

Young Onset Diabetes in South Asia-what should we contemplate on?

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Introduction and Epidemiology:

Questions which concern the pathogenesis of diabetes mellitus (DM) in the Indian Subcontinent are many, owing to the high prevalence of the disease, the lower age of onset and low body mass index.¹ The foetal origins of diseases-propounded by Barker and colleagues may in part be responsible; considering that the prevalence of low birth weight (LBW) approaches a figure of 15 to 20%.²

A study done by our institution in Rural Tripura (adjacent to the Bangladesh border) and Arunachal Pradesh (border with China) demonstrated an unexpectedly high prevalence of DM of up to 9%.³

Adolescent Health and the School Going Age:

The focus on academics rather than physical activities occurs from a very early age, driven by the Indian school curricular system. SPADES, the study done among young males aged 14-17 years had shown that one fifth were having impaired fasting glycaemia and more than half of them had dyslipidemia with HDL cholesterol of <40 mg/dl.

A subsequent follow up study showed a strong correlation between maternal and children waist circumference, indicating an unhealthy phenotype. If both parents had metabolic syndrome (MS), the child is 6 times greater risk in getting MS. In addition, the relationship between the FTO SNP and waist circumference of children, indicate a partial genetic relationship in inducing MS.⁴

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Thrifty Genotype Hypothesis

Genome-wide association studies (GWAS) from populations in the Vellore birth cohort (VBC), currently 45 years old, had explored genetic variants that modulate birth weight and had identified variants in the ADCY5 (Adenyl Cyclase 5) and CCNL1 (Cyclin L1) locus. This differential effect compared to Western population suggest that there could be other genetic variants influencing birth weight in Indians that are responsible for this "negating" effect.⁵

Thrifty Phenotype Hypothesis

Insulin resistance (IR) in itself is more prevalent in South Asian youth. We found that LBW adult males (N=60) were shorter in height and lighter in body weight compared to their NBW counterparts (N=60). Moreover, the LBW individuals had lower lean body mass and total body lean mass and lower bone mineral content. Interestingly, 8% of the LBW individuals had impaired glucose tolerance. However, this was not reflected in the 'm' values (measure of insulin sensitivity) - that were obtained from the hyperinsulinemic euglycemic clamp studies (HEC), who were all associated with a low median BMI (19.5 kg/m²) in both LBW and NBW groups.

The parents of LBW subjects were shorter than NBW subjects, suggesting an intergenerational influence on birth weight. The LBW group had greater Fat mass (FM)/fat free mass (FFM) and FM/body weight that reduced following a 45-minute exercise intervention for 6 weeks on a bicycle. However, there was no difference in ectopic fat storage (assessed using NMR spectroscopy) between the groups. Hence, it would be fair to consider a unifying hypothesis linking the thrifty genotype and phenotype hypothesis explain an increase in young onset diabetes.⁶

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Mendelian Disorders

We examined Mendelian disease as a harbinger of the epidemic of diabetes in India. Genetic testing to identify mutations in a comprehensive panel of ten MODY genes was carried out in 80 subjects with young onset diabetes. A novel multiplex polymerase chain reaction (PCR) based target enrichment was established, followed by Next Generation Sequencing (NGS) on the Ion Torrent Personal Genome Machine (PGM) that was confirmed by Sanger sequencing. We identified mutations in 11 (19%) of the 56 clinically diagnosed MODY subjects and seven of these mutations were novel. This was the first report of PDX1, HNF1B, NEUROD1 and PAX4 mutations from India. We identified a higher frequency and novel digenic mutation patterns involving NEUROD1 and PDX1. Subsequent work has shown that MODY 1, 2 and 3 are the more common forms, MODY 4, 6 and 13 are commoner.⁷

Young pregnant insulin requiring women also showed up to eighteen percent positive for MODY. Mutations for PDX1, NeuroD1, HNF1a, BLK, INS, ABCC8 and GCK were detected in this population.

Summarizing, NGS is the modality of choice for profiling young onset diabetes, MODY, mitochondrial, syndromic and neonatal diabetes. At present CMC has a single library preparation handling 62 genes, cost-effectively.

HIV/AIDS Syndrome

Acquired lipodystrophy in the young could be due to HIV/AIDS, wherein highly active antiretroviral therapy (HAART) precipitates this disorder. We studied male subjects with HIV aged between 25-50 years of age, comparing the body composition using DXA scans and metabolic parameters of those who had received HAART versus HAART naive, and with those who were HIV-negative.⁸

Fibrocalcific Pancreatic Diabetes Mellitus

FCPD is a condition wherein individuals present in the first decade of life with abdominal pain, steatorrhea in the second decade of life and

diabetes mellitus in the third decade and thought to be seen in tropical regions. The pre-diabetic phase characterized by chronic pancreatitis and steatorrhea is called tropical chronic pancreatitis (TCP).

Using Indirect Calorimetry, we determined the Resting Energy Expenditure (REE) in subjects with FCPD and demonstrated that these subjects had higher REE. These subjects need dietary requirements exceeding 2500 to 3500 kcal accounting for other factors. They had lower carbohydrate and thiamine intake when compared to T1DM subjects, but higher fat intake. In addition, these subjects have lowered bone mineral density (BMD) and was inversely related to stool fat excretion. HEC and intravenous glucose tolerance tests (IVGTT) along with oral glucose tolerance tests (OGTT) in those subjects showed a profound deficiency of insulin secretion.⁹

We discovered a paradoxical elevation in glucagon levels in those with FCPD. Based on this we subsequently proceeded to do OGTT and isoglycemic intravenous glucose infusion (IGI) to measure other pancreatic endocrine hormones. Despite high GLP-1, the incretin effect is lost, suggesting incretin resistance. (unpublished data).

Ketosis Prone Diabetes (KPD/Flatbush Diabetes)

We noticed a number of patients who had DM of fulminant onset in youth age who were GAD antibody negative (GAD-). We followed patients who were GAD+ve versus those who were GAD-ve, who had DKA over a period of a year. It was found that patients who were GAD-ve, a decline in insulin requirements occurred and all subjects were managed entirely on oral antidiabetic agents/nutritional medical therapy. We concluded, for the first time that KPD occurs in Asian Indians.¹⁰

'Malnutrition Modulated Diabetes' (MMD)

This condition was characterized in the 1960s and included: diabetes with fasting glucose > 200mg/dl, onset <30 years age, leanness (BMI < 18kg/m²), absence of DKA on insulin withdrawal, poor socioeconomic status, rural

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origin and insulin requirement of >60 units a day with no radiographic features of FCPD or exocrine dysfunction.

We performed advanced pancreatic HEC,IC and D2G measurements to quantify hepatic glucose output. All patients had a normal MRI abdomen, GAD-ve and were MODY genetics negative. Patients were found to be insulinopaenic; there was no exaggerated response of glucagon production. Hepatic IR was comparable to those with Type 1 diabetes.¹¹

Summary and Unifying Algorithm

In summary,multiple factors are responsible for young onset and low BMI related diabetes mellitus in India.In South Asia, one should consider LBW, FCPD, lipodystrophy,mitochondrial diabetes, MODY, KPD, MMD and the HIV- AIDS syndrome on HAART in diabetes in the young.

A proper evaluation involves a detailed history,pedigree charting,proper physical examination for syndromic features, C-peptide levels (fasting and postprandial),imaging of the pancreas,HOMA-IR and DXA where relevant and longitudinal Beta cell monitoring(for KPD). Quaternary facilities are required for genetics including NGS,Sanger sequencing and multiple ligation probe dependent amplification for deletions and insertions. This comprehensive algorithm will help in clenching the diagnosis and few patients will labelled as unclassified, that needs further research.

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