Understanding the rising incidence of type 2 diabetes in adolescence

J Weill, S Vanderbecken, P Froguel

A focus on its epidemiology, pathology, and therapeutic consequences

The definition of diabetes mellitus (DM) was recently changed by the American Diabetes Association to a fasting plasma glucose value of at least 126 mg/dl (6.9 mmol/l), on the basis of increased risk of the complication of retinopathy. It has been estimated that worldwide approximately 154 million people have diabetes, with up to one third of the cases remaining undiagnosed in developed countries such as the USA. Its human cost is considerable with morbidity from retinopathy, neuropathy, renal failure, and vascular disease, in addition to the socioeconomic burden. Additional lifetime costs attributable to DM have been estimated at £19 649 per affected individual in the UK.

Since the introduction of insulin therapy, a clear distinction has been established between the form of DM where insulin is immediately needed (type 1 or insulin dependent DM), and that where there is a danger of hypoglycaemia, where insulin therapy represents a “luxury” (type 2 diabetes (T2D) or non-insulin dependent DM). The latter is far more frequently associated with obesity and a “gluttonous appetite.” Age is a distinguishing feature; an age ≥40 years predicts T2D with a sensitivity of 97% and a specificity of 100%.

However, nearly 25 years ago, North American authors first drew attention to the occurrence of T2D in young Pima Indians. Pinhas-Hamiel from Cincinnati highlighted the incidence of this condition in black adolescents; subsequently Hispanic-American adolescents have been found to be affected. This concerned US health authorities sufficiently for the Centers for Disease Control and Prevention to order a specific committee to investigate.

EPIDEMIOLOGY

In greater Cincinnati, the incidence of T2D among young people suddenly increased from 0.3–1.2/100 000 new cases per year before 1992 to 2.4/100 000 by 1994 (one third of all juvenile DM cases). Black adolescents, especially females were mainly affected, but whites were not spared. Almost all patients were overweight, but there was no apparent link between body mass index in obese individuals, and incidence. Prevalence rates were recently reassessed as 0.41% of teenagers in the USA, and more specifically, in a population of US obese adolescents and children, the prevalence of impaired glucose tolerance and silent T2D was estimated as 25% and 0.4% respectively, independent of ethnicity.

In the Far East, the prevalence dramatically increased for Japanese schoolchildren between 1975 and 1980 from 1.3 to 6 per 100 000. In UK (West Midlands and Leicester), eight T2D affected female teenagers were first identified from non-native ethnic minority groups—Pakistani, Indian, and Arabic, but recently Drake et al described in this journal the condition in four white significantly obese adolescents. Furthermore, in the southern hemisphere several cases have been found in obese adolescents on the islands of Polynesia and Réunion which are French Overseas Departments (P Froguel, unpublished data).

PATHOLOGY

In order to understand the mechanisms of T2D in adolescence, one has to take into account epidemiological data, ethnicity, and obesity, as well as puberty status and insulin secretion. There is a complex interplay of factors, essentially linked to lifestyle and genetics.

Ethnicity

Carbohydrate metabolism is influenced by ethnicity. For example, post-pubertal Mexicanos show a bimodal glucose profile two hours after a glucose challenge. The first bell shaped distribution is seen in the majority, but a minority of the group have a separate, frankly diabetic curve. Resting energy expenditure and to a greater degree basal lipolysis are significantly lower in Afro-American prepubertal normal children than in their white counterparts.

Anthropometry and insulin resistance

Obesity

Resistance to the hypoglycaemic action of insulin is a prerequisite to glucose intolerance and T2D. Insulin resistance is more marked in normal black than normal white adolescents. Obesity causes, or at least, worsens insulin resistance, which is partially alleviated by diet induced slimming. Clinically, insulin resistance is shown by acanthosis nigricans, a velvety hyperpigmented cutaneous lesion, mainly located in the axillae and around the neck.

The mechanism of insulin resistance in obesity is a matter of debate involving two confronting theories, metabolic and hormonal. Metabolic: either endogenous or exogenous (supplied by food) non-esterified fatty acids, whose plasma levels are increased in obesity, antagonise glycolysis and thence glucose oxidation in skeletal muscles.

Hormonal: obesity is characterised by an increase of plasma levels of adipocyte secreted diabetogenic hormones (leptin, cytokines such as tumour necrosis factor (TNFα), interleukin 6, and resistin) and by the decrease of an insulin sensitising hormone, adiponectin. Insulin resistance is not universal in obesity, even in children with early onset and when it is severe. T2D occurs when insulin secretion becomes unable to overcome the insulin resistance, resulting in variable insulin secretion defects, with a range of diabetes from silent to ketoacidosis.

Intrauterine growth retardation

Children born small for gestational age and remaining short are characterised by insulin resistance, which is a risk factor for T2D. This emphasises the important influence of intrauterine development on later health.

Fetal macrosomia

Conversely, in the offspring of mothers with diabetes from predisposed American Indian tribes, macrosomia is predictive of future T2D of youth.

Puberty

Longitudinal studies have shown a drop in insulin sensitivity in late puberty, irrespective of changes in body fat, visceral fat, plasma insulin-like growth factor 1, or sex steroid levels. This reduced insulin sensitivity is probably due to a sex hormone primed increase in growth hormone secretion.

Lifestyle

Diet

The Japanese experience emphasises the role of saturated animal fats and proteins. The increase of juvenile T2D between 1975 and 1980 accompanied Westernisation of food, while the incidence of obesity progressed more slowly at that time. Saturated fats promote
obesity and insulin resistance, and reduce insulin secretion by way of lipotoxicity, with hyperglycaemia exacerbating pancreatic beta cell damage by glucotoxicity.

Physical activity
Physical training improves insulin sensitivity by increasing insulin dependent glucose transporter GLUT-4 expression in muscle. Furthermore, physical inactivity leads to an increased prevalence of obesity.

Toxicology
Research from inner city Los Angeles minority patients with T2D showed that consumption of alcohol and illicit drugs hastens the onset of the disease.

Genetics
A small proportion of patients presenting with T2D (5% at all ages) have a monogenic, autosomal dominant form of T2D (maturity onset diabetes of the young (MODY), 1–6 subtypes). These patients generally have a strong family history of T2D in two or more consecutive generations. They generally show an early onset of chronic hyperglycaemia. For instance, subjects with glucokinase deficiency (MODY 2) present with mildly raised glucose values in the first week of life.

In contrast, MODY 3 subtype (due to mutation in the transcription factor hepatocyte nuclear factor 3α) occurs at a later age, in general around or after puberty. In Caucasians, about 50% of all MODY cases have mutations in glucokinase, and this condition is not infrequent in children with abnormal glucose values and absence of pancreatic islet antibodies. In adolescents and young adults with severe non-type I diabetes, MODY 3 is the most prevalent MODY gene.

Recently, several papers have described atypical forms T2D in children or adolescents with “private” mutations in HNF1α. It is likely that besides HNF1, mutations in other key genes for β cell phenotype may have the same effect when present at a high prevalence in isolated populations experiencing an obesity epidemic.

Apart from MODY, T2D is a multifactorial disease, dependent on the complex interaction of environmental and genetic factors with the effects of multiple genes. A well documented Danish twin study assessed genetic predisposition for T2D itself as 61%, 26% for glucose intolerance, and 50% for an insulin secretory abnormality. In order to explain the higher incidence of T2D in diverse ethnicities, Neel proposed, in 1960, the thrifty genotype theory. Starvation selected genes efficient for energy storage, which are detrimental in affluent times, because of metabolic overload. At the present time, we are not aware of “original” thrifty genes in predisposed populations. The hypothesis of transethnically shared genes showing at-risk variants in a higher prevalence than in predisposed populations seems more likely. A recent example is the chromosome 2 NIDDM 1 CAP 10, encoding for the calpain 10 protease subtype. The same at-risk haplotype is present in more than 15% Mexican-Americans where it contributes to insulin resistance, compared to <5% in Caucasians where its effect on diabetes risk is marginal.

Whether adulthood and childhood onset T2D are genetically distinct entities remains unknown. Given the constant presence of obesity in patients with T2D, it is tempting to speculate that genes conferring a high risk for obesity in children may be the same as those linked to early onset T2D. In this regard VNTR promoter polymorphism in the insulin gene, which was known to be associated with low birth weight and with T2D, was recently shown to be also linked to both excess weight in the general population and to massive childhood obesity (P Froguel, unpublished data). Positional cloning strategies, which imply the genome scanning of dozens of families with multiple cases of children with severe obesity, and the mutation screening of candidate genes mapping to the regions of linkage will contribute to identify these genes, if they exist.

A recent wide genome scan of French families with childhood obesity has mapped a chromosomal region linked to both insulin resistance and obesity on chromosome 6q, at the same locus where a quantitative trait modulating glucose values was found in adults. The availability of large data sets of patients from various ethnic groups with early onset T2D will be necessary to search for susceptibility genes.

THERAPEUTIC CONSEQUENCES
Therapeutic interventions are based on the pathophysiology described above. Lifestyle changes, diet, and physical exercise, moderate but frequent, at least three times a week, constitute a prerequisite, but long term compliance is difficult to obtain in this age group. Oral medicines include insulin sensitisers and secretagogues. As a sensitiser, metformin (500 mg twice a day), compared to placebo, lowered fasting plasma glucose and HbA1C in adolescents with T2D, at the cost of transient abdominal discomfort and diarrhoea in some patients. Thiazolidinediones such as pioglitazone or rosiglitazone enhance insulin sensitivity in the liver, adipose tissue, and skeletal muscle. They reduce hepatic glucose output and increase muscle glucose uptake and can be used in combination with metformin, but age specific drug trials are needed.

Sulphonylurea insulin secretagogues act through binding to the β cell membrane receptor, to stimulate insulin output. For decades young people with diabetes suffering from the monogenic form MODY 2 responded to chlorpropamide, one of the older analogues, but trials remain to be conducted for newer drugs such as glibenclamide and gliclazide in multifactorial T2D of the young. Prandial glucose regulators such as repaglinide are used to control post-prandial hyperglycaemia in adults. Oral combination therapy is more efficient than monotherapy in lowering HbA1C.

Immediate insulin is required when there is significant ketonuria at presentation, and later if blood sugar control is inadequate with HbA1C levels >7% in spite of intensive oral medication, dietary, and exercise management.

Microvascular complications may be present from diagnosis in T2D. However, the aim is to achieve satisfactory blood glucose control, which may be difficult to adhere to in underprivileged minorities. Prevention of T2D through fighting obesity by reducing dietary fat intake and community led programmes to increase physical activity are political priorities for young people. The American “Diabetes Prevention Program Research Group” recently showed the efficacy of metformin and especially of physical activity in prevention of diabetes in T2D prone adults.

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Developing multi-faith chaplaincy
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For spirit’s sake …

T o be human, one has a spirit. That this spirit is named and nurtured in multiple ways around the globe does not detract from the fact that it exists at the core of each and every being. 1 So how, in modern day medical practice is this essential aspect of health catered for, for the children and their families from non-Christian faiths? Ever since the inception of the NHS, hospital authorities have attempted to “provide” for the spiritual needs of patients and staff. Almost every hospital in Britain boasts a chapel and during the past 50 years over 400 hospital chaplains have been appointed. In pluralist societies, it is however essential that the spiritual needs of all faith communities are identified and met. 2 Regrettably, this has not been the case with respect to many of the estimated three million Britons, or the one in ten children subscribing to non-Christian minority faith and ethnic communities.

Acculturation—the process by which minority cultures gradually adopt the values and ethos of the majority culture—has for many families resulted in the erosion of traditional support networks. Such lay alliances have hitherto often been crucial buffers during times of illness, turmoil, and grief. And minority communities have, as has

repeatedly been shown by government reports on health inequalities, more
than their fair share of morbidity and mortality, starting from the neonatal
period and extending over the life course. It is therefore important that,
as increasing demands are placed on chaplaincy services for support and
advice, mechanisms are developed to ensure that such services are competent
to cater for—and sensitive to the needs of, diverse populations.

Although some children from most religious backgrounds will have engaged
in religious practices, in our experience this is particularly so with the South
Asian and Jewish children who tend to absorb parental attitudes towards reli-
gion in the early years of their development without question or analysis. It is
therefore important that children are given age and developmentally specific
opportunities to share and explore their fears. Therefore in order to be effective,
multi-faith chaplains must be aware of their own values, prejudices, and world-
view as these will profoundly affect their response to cultures different from
their own. Their service should, as a result, be flexible where individual
needs are identified and accommodated, which is not possible with the present
ad hoc system.

All children irrespective of back-
ground, deserve the right to receive care
that helps them make sense of illness in
the context of their life, and in so doing
these children must be helped to live
and die meaningfully in ways that are
consistent with their own worldview.
Experience suggests that despite the
best of intentions, many of the current
cohort of chaplains face difficulties in
delivering spiritual care to those from
non-Christian backgrounds. This is only
to be expected since, in addition to the
theological “gap”, there is also a lack of
any in-depth appreciation of the
workings of these “other” cultures.
It is now increasingly being recognised
that all British chaplains need to undergo
a broader training programme than
hitherto in order to enable them to better
fulfil a more generic chaplaincy role. But
there still remains the issue of Christian
chaplains often being unable to join in
worship with patients of faiths other
than their own, thereby limiting the
potential to utilise the spiritual “tools”
that a particular faith community will
often employ in an attempt to restore a
sense of balance and wellbeing.

Symbolism is a universal religious
phenomenon that has the potential to
facilitate communion with an unseen
reality. During times of uncertainty and
spiritual pain, symbols such as incanta-
tions, sacred texts, and artefacts often
assume heightened importance. Our
experience suggests that this is certainly
very true among the faiths practised by
South Asian families in Britain. A bangle
for a young Sikh boy (Kara), the family
icon of a Hindu deity, and the Tawuz (a
black string tied round the neck or wrist
of a Muslim child) can all, if appropri-
ately employed help provide comfort,
hope, and an inner sense of peace. In
contrast, lack of understanding of the
role of such symbols can create misunder-
standing and further turbulence in
what are already trying times.

A wider appreciation of multicultural
symbolism is only one example of the
many ways in which cultural awareness
and empathy can enhance delivery of
health care. It is important for spiritual
carers not only to be familiar with particular religious rites but also to be
aware of the underlying narrative that
threads these practices together.

Cultural competence is an evolving
process that depends on self-reflection,
self-awareness, and acceptance of dif-
fferences. It is based on improving
understanding as opposed to an
increase in cultural knowledge. Evidence indicates that training is much
more likely to be effective if a “whole
staff” or “systems” approach is taken.
Implementation of culturally sensitive
care and not mere tokenism must be the
goal, and this is in our experience best
achieved if all health practitioners
involved with caring for children have
the opportunity for appropriate training.

With the Department of Health and the
Department of Education and Skills
(DES) now pushing forward the agenda
for developing a health and social care
workforce through the NHS University
(NHSU), this could be made possible
from 2003. The NHSU has been set up as
part of the NHS modernisation plan to
provide practical learning and skills for
everyone working in the health service—
that is, staff from all disciplines includ-
ing carers and volunteers. Such an
innovation can form part of a “continu-
ous professional development” for
“life long learning” for any section of
the workforce.

We believe that this important devel-
opment represents an excellent oppor-
tunity to incorporate generic issues on
diversity and specific issues on faith into
the training of chaplains so as to equip
them with the requisite “insight”
needed to facilitate and deliver multi-
faith care to the diverse populations
they serve. This will perhaps be most
effectively achieved by working in
collaboration with existing training
providers. For example, the Markfield
Institute based in Loughborough
University, which currently offers MA
and PhD programmes for Muslim
Imams wanting to become chaplains.

Inclusion of a question on religious
affiliations in the 2001 Census allows us
for the first time to accurately indicate
geographical areas where particular reli-
gious groups are concentrated, for
example, Hindus in Leicester, Muslims
in Bradford, and Sikhs in Southall. It is
therefore now possible to identify areas
in which it would be sensible and
feasible to employ specific faith cha-
plains.

The broken are often the bereaved,
the sick, and the lonely. This is particu-
larly so for those from cultures different
from those in the west. Happiness is
often heightened and tragedy lightened
when shared with the family. It is in the
understanding and meeting the needs of
such people that spiritual “doctors”
come into their own—whatever their
faith, whatever their background.

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