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Type 2 Diabetes in Young

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a disease normally seen to appear after the 40 years of age. But now it is emerging in young adults at the level of global epidemic because of the increasing burden of obesity. It is also evident that this young diabetic population is an aggressive phenotype and is leading to the premature development of complications. This condition not only have impact on the quality of life but also unfavourably influences the long term outcome, raising the possibility of a serious public health challenge.

INTRODUCTION

The age of onset of T2DM is falling and this condition is now not uncommon among children, adolescents and young adults even at the age of ten. The National Institute for Health and Clinical Excellence (NICE) defines early-onset T2DM as those subjects with current age below 40 years. This has been reported in many countries with different ethnic and cultural backgrounds with increasing prevalence of the sedentary lifestyle and obesity. These T2DM in young (T2DMY) are at high risk of developing premature microvascular complications (nephropathy, retinopathy and neuropathy) and macrovascular or cardiovascular diseases due to the adverse atherogenic risk factors and poor diabetes control. The clinical management is challenging as there no clinical trial evidence in this population.

Future research strategies should explore its natural history and the development of complications, and outcomes studies pertaining to structured patient education, screening for diabetes in at risk groups, intensive treatment of glucose control and associated cardiovascular risk factors.

EPIDEMIOLOGY

The global burden of T2DM is significant and rising in any age group, but there is strong evidence that it is becoming more common among young adults particularly as reported from USA and Japan. Newly diagnosed T2DM is evident in up to 45% of certain groups of young children in the USA and this is clustered in certain ethnic groups such as Pima Indians, Hispanics, Asians and Afro-Carribeans. In Japan, the prevalence of T2DM among junior high school children has become double between 1976-1980 and 1991-1995. In Japan the prevalence of T2DM was approximately 50% and 75% respectively between 10-19 and 20-29 year. Early-onset T2DM has also been reported in China, Mexico, India and Australia.

Bhatia, et al. from India found that, T2DMY accounted for 12% of cases (total 160 cases) of diabetes mellitus in children below 18 years of age.

The national survey of England in 2009 identified 328 youths under the age of 18 years with T2DM, representing 1.5% of the total diabetic population in this age group with peak prevalence in 10-14 year-olds. In the last 2 decades, obesity has increased by 70% in adults aged 30-39 years making young adults the fastest growing group for both obesity and T2DM.

PATHOPHYSIOLOGY OF T2DMY

The pathophysiology of early-onset T2DM subjects is similar to those above 40 years and is characterised by pancreatic β cell impairment and obesity-induced insulin resistance. Gungor et al showed that T2DMY subjects had pathophysiological features of β cell dysfunction, insulin resistance with reduced adiponectin levels and hepatic insulin resistance resulting in elevated hepatic glucose production. Compared with obese nondiabetic subjects, the insulin secretory defect and reduction in insulin sensitivity in obese diabetic patients were approximately 50-75% and 50% lower. This decline in β cell function is more rapid (15% per year) compared with the older T2DM cohort (6% per year) and as such these subjects were 80% more likely to require insulin therapy than the older subjects.

CLINICAL PRESENTATION AND DIAGNOSTIC CHALLENGES

The features of insulin resistance, often present in T2DMY are abdominal obesity, hypertension, dyslipidaemia, acanthosis nigricans, polycystic ovarian syndrome and non-alcoholic fatty liver. These features may be a forerunner of future T2DM.

In contrast, younger subjects with Type I diabetes mellitus (TIDM) present with minimal features of insulin resistance and the onset of clinical presentation may be more rapid with a short history of polyuria, polydipsia and weight loss, and may have ketosis or ketoacidosis in more severe cases. But keep in mind that up to 30% of patients with T2DM can present with ketosis or ketoacidosis.

Ketosis-prone T2DM occurs in a group of subjects with obesity, who presents with ketosis or ketoacidosis and subsequently enter a period of near normoglycaemic remission. At presentation, the β cell function is often severely impaired but improves after a few months of treatment with insulin, often allowing its discontinuation and responding to oral agents.

Monogenic diabetes with a prevalence between 1-2%, formerly known as maturity-onset diabetes in the young (MODY), is a diagnosis that should be also considered

as a differential diagnosis of T2DMY. It is an inherited condition arising from a seven different mutation in a single gene which regulates β cell function. This diagnosis is based on four clinical scenarios;

a. diabetes diagnosed before 6 months of age irrespective of the current age;

b. patients with mild, stable fasting hyperglycaemia between 5.5-8.0 mmol/L;

c. familial, young onset diabetes that does not fit with either T1DM or T2DM

d. young onset diabetes with extra-pancreatic involvement such as renal disease and deafness.

The diagnosis of monogenic diabetes is confirmed by genetic testing.

One should be cautious to make the diagnosis of T2DM in a younger person. A case misdiagnosed as T2DM, when they actually have TIDM and requires insulin rather than oral antidiabetic treatment, can be life-threatening due to diabetic ketoacidosis. Similarly, misdiagnosing a patient as T1DM whilst they have T2DM can have a substantial negative impact on the quality of life as they are unnecessarily subjected to life-long multiple insulin injections and numerous blood glucose tests. Likewise making the correct diagnosis of monogenic diabetes can result in a significant impact on the type of treatment and quality of life. The salient distinguishing features of TIDM, T2DM and monogenic diabetes are shown in Table 1.

DIABETES COMPLICATIONS

Nephropathy

The renal complications occur earlier and are common. The prevalence of microalbuminuria is 7-22%, 28-42% and 60% at diagnosis, 5 and 10 years after diagnosis respectively. The diabetes duration, poor glycaemic control and hypertension are the conditions associated with progression. The nephropathy is more prevalent and its progression more rapid in T2DMY compared to same age group of T1DM patients. Yoo et al found persistent microalbuminuria and macroalbuminuria were seen in 18.2% and 4.5% among T2DM cohort respectively compared to 11.3% and 2.8% of those with TIDM despite having similar glycaemic control.

Retinopathy

Like nephropathy, retinopathy can be present at diagnosis and can cause blindness at a younger age. In Japan out of 1065 subjects of T2DMY, 12.7% developed proliferative retinopathy before the age of 35 years and 24% of them were blind by a mean age of 32 years. Progression of retinopathy was determined by longer diabetes duration, poor diabetes control and hypertension. But when compared with TIDM, retinopathy appeared to be less common in T2DMY.

Neuropathy

The neuropathic complications can occur early among subjects with early-onset T2DM, perhaps to a greater degree than those with T1DM. A study from the UK showed 57% of T2DMY subjects had peripheral neuropathy while none of those with TIDM had this complication. Another study showed 40% subjects with T2DMY had evidence of peripheral neuropathy, six of whom had foot ulceration.

Macrovascular Disease

The T2DMY leads to adverse cardiovascular risk. A Canadian study with T2DM (n = 69, follow up 9 years), showed that the mortality during this period was 9% and among the survivors, 35% developed microalbuminuria, 45% were hypertensive and 6% were on dialysis in the background of poor glycaemic control. In a Japanese study, 1.3% of T2DMY subjects, diagnosed before the age of 30 years, developed atherosclerotic vascular disease at the mean age of 36 years.

T2DMY subjects manifest higher aortic pulse wave pressure and increased vascular stiffness of similar degree, greater carotid intima media thickness and carotid artery stiffness. The "Patho-biological Determinants of Atherosclerosis in Youth (PDAY)" study showed that the process of atherosclerosis began in childhood or early

Table 1: Showing the main distinguishing features of TIDM, T2DM and monogenic diabetes

Frequency	>90%	<10%	1-2%
Clinical Picture	Acute onset; symptomatic with weight loss, polyuria, polydipsia	Often asymptomatic	Variable, can be incidental finding
Obesity	Population frequency	Increased frequency	Population frequency
Parents with Diabetes	2-4%	80%	90%
Ketosis	Present	Usually absent	Common in neonatal forms, rare in others
Diabetes related Antibodies	Positive	Negative	Negative
Therapy	Insulin	Oral hypoglycaemics	Variable depending on subtypes
Associated autoimmune diseases	Yes	No	No

adulthood and its rate of progression was determined by the same risk factors (such as obesity, hypertension, dyslipidaemia, glucose intolerance and smoking) as in older individuals with cardiovascular disease.

The T2DMY subjects also appear to be more resistant to the metabolic benefits of physical activities and raise the notion that this population may be non-responders to exercise.

Mohan et al noted that over 40% of the children with T2DM had two or more cardiovascular risk factors, e.g. central obesity, dyslipidemia or hypertension, compared to 13.6% among T1DM subjects of similar age.

CHALLENGES IN CLINICAL MANAGEMENT

The important goal in diabetes management is to prevent the development or reduce the progression of micro- and macrovascular complications and allow healthy growth and acceptable active life.

A study by Song et al showed that early-onset T2DM subjects developed significant diabetes-related complications up to 20 years earlier, particularly for microvascular disease, compared to the later-onset cohort. Cardiovascular disease is the major cause of morbidity and mortality in T2DM.

Due to the lack of definitive clinical evidence,there is suboptimal administration of cardio-protective treatment, particularly in relation to primary prevention of cardiovascular disease. One study has shown that only 23.9% and 39.6% of early-onset subjects received statin and antihypertensive treatment respectively and this is in contrast to the later-onset subjects where 67% and 75.8% received statin and antihypertensive treatment respectively, although the two groups had similar numbers of co-existing cardiovascular risk factors.

Another study from Japan showed approximately 60% ofT2DM subjects aged between 10-19 years failed to attend regular clinic follow-up for up to 2 years. The irregular patients had higher obesity and blood pressure, a more adverse glycaemic and lipid profile and were less likely to have regular exercise or a proper diet. The periodic discontinuation of medications are common in T2DMY.

MANAGEMENT

Explain to the children and young people with type 2 diabetes and their family members that an HbA1c target level of 6.5% (48 mmol/mol) or lower is ideal to minimise the risk of long-term complications.

Treatment is based on lifestyle interventions and metformin as the first-line drug. Offer to the children and young people with type 2 diabetes, dietetic support to optimise body weight and blood glucose control. Encourage children and young people with type 2 diabetes to eat at least 5 portions of fruit and vegetables each day. At each clinic visit for children and young people with type 2 diabetes measure height and weight and plot on an appropriate growth chart, calculate BMI and decide the diet plan. At each contact with a child or young person with type 2 diabetes who is overweight or obese, advise them and their family members about the benefits of physical activity and weight loss, and provide support towards achieving this.

Till date, metformin is the only oral hypoglycemic agent approved for T2DMY by FDA, older than 10 years. Metformin should be initiated as 500 mg orally daily or twice daily with meals and slowly titrated to 1000 mg orally twice daily over 3 - 4 weeks. There is limited experience with other oral agents (which may be beneficial in youth with type 2 diabetes) and hence not approved by FDA. Above the age of 16 any drug as per guidelines can be used.

Initial treatment of youth with T2D should include metformin and/or insulin alone or in combination. Insulin should be initiated in youth with type 2 diabetes and metabolic decompensation or in cases of difficult controls with oral agents.

The decision for the initial treatment modality is determined by symptoms, severity of hyperglycemia, and presence or absence of ketosis/ketoacidosis. If the patient is metabolically stable (HbA1c<9 and no symptoms), metformin monotherapy is the treatment of choice. If the patient is not metabolically stable, insulin will be required at least initially. A variety of insulin regimens are effective, but once a day NPH or basal insulin (0.25–0.5 units/kg starting dose) is often effective in attaining metabolic control.

FUTURE RESEARCH DIRECTIONS

There are important gaps in the understanding of the natural history in the evolution and progression of T2DMY including the development of diabetes-related complications among children, adolescents and young adults. Because of the epidemic of obesity affecting this population, there is a need for cost-effective screening strategies designed for the younger population to detect undiagnosed T2DM and to identify those at risk of T2DM to ensure they are effectively managed.

CONCLUSION

The condition of T2DMY raises both clinical and social problems. These group of affected persons have longer disease duration and exposure to the adverse diabetic state leading to higher risk of premature development of complications with significant morbidity and mortality occurring at much unexpected early age. As a result the young and productive workforce,who actually is the future of the society may be lost or become less effective together with the financial cost of treating these complications and daily man power loss.

In absence of definite worldwide accepted guideline based on large prospective multi-centric trials, there is also hesitancy or therapeutic inertia as a consequence of clinicians' uncertainty in treating these young individuals appropriately add to the problem.

We need early diagnosis and preventive measures particularly in terms of obesity. The awareness should

be created amongst the primary care physicians, people at large, school teachers and should be started from the school level. Every school and college must have compulsory playground and play/exercise intervals, teaching about healthy food habit and its canteen should not vendor unhealthy fast foods.

We need better understanding of the factors involved in the development of T2DMY and its complications. This effort should be coupled with the implementation of public health initiatives to control and avert future increases in obesity to prevent this impending devastating disease of the society.

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