girls, the prevalence rates being directly proportionate to age and socioeconomic status and indirectly with physical activity.[2,7] Sedentary lifestyle and inactivity are the main reasons for overweight and obesity. It has been reported that cigarette smoking, higher body mass index and lower parental education at baseline are associated with reduced bodily activity. Dependence and fixation with television, electronic gadgets and computer devices have been linked with childhood obesity and have also been related to consumption of high fat, high calorie foods.[8] Socioeconomic status, lower status in developed nations and higher in developing countries, also plays a contributory role.[2] The risk for obesity and glucose intolerance in adulthood increases with low birth weight babies. Gestational diabetes also adds to the chances of the progeny developing impaired glucose tolerance (IGT) and T2DM. High insulin levels in the amniotic fluid at 33-38 weeks of gestation forecasts IGT later.[2, 9]

Most studies in the young with T2DM suggest that insulin resistance is an early feature in these children. To begin with, insulin presents as compensatory hyperinsulinemia. Insulin resistance in liver is revealed in the form of decreased hepatic glucose uptake and impaired suppression of glucose production rather there is overproduction of glucose inspite of the hyperinsulinemia.[4] Similarly, insulin resistance in the muscle causes a decreased glucose transport and uptake by the myocytes presenting as postprandial hyperglycemia.[4] As the disease progresses and β cell failure ensues and the β cell is unsuccessful in counteracting the peripheral resistance state.[1,2] Severe insulin resistance is associated with fat accumulation in liver and muscle tissues and decreased sensitivity of β cell insulin secretion.[1,4] Elevated free fatty acids (FFA), fat derived inflammatory cytokines and low adiponectin levels in obese children may be the potential triggers for accelerated β cell failure.[1,4] Lipotoxicity induced by chronically elevated FFA gives rise to further gluconeogenesis and hepatic/muscle insulin resistance. Deposition of fat in the β cell results in impaired secretion of insulin and β cell failure.[4] Hypersecretion of islet amyloid polypeptide and amyloid deposition within the pancreas have also been incriminated in progressive β cell failure.[4]

Obese adolescents with T2DM have approximately 80% reduction or loss of β cell function.[4,10,11] In their study in obese adolescents, Cali et al reported that the individuals with abnormal fasting glucose (AFG) had decreased glucose sensitivity of first phase insulin secretion and liver insulin sensitivity as compared to those with IGT who had more severe degrees of peripheral insulin resistance and subjects with normal glucose tolerance.[12] Obese adolescents with IGT are more insulin resistant than those with normal glucose tolerance (NGT) despite the comparable degree of adiposity.[1] Progression to AFG from NGT is associated with 50% decline in β cell volume indicating a significant loss of β cell mass even before the onset of T2DM.[4] Also the insulin secretion relative to insulin sensitivity shows a significantly declining pattern, highest in youth with NGT, intermediate in youth with IGT and lowest in those with T2DM.[13]

Obese adolescents who show signs of glucose dysregulation, including AFG, IGT or both are more likely to have

impaired insulin secretion rather than reduced insulin sensitivity. Hence they are at high risk for progression to T2DM. Any further loss of insulin sensitivity or secretion will further enhance the chances for this progression. The development of T2DM from a stage of insulin resistance is much faster in obese children.[1] The increase in the prediabetes conditions parallels the rise in prevalence of T2DM with IGT being reported in 25% of children and 21% of adolescents with marked obesity, irrespective of the ethnic backgrounds.[14] The deterioration of β cell function is faster (about 15% per year) in children/ adolescents with T2DM as compared to adults.[15]

There is a hyperbolic relationship between insulin sensitivity and secretion. When there is a fall in insulin sensitivity an increase in insulin secretion maintains euglycemic level. This is termed as the 'disposition index' (DI).[1,4,16] The β cell is considered as a responsive organ to stimuli generated by insulin target tissues such as muscle, liver or fat. Hyperglycemia may therefore be an adaptive response, to trigger a signal for β cell to secrete insulin to meet the increased demand. Weiss et al used oral glucose tolerance test (OGTT) to demonstrate the phenomenon of glucose allostasis i.e., an increase in ambient glycemia in order to maintain a constant DI when the sensitivity to insulin is diminishing. Overweight children who progress to IGT exhibit lower DI values as compared with those whose glucose tolerance is maintained, suggesting an early defect in β cell function may trigger the development of IGT and T2DM in the obese youth.[17]

The detection of hepatic steatosis is a significant marker of multi-organ insulin resistance and risk of T2DM.[1,18] Insulin resistance is directly related to percent hepatic fat. 60-90% of adolescents with T2DM have acanthosis nigricans, a physical marker of insulin resistance. Obese youngsters with polycystic ovarian syndrome also have a 50% loss of peripheral insulin sensitivity with development of hepatic insulin resistance and compensatory hyperinsulinemia.[1,2]

In conclusion, in the pediatric population, the speedy rate of development of alterations in glucose homeostasis and progression to T2DM is driven by the rapid loss of β cell function suggesting a more aggressive disease course when compared to adults.

References:

1. D'Adamo E, Caprio S. Type 2 Diabetes in Youth: Epidemiology and Pathophysiology. Diabetes Care 2011; 34:S161-165; http://dx.doi.org/10.2337/dc11-s212

2. Alberti G, Zimmet P, Shaw J, Bloomgarden Z, Kaufman F, Silink M. Type 2 diabetes in the young: the evolving epidemic. Diabetes Care 2004; 27:1798-1811; http://dx.doi.org/10.2337/diacare.27.7.1798

3. Pinhas-Hamiel O, Zeitler P. The global spread of type 2 diabetes mellitus in children and adolescents. J Pediatr 2005; 146: 693-700.

4. DeFronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 2009; 58:773-795; http://dx.doi.org/10.2337/db09-9028

5. Stern MP. The search for type 2 diabetes susceptibility genes using whole-genome scans: an epidemiologist's perspective. Diabete Metab Res Rev 2002; 18: 106-113.

6. Gloyn AL, Weedon MN, Owen KR, Turner MJ, Knight BA, Hitman G, et al. Large scale association studies of variants in genes encoding the pancreatic β cell KATP channel subunits Kir6.2(KCNJ11) and SUR1(ABCC8) confirm that the KCNJ11 E23K variant is associated with type 2 diabetes. Diabetes 2003; 52:568-572;

http://dx.doi.org/10.2337/diabetes.52.2.568

7. Ramachandran A, Snehalatha C, Satyavani K, Sivasankari S, Vijay V. Type 2 diabetes in Asian- Indian urban children. Diabetes Care 2003; 26:1022-1025; http://dx.doi.org/10.2337/diacare.26.4.1022

8. Lowry R, Wechsler H, Galuska DA, Fulton JE, Kann L. Television viewing and its association with overweight, sedentary lifestyle, and insufficient consumption of fruits and vegetables among US high school students: differences by race, ethnicity, and gender. J Sch Health 2002; 72:413-421.

9. Silverman BL, Metzer BE, Cho NH, Loeb CA. Impaired glucose tolerance in adolescent offspring of diabetic mothers: relationship to fetal hyperinsulinemia. Diabetes Care 1995; 18:611-617; http://dx.doi.org/10.2337/diacare.18.5.611

10. Weiss R, Caprio S, Trombetta M, Taksali SE, Tamborlane WV, Bonadonna R. Beta-cell function across the spectrum of glucose tolerance in obese youth. Diabetes 2005; 54:1735-1743; http://dx.doi.org/10.2337/diabetes.54.6.1735

11. Bacha F, Lee SJ, Gungor N, Arslanian SA. From pre-diabetes to type 2 diabetes in obese youth: pathophysiological characteristics along the spectrum of glucose dysregulation. Diabetes Care 2010; 33:2225-2231; http://dx.doi.org/10.2337/dc10-0004

12. Cali AM, Bonadonna RC, Trombetta M, Weiss R, Caprio S. Metabolic abnormalities underlying the different prediabetic phenotypes in obese adolescents. J Clin Endocrinol Metab 2008; 93:1767-1773; http://dx.doi.org/10.1210/jc.2007-1722

13. Bacha F, Gungor N, Lee SJ, Arslanian SA. In vivo insulin sensitivity and secretion in obese youth what are the differences between normal glucose tolerance, impaired glucose tolerance and type 2 diabetes? Diabetes Care 2009; 32:100-105; http://dx.doi.org/10.2337/dc08-1030

14. Sinha R, Fisch G, Teague B, Tamborlane WV, Banyas B, Allen K, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. N Engl J Med 2002; 346:802-810.

15 Gungor N, Arslanian S. Progressive beta cell failure in type 2 diabetes mellitus of youth. J Pediatr 2004; 144: 656-659.

16. Weiss R, Cali AM, Dziura J, Burgert TS, Tamborlane WV, Caprio S. Degree of obesity and glucose allostasis are major effectors of glucose tolerance dynamics in obese youth. D C 2007: 30:1845-1850; http://dx.doi.org/10.2337/dc07-0325

17. Cali AM, Man CD, Cobelli C, Dziura J, Seyal A, Shaw M et al. Primary defects in beta cell function further exacerbated by worsening of insulin resistance mark the development of impaired glucose tolerance in obese adolescents. Diabetes Care 2009; 32: 456-461; http://dx.doi.org/10.2337/dc08-1274

18. Cali AM, De Oliveira AM, Kim H, Chen S, Reyes-Mugica M, Escalera S, et al. Glucose dysregulation and hepatic steatosis in obese adolescents: is there a link? Hepatology 2009; 49:1896-1903; http://dx.doi.org/10.1002/hep.22858

****

SECTION B

Clinical scenario of Type 2 Diabetes mellitus in children

Mallikarjungowda S Patil

Abstract:
Type 2 diabetes mellitus (T2DM) is a heterogeneous disorder, characterized by peripheral insulin resistance and failure of beta cells to keep up with increasing insulin demand. T2DM children are usually obese, may present with mild symptoms of polyuria and polydypsia.
A systemic approach for treatment of T2DM should be implemented according to the natural course of the disease, including adding insulin when oral hypoglycemic agents failure occurs. Life style modification is an essential part of management. When lifestyle interventions fail to normalize blood glucose, oral hypoglycemic agents are introduced for management of persistent hyperglycemia.
Key words: Type 2 diabetes mellitus, polyuria, polydipsia, oral hypoglycaemic agents

Introduction:

Type 2 diabetes in children was formerly known as non-insulin dependent diabetes or adult onset diabetes. Type 2 diabetes is a heterogeneous disorder, characterized by peripheral insulin resistance and failure of beta cells to keep up with increasing insulin demand. Generally they are not ketosis prone, but ketoacidosis may develop. T2DM is considered a polygenic disease aggravated by environmental factors, such as low physical activity and excessive caloric intake. Most patients are obese, though the disease can occasionally be seen in normal weight individuals[1].

Risk factors: Childhood obesity, sedentary life style, decreased physical activity, Low economic status, maternal smoking, smoking in young[2].

Clinical features:

T2DM in children more likely to be diagnosed in native Americans, Hispanic Americans, and African American youth. Its highest incidence is in Pima group Indians Youth (15- 19 years prevalence is 5%)(Pima are group of indigenous Americans living in an area consisting of what is now central and southern Arizona) . Most are diagnosed at adolescence, incidence increases with increasing age. Family history of T2DM will be present practically in all cases. T2DM children are usually obese, may present with mild symptoms of polyuria and polydypsia. They may also present with no symptoms and detected on screening tests.

On physical examination they may have acanthosis nigricans - skin lesions seen in neck and flexural areas, Striae, increased waist to hip ratio. T2DM children may have polycystic ovarian disease, lipid disorders and hypertension.[3]

Maturity onset diabetes of young **(MODY**)—A rare form of DM in children, that includes several disorders caused by monogenic defects in beta cell function inherited as autosomal dominant fashion[4].

Testing for T2DM in children [1, 3]

Criteria

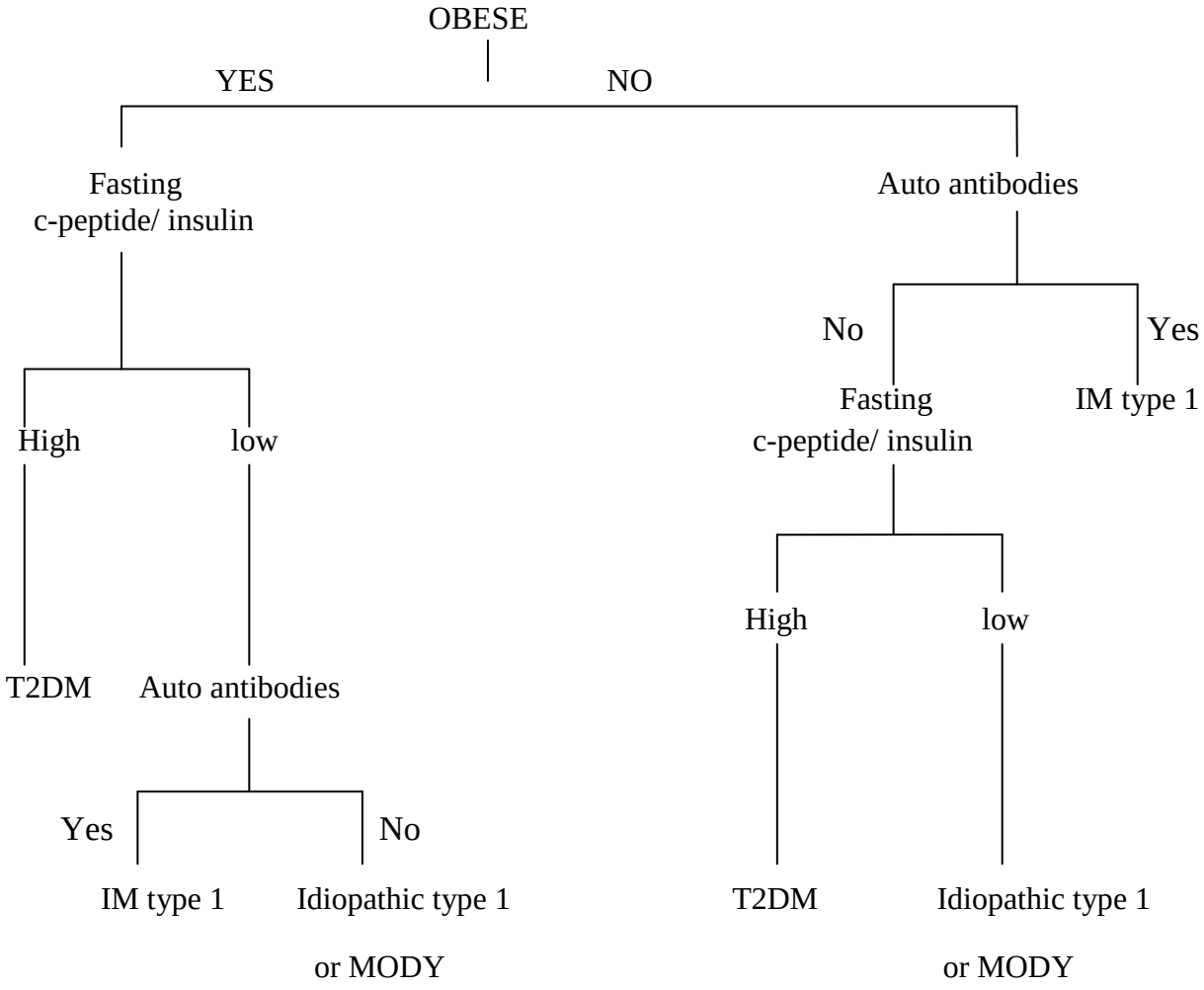
• Overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)

Plus Any 2 of the following risk factors:

• Family history of type 2 diabetes in 1st or 2nd degree relative

• Race/ethnicity (American Indian, African American, Hispanic, Asian/Pacific Islander)
Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome)
Age of initiation: Age 10 yr or at onset of puberty if puberty occurs at a younger age
Frequency: Every 2 years
Test: Fasting plasma glucose preferred
Laboratory testing reveals elevated HbA1c levels and HbA1c values are higher at diagnosis among less percentage of youth. Hyperlipidemia characterized by elevated triglycerides and low density lipoprotein (LDL) cholesterol levels are commonly seen in patients with T2DM at diagnosis. Therefore lipid screening is indicated in all new cases of T2DM. The current recommendation is to use fasting blood glucose as a screening test, but some authorities now recommend that HbA1c be used as a screening tool and it has the advantage that a fasting sample is not required. In borderline or asymptomatic cases, the diagnosis may be confirmed.

RESEARCH SCHEME FOR CLASSIFICATION OF DIABETES IN CHILDREN AND YOUTH [3]:



Complications of T2DM and their monitoring [7]

Hypertension	Blood pressure
Fatty liver	AST, ALT, USG
Polycystic ovarian disease	Menstrual history, assessment of androgen excess with total / free testosterone, DHEA
Microalbuminuria	Urine albumin concentration, urine/creatinine ratio
Dyslipidemia	Fasting lipid profile. Obtain at diagnosis and every 2 yrs
Sleep apnea	Sleep study to assess overnight oxygen saturation.

Treatment:

Type 2 diabetes mellitus is a progressive syndrome that gradually leads to complete insulin deficiency during a patient's life. A systemic approach for treatment of T2DM should be implemented according to the natural course of the disease, including adding insulin when oral hypoglycemic agents failure occurs. Lifestyle modification is an essential part of management. There is no definite dietary or exercise regimen, but most centers recommend low fat, low calorie diet, with 30-60 minutes physical activity atleast 5 times per week. When lifestyle interventions fail to normalize blood glucose, oral hypoglycemic agents are introduced for management of persistent hyperglycemia.

Patients who present with diabetic keto acidosis or with markedly elevated **HbA1c (>9.0%)** will require treatment with insulin using protocols similar to those used for treating T1DM. Once blood glucose levels are under control most cases can be managed with oral hypoglycemic agents and lifestyle changes, but some patients will continue to require insulin therapy.

The most commonly used oral agent is **metformin**. Renal function must be assessed before starting metformin as impaired renal function has been associated with potentially fatal lactic acidosis in adults. Significant hepatic dysfunction is also a contraindication, though mild elevations in liver enzymes may not be an absolute contraindication. The usual starting dose is 500 mg bid and this may be increased to a maximum dose of 2,500 mg per day. Abdominal symptoms are common early in the course of treatment, but in most cases will resolve with time. Other agents like thiazolidinediones (TZDs), sulfonylureas, acarbose, pramlintide, and incretin mimetics are being used routinely in adults, but in pediatrics they constitute 2nd line agents at this time. Sulfonylureas are widely used in adults, but experience in pediatrics is limited. Sulfonylureas cause insulin release by closing the potassium channel (KATP) on β cells. They are occasionally used when metformin monotherapy is unsuccessful or

contraindicated for some reason (use in certain forms of neonatal diabetes) [1, 5]
Pramlintide (Symlin) is an analog of IAPP (islet amyloid polypeptide), which is a peptide that is co-secreted with insulin by the β cells and acts to delay gastric emptying, suppress glucagon, and possibly suppress food intake. It is not yet approved for pediatric use[5]. The term impaired glucose tolerance (IGT) is suggested as a replacement for terms such as asymptomatic diabetes, chemical diabetes, subclinical diabetes, borderline diabetes, and latent diabetes in order to avoid the stigma associated with the term diabetes mellitus. Although IGT represents a biochemical intermediate between normal glucose metabolism and that of diabetes, experience has shown that few children with IGT go on to acquire diabetes; estimates range from zero to 10% [6].

References:

1. Kliegman RM, Stanton BMD, Behrman RE. Nelson textbook of pediatrics. 19th ed. Philadelphia: Saunders; 2012. Type 2 diabetes in children; p.1990-1993.
2. Pinhas-Hamiel O, Dolan LM, Daniels SR, Standiford D, Khoury PR and Zeitler P. Increased incidence of non-insulin dependent diabetes mellitus among adolescents. J Pediatr 1996; 128: 608–615.
3. American Diabetes Association. Type 2 diabetes in children and adolescents. Pediatrics 2000; 105(3): 671-680.
4. Winter WE, Maclaren NK, Riley WJ, Clarke DW, Kappy MS, Spillar RP: Maturity-onset diabetes of youth in black Americans. N Engl J Med 1987; 316:285–291.
5. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. Ann Intern Med 1999; 131: 281–303
6. Wiegand S, Maikowski U, Blankenstein O, Biebermann H, Tarnow P and Gruters A. Type 2 diabetes and impaired glucose tolerance in European children and adolescents with obesity – a problem that.
is no longer restricted to minority groups. Eur J Endocrinol 2004; 151: 199–206
7. Canadian Diabetes Association. Type 2 diabetes in children and adolescents. Can J Diabetes 2013; 37: S163-167.

****

SECTION C

Epidemiology and Prevention of Type 2 Diabetes Mellitus in children

Savindika Nawarathna, Animesh Jain

Abstract:
Type 2 diabetes mellitus was considered rare amongst children, but recently the incidence has increased worldwide with almost half of the newly diagnosed cases being children and adolescents. Type 2 diabetes mellitus (T2DM) is primarily characterized by insulin resistance detected at the level of skeletal muscle, liver, and adipose tissues with a failure of β-cell compensation and a relative insulin deficiency.
A variety of risk factors like race, obesity, insulin resistance, family history, psychococial factors, birth weight, exposure to maternal DM and breastfeeding can influence the development of T2DM. Type 2 DM screening in the paediatric population should be clinically focused and take into account not only those risk factors identified in the American Diabetes Association guidelines, but also the clinical context, pubertal status, and the results of simple screening measures such as fasting glucose and triglycerides. More outcome-based research is required before general screening, to identify children and adolescents with pre-diabetes or insulin resistance can be recommended.
Key words: Type 2 diabetes mellitus, insulin, children

Introduction:

Considered a silent killer, diabetes has affected about 382 million people globally with a rapidly increasing epidemic amongst children. Previously, type 2 diabetes mellitus was considered rare amongst children, but recently the incidence has increased worldwide with almost half of the newly diagnosed cases being children and adolescents[1]. Originating from the Greek word 'Diabeinein' meaning 'siphon' or 'pass through', diabetes is a complex metabolic disorder characterized by chronic hyperglycaemia resulting from defects in insulin secretion and/ or action which in turn leads to abnormalities of carbohydrate, fat and protein metabolism [2, 3].

Type 2 diabetes mellitus (T2DM) is primarily characterized by insulin resistance detected at the level of skeletal muscle, liver, and adipose tissues with a failure of β-cell compensation and a relative insulin deficiency. Once thought to be a disease of adulthood, T2DM is becoming increasingly common in children and adolescents. In adults, there is an established progression from insulin resistance to glucose intolerance (IFG or IGT) toT2DM. Progression through these stages can occur over many years and is often unaccompanied by symptoms of disease. The extent to which children progress through stages of obesity, insulin resistance, and glucose intolerance is not fully understood; however, it appears that the pathway to disease is much shorter and less predictable in children than in adults. Paediatric patients with T2DM are usually overweight or obese (BMI>85thpercentile for age and sex), and co morbidities such as hypertension and dyslipidemia can be present at diagnosis. Polycystic ovarian syndrome is a common co-morbidity in adolescent girls diagnosed with T2DM. Often there is a strong family history amongst family members. Diet and exercise are the mainstays of treatment for T2DM. Unlike T1DM, T2DM can

successfully be treated with oral hypoglycemic agents [4, 5, 6].

Risk Factors:

Race/ Ethnicity

Race and ethnicity is a very significant factor amongst adults diagnosed with Type 2 DM, and it is suggested that holds the same importance for the youth. Certain races are seen to have a greater affinity towards developing the condition. In multiple studies, the only paediatric cases of Type 2DM are of non-European backgrounds. Higher prevalence have been seen in Asians, Hispanics, indigenous peoples (U.S.A., Canada, Australia), and African-Americans, with the highest rates in the world being observed in Pima Indians [7, 8, 9].

Obesity

The risk of Type 2 DM increases with increasing weight, weight gain, body mass index (BMI),waist-to-hip ratio and central fat deposition [10, 11]. Japanese studies demonstrate a rise in paediatric Type 2DM incidence, paralleling rises in obesity from 1975 to 1995 [12]. A Turkish study of 196 obese 7 to18 year olds, found that 35 (18%) had IGT and six (3%) had T2DM [13]. A lifestyle predisposing to obesity also seems to characterize families of adolescents with T2DM [14].The problem of obesity also extends to developing nations, particularly in relatively affluent urban areas. In India, a recent study reported that 18% of 13 to18 year old children were found to be overweight [15], with the prevalence correlating positively with age and socioeconomic status and negatively with physical activity. Considering that obesity goes hand in hand with numerous non communicable diseases, type 2 DM holds a strong correlation with it, leading us to believe that lifestyle modification has a huge role to play in the reduction of the epidemic.

Insulin Resistance

Type 2DM in youth typically occurs during puberty and is thought to coincide with a physiologic rise (as high as 50%) in insulin resistance [16, 17]. Healthy adolescents are able to compensate for the pubertal rise in insulin resistance with an increase in insulin secretion. However, some adolescents' pancreatic β-cells cannot overcome this rise in insulin resistance, and therefore a relative insulin deficiency develops, eventually leading to Type 2DM [13, 18].Since puberty occurs on average a year earlier in females than males, pubertal insulin resistance also begins earlier in females [19]. This may partly explain the female predominance in adolescent Type 2DM, and the earlier age of onset in females. Using frequently sampled intravenous glucose tolerance tests, other authors demonstrated that both African-American and Hispanic children have more insulin resistance than those of European ancestry [18, 20].

Family History

Many studies show a strong family history among affected youth, with 45–80%having at least one parent with DM and 74–100% having a first- or second-degree relative with Type 2DM [21].

Psychosocial Factors

Many youth with Type 2DM are obese, and obesity may play a role in the development of depression [22-24]. In addition, negative body image and weight concerns have been associated with subsequent depression in girls in several studies [25]. Hence, it can be considered more or less to be a vicious cycle, which can be altered by lifestyle modification and parental guidance.

Birth weight

Several risk factors for Type 2DM during the foetal or neonatal period have been described. They all appear to act through increasing the risk of obesity at earlyages. Being either small for gestational age (SGA) or large for gestational age (LGA) was associated with the development of

Type 2DM later in life [26-32]. Both genetic and environmental factors are likely to be involved in mediating these relationships. Studies of monozygotic and dizygotic twins have shown that the lower birth weight twin has a greater risk of DM in adulthood, suggesting the importance of environmental and intrauterine factors. Children born SGA were also more likely to develop hypertension and dyslipidemia later in life. In case-control studies including French subjects selected from a population-based registry of births [33, 34], individuals born SGA demonstrated hyperinsulinemia and insulin resistance as early as the age of 20 years when compared with controls born with normal size. In a recent German study, lower birth weight was associated with higher HbA1c among healthy non-diabetic youth [35, 36].

Exposure to maternal DM

Several reports have convincingly shown that exposure to maternal DM in utero isa significant risk factor for obesity, IGT, and Type 2DM in youth[37].

Breastfeeding

In population-based studies, breastfeeding is protective against later development of obesity and Type 2DM[38-41]. Even as infants, bottle-fed babies have significantly higher plasma insulin levels and a prolonged insulin response to glucose[42]. A longer duration of exclusive breastfeeding also appears highly protective in a dose dependent manner against overweight and obesity in children of various age groups.

Epidemiology:

The epidemiology of Type 2 DM in youth is yet unclear because of its relative rarity, the infrequency of comprehensive registries, and the small number of appropriate, population and clinical based studies. There is, therefore, a need for large population-based studies using standardized case definitions to define the magnitude of the problem of childhood T2DM. Population-based studies, where all individuals within a geographical area undergo diabetes screening, are ideal to determine prevalence, as they capture even undiagnosed cases. However, among the limited number of available population-based studies of Type 2 DM in youth, few test oral glucose tolerance [the gold standard for diabetes mellitus diagnosis] and many lack key data essential to differentiate Type 2 DM from Type 1 DM. A couple of population and clinic based studies had been done over the years which have determined the incidence and prevalence of Type 2 DM in those particular areas and ethnicities. The studies have been summarized in Table I and II.

Screening and Prevention:

Prevention can occur at multiple stages in the development of the disease. Primordial prevention refers to efforts to prevent the development of risk factors for the disease, while primary prevention refers to efforts to prevent the development of the disease in the presence of risk factors. Secondary prevention aims to identify existing but undiagnosed cases in an attempt to alter the early natural history of the clinical condition. Finally, tertiary prevention refers to efforts focused on prevention and control of complications once the disease is present.

Type 2 DM should itself be considered a complication of obesity in susceptible children. Therefore, primordial prevention of Type 2DM entails the prevention of obesity in children and adolescents in general, as well as in those patients who are most at risk for development of Type 2DM and its associated disorders. Primary prevention efforts focus on the prevention of the development of diabetes once obesity is established. These can be divided into interventions to reduce obesity and other risk factors, either through behavioural or pharmacologic

Table I: Studies of Prevalence of Type 2 Diabetes in Youth

Study/Location	Age Group	Prevalence per 1000	Period	Reference
NHANES III/U.S.A.	12-19	1.3	1988-1994	43
NHANES/U.S.A.	12-19	3	1999-2002	44
Canada	4-19	11.1	1996-1997	45
Indian Health Service	15-19	5.4	1998	46
Arizona, USA	10-14	22.3	1992-1996	47
	15-19	50.9		
Taiwan	6-18	0.09(males)	1993-1999	48
		0.15(females)		
Israel	17	0.36(males)	2005	49
		0.1(females)		
Saudi Arabia	<14	1.2	2000	50
	14-29	7.9		

Table II: Studies of Incidence of Type 2 Diabetes in Youth

Study/Location	Age Group	Incidence per 100,000	Period	Reference
Chicago, USA	0-17	15.2(African American)	1985-1999	51
		10.7(Latino)		
Cincinnati	10-19	7.2	1994	52
UK	0-17	2.9(Blacks)	2004-2005	53
		1.25(South Asians)		
Japan	<15	2.0/105 (primary grades)		54,55
		13.9/105 (junior high)		
		0.35(Whites)		
Australia	0-17	17	1990-2000	56

intervention, and those designed specifically to prevent the onset of diabetes. Medications to reduce the weight of the child are proven to be useful tools. On the other hand, Behavioural methods and lifestyle modification have proven to

be effective too. It is suggested that there may be some benefit to interventions where the parent is given responsibility for behaviour change, rather than the child. Secondary prevention includes screening for Type 2DM in order to modify the clinical course of diabetes. Tertiary intervention would involve efforts to prevent and control complications of Type 2 DM in affected children.

The micro vascular complications of Type 2 DM, such as hypertension, nephropathy, and retinopathy, are frequently identified at the time of diagnosis of Type 2 DM in children and adolescents[57]. The presence of complications at diagnosis implies the existence of long standing hyperglycaemia and suggests that the diagnosis of Type 2 DM could have been made earlier, allowing for earlier intervention. In addition to the presence of complications at diagnosis, adolescents with Type 2 DM may have acute diabetes presentations, including hyperglycaemic hyperosmolar state (HHS) [58] and malignant hyperthermia like syndrome with rhabdomyolysis [59]. These conditions are associated with high rates of morbidity and mortality that might be preventable if diagnosis were made earlier in the course of disease development. Therefore, there has been great interest in the development of screening strategies aimed at identifying early diabetes in children at risk in order to avoid life threatening presentations and the development of chronic complications that are associated with significant patient and economic burden.

In 2000, the American Diabetes Association (ADA) issued recommendations for Type 2 DM screening among children. These recommendations were based on clinical reports, showing that affected children were obese, pubertal, had a family history of Type 2 DM, and other clinical signs of insulin resistance. The guidelines from 2007 are presented in Table III.

Table III: Testing for T2DM in Children—ADA Recommendations [60]

Criteria:
-Overweight (BMI > 85th percentile for age and sex, weight for height > 85th percentile, or weight >120% of ideal for height)
Plus any two of the following risk factors:
-Family history of T2DM in first- or second-degree relative
-Race/ethnicity (Native American, African-American, Latino, Asian-American, Pacific Islander)
-Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans,
hypertension, dyslipidemia, or PCOS)
-Maternal history of diabetes or GDM
Age of initiation: age 10 yr or at onset of puberty, if puberty occurs at a younger age Frequency: every 2 yr Test: Fasting plasma glucose preferred

There are several tests that could be used in a screening program for IGT and DM in adolescents. These include urine glucose, casual (non-fasting) blood glucose, fasting glucose, formal glucose tolerance tests, and hemoglobinA1c. In general, urine

testing, though convenient and amenable to wide-spread screening that does not require a blood draw [61], has been considered too insensitive for identification of cases of diabetes in high-risk patients. Blood tests are considered specific, but till date they have been specific in determining diabetes mellitus in general, rather than specifically pin pointing on Type 2 DM. Hence screening for cases, at this point is not considered very confirmatory for Type 2 DM. Therefore, a specific test for determining the condition must be introduced making it easier for clinicians and for researches in finding the exact prevalence and incidence of Type 2 DM amongst the youth.

Conclusions:

Today, we stand in challenging times where diabetes amongst children has to be defined in completely different words. From Type 1 DM being the sole cause of DM amongst children approximately ten years back, today, Type 2 DM with its questionable pathogenesis and sparse literature, it makes it very difficult for the doctors to calm this roaring epidemic down, especially in the developing and under developed countries, where resources are limited. Encouragement towards this subject is an immediate requirement.

Type 2 DM screening in the paediatric population should be clinically focused and take into account not only those risk factors identified in the ADA guidelines, but also the clinical context, pubertal status, and the results of simple screening measures such as fasting glucose and triglycerides. More outcome-based research is required before general screening, to identify children and adolescents with pre diabetes or insulin resistance can be recommended. With the trend of increase of Type 2 DM in children, further research into risk factors, associations, prevention and control should be conducted and encouraged. The studies shown above are insufficient to determine the worldly growth of Type 2 DM amongst the children since they have been conducted a couple of years back, where in diabetes amongst children was synonymous to Type 1 DM. In addition, research determining screening techniques specific to Type 2 DM must be established because determining trends become hard when clinicians or researchers have to solely depend on a patient's history and examination to arrive a confident diagnosis.

Furthermore, Care for diabetic children should be improved in developing countries to avoid the progression of the disease to a complicated state. Parents and guardians should be given proper training and lessons to monitor and manage their child's condition and make them as comfortable as possible.

References:

1. Diabetes Atlas. 6th ed. International Diabetes Federation; 2013.

2. World Health Organization. Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia: Report of a WHO/IDF Consultation.Geneva, Switzerland: World Health Organisation, 2006.

3. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014: 37 (Suppl. 1): S81–S90; http://dx.doi.org/10.2337/dc14/S081

4. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1998; 21 (Suppl. 1):S5–S19; http://dx.doi.org/10.2337/diacare.21.1.S5

5. Riley WJ, Maclaren NK, Krischer J, Spillar RP, Silverstein JH, Schatz DA, et

al. A prospective study of the development of diabetes in relatives of patients with insulin-dependent diabetes. N Engl J Med 1990; 323(17): 1167–1172.
6. Srikanta S, Ganda OP, Eisenbarth GS, Soeldner JS. Islet-cell antibodies and beta-cell function in monozygotic triplets and twins initially discordant for Type I diabetes mellitus. N Engl J Med 1983; 308(6): 322-325.
7. Scott CR, Smith JM, Cradock MM and Pihoker C. Characteristics of youth-onset non-insulin dependent diabetes mellitus and insulin-dependent diabetes mellitus at diagnosis. Pediatrics 1997; 100:84–91
8. Acton KJ, Rios Burrows NR, Moore K, Querec L, Geiss LS, Engelgau MM. Trends in diabetes prevalence among American Indian and Alaska Native children, adolescents and young adults. Am J Public Health 2002; 92:1485–1490.
9. Fagot-Campagna A, Pettitt DJ, Engelgau MM, Burrows NR, Geiss LS, Valdez R et al. Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. J Pediatr 2000; 136: 664–672.
10. Haffner SM, Mitchell BD, Hazuda HP, Stern MP. Greater influence of central distribution of adipose tissue on incidence of non-insulin-dependent diabetes in women than men. Am J Clin Nutr 1991; 53:1312–1317.
11. Feskens EJ, Kromhout D. Effects of body fat and its development over a ten-year period on glucose tolerance in euglycaemic men: the Zutphen Study. Int J Epidemiol 1989; 18: 368–373.
12. Kitagawa T, Owada M, Urakami T, Yamauchi K. Increased incidence of non-insulin dependent diabetes mellitus among Japanese schoolchildren correlates with an increased intake of animal protein and fat. Clin Pediatr (Phila) 1998; 37: 111–115.
13. Atabek ME, Pirgon O, Kurtoglu S. Assessment of abnormal glucose homeostasis and insulin resistance in Turkish obese children and adolescents. Diabetes Obes Metab 2007; 9:304–310.
14. Pinhas-Hamiel O, Standiford D, Hamiel D, Dolan LM, Cohen R, Zeitler PS. The type 2 family: a setting for development and treatment of adolescent type 2 diabetes mellitus. Arch Pediatr Adolesc Med 1999; 153:1063–1067.
15. Ramachandran A, Snehalatha C, Vinitha R, Thayyil M, Kumar CK, Sheeba L et al. Prevalence of overweight in urban Indian adolescent school children. Diabetes Res Clin Pract 2002; 57:185–190.
16. Hannon TS, Janosky J, Arslanian SA. Longitudinal study of physiologic insulin resistance and metabolic changes of puberty. Pediatr Res 2006; 60:759–763.
17. Goran MI, Gower BA. Longitudinal study on pubertal insulin resistance. Diabetes 2001; 50: 2444–2450; http://dx.doi.org/10.2337/diabetes.50.11.2444
18. Goran MI, Bergman RN, Cruz ML and Watanabe R. Insulin resistance and associated compensatory responses in African-American and Hispanic children. Diabetes Care 2002; 25: 2184–2190; http://dx.doi.org/10.2337/diacare.25.12.2184
19. Travers SH, Jeffers BW, Bloch CA, Hill Jo and Eckel RH. Gender and Tanner stage differences in body composition and insulin sensitivity in early pubertal children. J Clin Endocrinol Metab 1995; 80:172–178.
20. Narayan KM, Fagot-Campagna A and Imperatore G. Type 2 diabetes in children: a problem lurking for India? Indian Pediatr 2001; 38:701–704.
21. Atabek ME, Pirgon O, Kurtoglu S. Assessment of abnormal glucose homeostasis and insulin resistance in Turkish obese children and adolescents. Diabetes Obes Metab 2007; 9: 304–310.
22. Britz B, Siegfried W, Ziegler A, Larnertz C, Herpertz-Dahimann BM, Remschmidt H, et al. Rates of psychiatric

disorders in a clinical study group of adolescents with extreme obesity and in obese adolescents ascertained via a population based study. Int J Obes Relat Metab Disord 2000; 24:1707–1714.
23. Pesa JA, Syre TR, Jones E. Psychosocial differences associated with body weight among female adolescents the importance of body image. J Adolesc Health 2000; 26: 330–337.
24. Vila G, Robert JJ, Nollet-Clemencon C, Vera L, Crosnier H, Rault G, et al. Eating and emotional disorders in adolescent obese girls with insulin-dependent diabetes mellitus. Eur Child Adolesc Psychiatry 1995; 4:270–279.
25. Stice E, Hayward C, Cameron RP, Killen JD, Taylor CB. Body-image and eating disturbances predict onset of depression among female adolescents: a longitudinal study. J Abnorm Psychol 2000; 109:438–444.
26. Ozanne SE, Hales CN. Early programming of glucose-insulin metabolism. Trends Endocrinol Metab 2002; 13: 368–373.
27. Phillips DI. Birth weight and the future development of diabetes. A review of the evidence. Diabetes Care 1998; 21(suppl 2): B150–B155.
28. Dabelea D, Pettitt DJ, Hanson RL, Imperatore G, Bennett PH and Knowler WC. Birth weight, type 2 diabetes, and insulin resistance in Pima Indian children and young adults. Diabetes Care 1999; 22: 944–950;
http://dx.doi.org/10.2337/diacare.22.6.944
29. Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, et al. Fetal and infant growth and impaired glucose tolerance at age 64. BMJ 1991; 303: 1019–1022.
30. Phipps K, Barker DJ, Hales CN, Fall CH, Osmond C and Clark PM. Fetal growth and impaired glucose tolerance in men and women. Diabetologia 1993; 36: 225–228.
31. Valdez R, Athens MA, Thompson GH, Bradshaw BS and Stern MP. Birthweight and adult health outcomes in a biethnic population in the USA. Diabetologia 1994; 37: 624–631.
32. McCance DR, Pettitt DJ, Hanson RL, Jacobsson LT, Knowler WC and Bennett PH. Birth weight and non-insulin dependent diabetes: thrifty genotype, thrifty phenotype, or surviving small baby genotype? BMJ 1994; 308: 942–945.
33. Leger J, Levy-Marchal C, Bloch J, Pinet A, Chevenne D, Porquet D, et al. Reduced final height and indications for insulin resistance in 20 year olds born small for gestational age: regional cohort study. BMJ 1997; 315: 341–347.
34. Jaquet D, Gaboriau A, Czernichow P and Levy-Marchal C. Insulin resistance early in adulthood in subjects born with intrauterine growth retardation. J Clin Endocrinol Metab 2000; 85:1401–1406.
35. Wei JN, Sung FC, Li CY, Chang CH, Lin RS, Lin CC, et al. Low birth weight and high birth weight infants are both at an increased risk to have type 2 diabetes among school children in Taiwan. Diabetes Care 2003; 26: 343–348; http://dx.doi.org/10.2337/diacare.26.2.343
36. Pfab T, Slowinski T, Godes M, Halle H, Priem F and Hocher B. Low birth weight, a risk factor for cardiovascular diseases in later life, Is already associated with elevated fetal glycosylated hemoglobin at birth. Circulation 2006; 114:1687–1692.
37. Fetita LS, Sobngwi E, Serradas P, Clavo F and Gautier JF. Review: consequences of fetal exposure to maternal diabetes in offspring. J Clin Endocrinol Metab 2006; 91:3718–3724.
38. Dorner G. Influence of early postnatal nutrition on body height in adolescence. Acta Biol Med Ger 1978; 37: 1149–1151.
39. Kramer MS, Barr RG, Leduc DG, Boisjoly C and Pless IB. Infant determinants of childhood weight and adiposity. J Pediatr 1985; 107: 104–107.

40. Dewey KG, Heinig MJ, Nommsen LA, Peerson JM and Lonnerdal B. Breast-fed infants are leaner than formula-fed infants at 1 y of age: the DARLING study. Am J Clin Nutr 1993; 57:140–145.
41. Burke V, Beilin LJ, Simmer K, Oddy WH, Blake KV, Doherty D, et al. Breastfeeding and overweight: longitudinal analysis in an Australian birth cohort. J Pediatr 2005; 147: 56–61.
42. Lucas A, Sarson DL, Blackburn AM, Adrian TE, Aynsley-Green A and Bloom SR. Breast vs bottle: endocrine responses are different with formula feeding. Lancet 1980; 1:1267–1269.
43. Fagot-Campagna A, Saaddine JB, Flegal KM and Beckles GLA. Diabetes, impaired fasting glucose, and elevated HbA1c in U.S. adolescents: the Third National Health and Nutrition Examination Survey. Diabetes Care 2001; 24:834–837; http://dx.doi.org/10.2337/diacare.24.5.834
44. Duncan GE. Prevalence of diabetes and impaired fasting glucose levels among US adolescents: National Health and Nutrition Examination Survey, 1999–2002. Arch Pediatr Adolesc Med 2006; 160:523–528.
45. Dean HJ, Young TK, Flett B, Wood-Steiman P. Screening for type-2 diabetes in aboriginal children in northern Canada. Lancet 1998; 352:1523–1524.
46. Acton KJ, Burrows NR, Moore K, Querec L, Geiss LS, Engelgau MM. Trends in diabetes prevalence among American Indian and Alaska native children, adolescents, and young adults. Am J Public Health 2002; 92:1485–1490.
47. Dabelea D, Hanson RL, Bennett PH, Roumain J, Knowler WC and Pettitt DJ. Increasing prevalence of Type II diabetes in American Indian children. Diabetologia 1998; 41:904–910.
48. Wei JN, Sung FC, Lin CC, Lin RS, Chiang CC and Chuang LM. National surveillance for type 2 diabetes mellitus in Taiwanese children. JAMA 2003; 290:1345–1350.
49.Bar Dayan Y, Elishkevits K, Grotto I, Goldstein L, Goldberg A, Shvarts S, et al. The prevalence of obesity and associated morbidity among 17-year-old Israeli conscripts. Public Health 2005; 119:385–389.
50. El-Hazmi MA, Warsy AS. Prevalence of overweight and obesity in diabetic and non-diabetic Saudis. East Mediterr Health J 2000; 6:276–282.
51. Lipton R, Keenan H, Onyemere KU and Freels S. Incidence and onset features of diabetes in African-American and Latino children in Chicago, 1985–1994. Diabetes Metab Res Rev 2002; 18:135–142.
52. Pinhas-Hamiel O, Dolan LM, Daniels SR, Standiford D, Khoury PR and Zeitler P. Increased incidence of non-insulin dependent diabetes mellitus among adolescents. J Pediatr 1996; 128: 608–615.
53. Kitagawa T, Owada M, Urakami T, Tajima N: Epidemiology of type 1 (insulin- dependent) and type 2 (non-insulin-dependent) diabetes mellitus in Japanese children. Diabetes Res Clin 1994; 24 (Suppl.): S7–S13.
54. Kitagawa T, Owada M, Urakami T, Yamauchi K: Increased incidence of non-insulin dependent diabetes mellitus among Japanese school children correlates with an increased intake of animal protein and fat. Clin Pediatr 1998; 37: 111–115.
55. Haines L, Wan KC, Lynn R, Barrett TG and Julian PH. Rising incidence of type 2 diabetes in children in the U.K. Diabetes Care 2007; 30:1097–1101; http://dx.doi.org/10.2337/dc06-1813
56. McMahon SK, Haynes A, Ratnam N, Grant MT, Carne CL, Jones TW, et al. Increase in type 2 diabetes in children and adolescents in Western Australia. Med J Aust 2004; 180:459–461.
57. Pinhas-Hamiel O, Zeitler P. Acute and chronic complications of type 2 diabetes

mellitus in children and adolescents. Lancet 2007; 369:1823–1831.
58. Fourtner SH, Weinzimer SA, Levitt Katz LE. Hyperglycemic hyperosmolar non-ketotic syndrome in children with type 2 diabetes. Pediatr Diabetes 2005; 6:129–135.

59. Hollander AS, Olney RC, Blackett PR and Marshall BA. Fatal malignant hyperthermia-like syndrome with rhabdomyolysis complicating the presentation of diabetes mellitus in adolescent males. Pediatrics 2003; 111:1447–1452.
60. American Diabetes Association. Type 2 Diabetes in Children and Adolescents. Pediatrics 2000; 105(3): 671-680.
61. Urakami T, Morimoto S, Nitadori Y, Harada K, Owada M and Kitagawa T. Urine glucose screening program at schools in Japan to detect children with diabetes and its outcome-incidence and clinical characteristics of childhood type 2 diabetes in Japan. Pediatr Res 2007; 61:141–145.

****