DOI: http://doi.org/10.4038/sjdem.v9i2.7392

Forays into the Pathogenesis and Differential Diagnosis of Young Onset Diabetes in India- Insights from Vellore.

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Introduction and Epidemiology

Questions which concern the pathogenesis of diabetes mellitus in the Indian Subcontinent are many, owing to the high prevalence of the disease, the lower age of onset and low body mass index amongst Asian Indians. The reasons as to why these characterize Asian Indian phenotype are innumerable. For one, consanguinity/inbreeding is common in the Indian population enabling certain haplotypes to be expressed with a greater frequency. Changes in lifestyle have occurred which herald the current problem to a significant extent. The foetal origins of diseases- propounded by Barker and colleagues may in part be responsible; considering that the prevalence of low birth weight (LBW) in India is amongst the highest in the world and approaches a figure of 15 to 20% of all live births in some parts of the country.

A study done by our institution and organized in Rural Tripura, the first of its kind in the North East, adjacent to the Bangladesh border- demonstrated a prevalence of diabetes of 9%. A similarly unexpectedly high prevalence was seen in rural Arunachal Pradesh on the border with China.

Adolescent Health and the School Going AgeThe focus on academics rather than physical activities occurs from a very early age driven by the Indian school curricular system (SPADES study). Young males aged 14-17 were studied with regards to their glycaemic profile. Impaired fasting glycaemia was present in 20% and nearly 60% of them had an HDL cholesterol of <40 mg/dl; implying that prediabetes had its onset in adolescence. This could be transpolated to full blown diabetes a couple of decades later.

Few years later we analyzed children along with their parents with their anthropometry along with the biochemical analytes. Maternal weight circumference strongly correlated with the waist circumference of the children, indicating an unhealthy phenotype. There were relationships of the maternal waist circumference with the children's waist circumference, lipids and the systolic and diastolic blood pressure measurements. If both parents had the metabolic syndrome (MS), the chance of the child having the metabolic syndrome was 6 times greater.

Though this may have been due to learned behaviour transmitted vertically, we undertook a study to see if there was a genetic component. Subjects from the SPADES study were studied for the impact of the FTO single nucleotide polymorphism (SNP) on body habitus. The FTO SNP was had a clear relationship with the waist circumference of children, indicating a partial genetic relationship with the body habitus of these subjects, inducing MS.

Thrifty Genotype HypothesisIn1961, Neel et al proposed that an individual's adaptation to the environment was dependent on genes selected over a prolonged period (thrifty-genotype). Hales and Barker proposed that suboptimal foetal nutrition, at critical points of time in intrauterine development may cause permanent change in foetal structure, function and metabolism due to foetal programming (thrifty phenotype).

Genome–wide association studies (GWAS) from populations in the Vellore birth cohort (VBC), currently 49 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 to have a more robust association with LBW in European populations. The GWAS have also shown that the association with the ponderal index was strong for the near CCNL1 variants, suggesting a greater association of these variants with fat mass than with skeletal growth at birth, there was no association found with adult BMI or the obesity related traits in adulthood.

Interestingly, the birth weight–lowering variants in both Europeans (ADCY5,CDKA L1[Cyclin- dependent kinase 5 regulatory subunit-associated protein like-])and Indians (ADCY5) have displayed significant associations with impaired glucose–insulin homeostasis in adulthood, reinforcing the genetic link between in utero growth, birth weight and type 2 diabetes mellitus (T2DM).

Why do genetic variants fail to influence both ends of the spectrum (birth weight and adult metabolic phenotype) especially in Indians, unlike the Western population? There could be other genetic variants that influence birth weight in Indians and those upstream or downstream exons/mutations responsible for this "negating" effect. Alteration in metabolic capacity in adulthood is resultant to an epigenetic effect in the foetus and infancy. They may have a long-term impact on DNA expression.

Thrifty Phenotype HypothesisInsulin resistance (IR) in itself is more prevalent in South Asian youth. These are studies that have been largely done using the HOMA index. There had not been any advanced studies in India to study the insulin sensitivity dynamics in subjects born LBW prior to 2012. Few published studies on indirect calorimetry (IC) prior to this in the metabolic arena in India which were done by us in Fibrocalcific pancreatic diabetes (FCPD) and weightlifters and none in MR resonance spectroscopy in LBW subjects or with a baseline normal metabolic status.

We enrolled 60 LBW and 60 NBW males, born and living in rural environments. LBW adult males were shorter in height and lighter in body weight compared to their NBW counterparts. Moreover, the LBW individuals had a lower lean body mass when compared to NBW counterparts. This difference was present in total body lean mass and extended to the upper and lower limbs of these subjects and was associated with lower bone mineral content in the LBW group.

Interestingly, 8% of the LBW individuals had impaired glucose tolerance, which was not present in the NBW individuals. This was not reflected in the 'm' values (measure of insulin sensitivity) - that were obtained from the hyperinsulinemic euglycaemic clamp studies(HEC) done on these individuals, who were all associated with a low median BMI (19.5kg/m2) in both LBW and NBW groups. LBW subjects had a marginally significant higher supine resting diastolic blood pressure level when compared to NBW subjects. The measurements in HDL between LBW and NBW subjects were similar.

IC is another tool wherein our group has acquired a lot of experience in using over the years. There was no difference in resting energy expenditure (REE) when measured by IC between the LBW and the NBW group of subjects, nor was there any difference in Glucose or Fat oxidation between the groups. When the data of all 120 subjects were taken as a whole, and the m-value correlated with the IR indices including HOMA-IR, QUICKI, Fasting Insulin levels, Glucose insulin ratio (FGIR), McCauley's index and Matsuda Index: the strongest correlation was obtained between the m-value and McCauley's index and Matsuda index. Complex calculations apart, our group showed that the FGIR correlates well with HEC and is superior to HOMA-IR, QUICKI and McCauley's index, in recent studies. We have evolved a novel equation for calculating fat free mass utilizing bioimpendance measurements.

Dietary intake of protein was significantly lower in LBW subjects when compared to NBW subjects at the time of recruitment. This was associated with a lower proportion of energy being extracted from the intact protein. The parents of LBW subjects were shorter than NBW subjects, suggesting an intergenerational influence on birth weight.

Epigenetic imprinting of LBW maybe profound, however there was uncertainty as to whether the phenotypic disadvantages imbibed in utero would impair the ability to exercise or interfere with improving body composition.

The LBW group had a greater Fat mass (FM)/ fat free mass (FFM) reduction when compared to their pre-exercise baseline status and a significant decline in FM/body weight following a 45 minute exercise intervention for 6 weeks on a bicycle. The NBW subjects had a small increase in fat percentage. Moreover, there was a significant reduction in fasting plasma insulin levels in the LBW group, while the reduction was not statistically significant in the NBW. Reductions in insulin secretion, HOMA-IS changes were significant in the LBW and NBWs. Reduction in HOMA-IR was only significant in the NBW.

The same subjects had NMR spectroscopic assessment of micro-quantities of fat in liver and muscle. There was negligible ectopic fat storage in the liver in particular, and to some extent in the muscle, unlike Caucasian subjects. There was no difference in ectopic fat storage between NBW and LBWs. Measurements of IR (HOMA-IR) did not have any relationship with hepatic, intramyocellular or extramyocellular fat content. The only independent predictor of intra-myocellular and extramyocellular fat content was with the total body fat percentage.
It would be fair to consider a unifying hypothesis linking the thrifty genotype and phenotype hypothesis, although the exclusive combination would be inadequate to explain an endogenous origin for the increase in young onset diabetes South Asia.

Mendelian Disorders

We examined Mendelian disease as a harbinger of the epidemic of diabetes in India. Maturity Onset Diabetes of the Young (MODY) accounts for up to 2% of patients with diabetes in India. There has also been a trend towards a shift in the age of onset of T2DM to a younger age, ranging from 25 to 34 years. The overlapping clinical feature of MODY with classical polygenic diabetes presents a challenge and requires genetic testing for differentiation.

Genetic testing to identify mutations in a comprehensive panel of ten MODY genes was carried out in 80 subjects of Asian-Indian origin 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). All the mutations and rare variants were confirmed by Sanger sequencing. We identified mutations in 11 (19%) of the 56 clinically diagnosed MODY subjects and seven of these mutations were novel. The identified mutations include p.H241Q, p.E59Q, c.-162G>A 5' UTR in NEUROD1, p.V169I co- segregating with c.493-4G>A and c.493-20C>T, p.E271K in HNF4A, p.A501S in HNF1A, p.E440X in GCK, p.V177M in PDX1, p.L92F in HNF1B and p.R31L in PAX4 genes. These patients with co-existing NEUROD1-PDX1 mutations showed a marked reduction in glucose induced insulin secretion. None of the subjects who had not met the clinical criteria of MODY were positive for mutations. This was the first report of PDX1, HNF1B, NEUROD1 and PAX4 mutations from India. Multiplex PCR coupled with NGS provides a rapid, cost-effective and accurate method for genetic testing of MODY. When compared to earlier reports, we identified a higher frequency and novel Digenic mutation patterns involving NEUROD1 and PDX1. Subsequent work has shown that unlike the western population where MODY 1, 2 and 3 are the more common forms, MODY 4, 6 and 13 (PDX1, NeuroD1 and ABCC8) are commoner.

We asked as to why pregnant young ladies in the early part of the third decade who were non-obese develop gestational/pregestational diabetes (GDM/Pre-GDM). Could they be a subset of individuals with MODY? Young pregnant insulin requiring women were screened for MODY utilizing the same NGS platform. Eighteen percent of subjects who were diagnosed to have GDM/Pre-GDM were MODY positive. Mutations for PDX1, NeuroD1, HNF1a, BLK, INS, ABCC8 and GCK were detected in this population. Therefore, MODY may be responsible for at least one-fifth of GDM or Pre-GDM in those with insulin requiring disease.

There are other forms of monogenic diabetes underdiagnosed when utilizing standard Sanger sequencing. For example in Wolfram's syndrome, there are 8 exons and screening only the 8th exon could miss the appropriate diagnosis in WFS1. The NGS has been utilized for studying the genetic profile of IR in lipodystrophy, an important cause for lean diabetes in the young and requires mega-doses of insulin or respond to pioglitazone; there are milder varieties ranging from Dunnigan Syndrome to the severe Bernedelli-Siep syndrome. NGS is effective in diagnosing H-syndrome.

Sanger sequencing identifies mitochondrial mutations. However, it may depend on the degree of heteroplasmy. In situations of lower heteroplasmy, Sanger sequencing can miss the disorder, and NGS would detect the condition precisely.

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 40 genes simultaneously and 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. Nucleoside reverse

transcriptase inhibitors cause selective loss of fat in the face/limbs, and accumulation of abdominal fat. 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. Those subjects, who had received HAART having lipodystrophy, had the highest odds of predicting MS. These patients had a higher proportion of IR, hypertriglyceridemia and lower levels of HDL cholesterol.

Fibro calcific Pancreatic Diabetes Mellitus

FCPD is a condition wherein individuals present in the first decade of life with abdominal pain, steathorrea in the second decade of life and diabetes mellitus in the third decade. The disorder is exclusively present in tropical regions across the world. The pre-diabetic phase characterized by chronic pancreatitis and steathorrea is called tropical chronic pancreatitis (TCP). The clinical phenotype is well characterized. However, dynamic studies examining insulin secretion, peripheral IR, energy expenditure dynamics, alpha cell function, and incretin output and body composition have not been elucidated. Disease mechanisms are poorly understood.

We undertook several studies to understand these aspects. Using IC we determined the REE in subjects with FCPD. Subjects with FCPD had much higher REE than anticipated. The added factors of poorly controlled diabetes mellitus and malabsorption need correction; this factor in addition to increased REE, indicates that dietary requirements would exceed 2500 to 3500 kcal, since they were underweight at diagnosis. These subjects had a significantly higher intake of fat, fiber, calcium, phosphorus, niacin and higher calorie intake from fat. They had lower carbohydrate and thiamine intake when compared to T1DM subjects.

Studies of body composition showed lowered bone mineral density (BMD) when compared to controls. BMD was inversely related to stool fat excretion and unrelated to vitamin D status. Pancreatic Osteodystrophy was a conglomeration of osteoporosis and Osteomalacia.

We performed HEC and intravenous glucose tolerance tests (IVGTT) along with oral glucose tolerance tests (OGTT) in those subjects with chronic pancreatitis. There was a profound deficiency of insulin secretion, not as severe when compared to matching the insulin secretory defect seen in subjects with T1DM. Patients with TCP had a normal insulin reserve. Studies utilizing the Deuterated glucose measurements (D2G) were performed, which indicated that mild hepatic IR was present (unpublished data).We discovered a paradoxical elevation in glucagon levels in those with FCPD; the levels were somewhere intermediate in comparison to normal controls. Based on this we subsequently proceeded more recently to do OGTT and IVGTT to measure glucagon, pancreatic polypeptide (PP), GLP-1, GIP and Oxyntomodulin levels. The findings were as follows: PP levels were reduced commensurate with depleted islet cell function (p-cell function). The GLP-1 levels were elevated during OGTTs and suppressed during IVGTTs along with the glucagon levels. GIP response was blunted during OGTT and IVGTT as well. Oxyntomodulin was elevated for subjects with FCPD. There is possibly an extra-pancreatic glucagon secretion suggested by the higher level on OGTT with minimal c-peptide and PP response. The source is probably the L-cells, suggested by increased GLP-1, Oxyntomodulin and the correlation between GLP-1 and glucagon. Despite high GLP-1, the incretin effect is lost, suggesting incretin resistance. K-cell function is probably impaired considering the low GIP response and could be related to hyperglucagonemia (unpublished data).

Ketosis Prone Diabetes (KPD/Flatbush Diabetes)In India, it was thought that patients with diabetic ketoacidosis (DKA) were essentially those presenting with early T1DM and perhaps the older ones presenting with Latent autoimmune diabetes in Adults (LADA). We noticed a number of patients who had diabetes of fulminant onset in youth/early middle age who were GAD antibody negative (GAD-ve). We compared patients who were GAD+ve versus those who were GAD-ve, who had DKA. These two groups of patients were followed up over a period of a year. On following up and monitoring serial c-peptide over 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.

'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/childhood history of malnutrition, rural origin and insulin requirement of >60 units a day. There are no radiographic features of FCPD or laboratory evidence of exocrine dysfunction. It is present across lower socioeconomic parts of the world, receding with improvement in socioeconomic status of the region. The cause and pathophysiology remain unknown.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.

Summary and Unifying Algorithm

In summary, multiple factors are responsible for shift in the phenotype towards the left in India with regards to leanness of body habitus as well as age of these patients with diabetes. 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. More work is required to identify the cellular pathogenesis to establish the reasons for this propensity.
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.

Future directions for research include whole Exome and genome sequencing to elucidate genetic causes for young onset diabetes, fat and muscle biopsies to look for features of peripheral resistance, possible intestinal biopsies with RNA expression and immunostaining for subjects with FCPD, and therapeutic trials of pharmaceutical agents for MODY, FCPD and MMD.

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