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Diabetes And Insulin Resistance Syndrome In Indians

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Diabetes is on the increase in India[1] (Table 1). The oft-quoted multicentre ICMR study (1972) showed a prevalence of 2.5 per cent in the urban and 1.8 per cent in the rural population above the age of 15 years.

Most studies after 1986 have, however, shown a much higher prevalence of diabetes, especially in the urban populations. While a part of the reported rise in the prevalence of diabetes could be due to the differences in the methods used, there seems to be a rapid rise in the true prevalence of diabetes, especially in urban India. Even in clinical practice the increasing burden of diabetes is obvious.

The predominant type of diabetes in India is the Type 2, non-insulin dependent variety (NIDDM). Type 1, insulin dependent (IDDM) is relatively rare. An unusual variety was described in the 1960s, now called the malnutrition related diabetes (MRDM) by the WHO[2]. These patients present with severe malnutrition at the time of diagnosis (BMI <18kg/m^2) and require relatively large doses of insulin for glycaemic control. An interesting characteristic is the absence of ketosis when insulin is stopped for long periods of time. The aetiological role of malnutrition, the time course of the pathogenetic processes and the overlap with other more common varieties of diabetes (Type 1 and 2) are a matter of much debate[3,4].

Table 1
Prevalence of diabetes in India

		Urban	Rural
ICMR (1972)		2.3%	1.5% (>15yrs)
Multi-centre (1979)		3.0%	1.3%
Daryaganj (1986)		9.0%(>40 yrs)	
Kudremukh (1988)		5.0%(>20 yrs) 21.0%(>40 yrs)	
Eluru (1989)			6.1%(>40 yrs)
Madras (1992)	DM	8.2% 17.4%	2.4%(>20 yrs) 3.2%(>35 yrs)
	IGT	8.7% 13.5%	7.8%(>20 yrs) 11.5%(>35 yrs)

DM: Diabetes Mellitus; IGT: Impaired Glucose Tolerance

Population-based studies have not shown increased risk of diabetes in malnourished subjects and there are few prospective studies of diabetes in subjects who suffered malnutrition in childhood. Clearly, further studies are needed in a country like India where malnutrition and diabetes are both commonly seen.

INSULIN RESISTANCE SYNDROME

We have investigated different aspects of diabetes in patients attending our diabetic clinic. Our hospital caters to the middle and lower clases population and 25 per cent of the patients are treated free.

Newly diagnosed and untreated hyperglycaemic patients in our clinic were studied.The study included anthropometric, metabolic and endocrine measurements and serial follow-up. All patients underwent a 75g oral glucose tolerance test (OGTT)

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and were classified as non-diabetic, impaired glucose tolerant (IGT) and diabetic as per WHO criteria. Table 2 shows their basic characteristics. We noted that NIDDM is diagnosed at a younger age in our patients compared to those in Western populations (one-fifth of our patients were diagnosed before 35 years and half below 40 years of age). Obesity (body mass index, BMI criteria) was uncommon in our patients compared to Western data (22 per cent men and 47 per cent women diabetic patients in our study compared to 80 per cent in Western clinics), but central obesity (increased waist-hip ratio) was a very characteristic feature of our patients. The highest glucose concentrations were found in subjects who were thin but centrally obese[5].

Hypercholesterolemia was uncommon in our patients (5 per cent) but plasma triglycerides and non-esterified fatty acids (NEFA) were significantly elevated in both IGT and diabetic patients. Blood pressure was significantly higher in both IGT and diabetic patients compared to non-diabetic subjects and half the patients in the hyperglycaemic groups were hypertensive. Thus, the cardiovascular risk factors (obesity, central obesity, hypertension and high plasma triglycerides and NEFAs) were increased not only in diabetic patients but also in the IGT stage which precedes diabetes by many years (Table 3).

Fasting plasma immunoreactive insulin (IRI) concentrations were elevated in IGT and diabetic patients compared to non-diabetic subjects (Table 2), suggesting insulin resistance but post-glucose plasma IRI concentrations were diminished in diabetic patients suggesting insulin deficiency. A comparison of plasma IRI concentrations in non-diabetic controls, IGT and diabetic patients showed the inverted U distribution ('Starling's curve of pancreas') suggesting that insulin resistance and compensatory hyperinsulinaemia precede diabetes.

Very interestingly, the cardiovascular risk factors were all related to plasma glucose and insulin levels[6] and can be thought of as occurring as a part of the complex metabolic profile called the 'insulin resistance syndrome' (Reaven's syndrome X) (Figure 1). Ischaemic electrocardiographic changes (Minnesota code) were seen more frequently in diabetic patients (Table 3) and were associated with older age, higher blood pressure, higher plasma triglycerides and IRI concentrations, lending further support to the concept of the insulin resistance syndrome. It would appear that hyperinsulinaemia, over many years, is associated with increased cardiovascular risk.

Comparative studies in migrant Asians in the UK suggest that Indians are more centrally obese for a given BMI compared to white Caucasians and that Indians are more insulin resistant. This could explain the higher prevalence of ischaemic heart disease in Indians[7].

Table 2
Characteristics of newly diagnosed hyperglycaemic subjects in an urban diabetic clinic

	Non-diabetic (I32)	IGT (79)	Diabetic (I89)
Men %	57%	56%	65%
Age (yrs)	40	47	43
Body Mass Index (kg/m^2)			
Men	23.3	25.5	23.9
Women	23.6	26.6	24.9
Waist-Hip Ratio			
Men	0.88	0.93	0.92
Women	0.77	0.79	0.80
Blood Pressure(mmHg)	121/83	129/85	129/87
Plasma Cholesterol (mg/dl)	163	180	167
Plasma Triglycerides (mg/dl)	79	104	126
Plasma NEFA (mmol/L)	0.81	1.02	1.02
Plasma Immunoreactive Insulin (mU/L)			
Fasting	7.5	11.0	16.0
2 hour post glucose	82.5	148.0	55.5

All values medians. NEFA: Non-esterified fatty acids

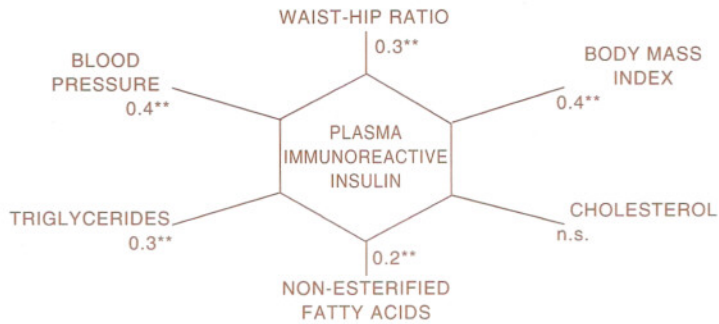
Table 3
Cardiovascular risk factors, glucose tolerance and ischaemic electrocardiograms in an urban diabetic clinic

	Non-diabetic	IGT	Diabetic
Obese			
Men (BMI >27kg/m^2)	15%	30%	22%
Women (BMI >25kg/m^2)	40%	71%	47%
Hypertensive	18%	34%	33%
Cholesterol>240mg/dL	5%	5%	6%
Triglycerides>150 mg/dL	15%	28%	38%
Ischaemic Electrocardiogram			
Men	3%	16%	11%
Women	12%	18%	23%

THRIFTY GENOTYPE

Traditionally, the epidemic of NIDDM (and insulin resistance syndrome) is explained by the so called 'thrifty genotype' hypothesis[8]. It postulates that during evolution, genes

Figure 1
Relationship between cardiovascular risk factors and plasma immunoreactive insulin



*Figures represent correlation coefficients; **p < 0.01; n.s. = not significant.*

were selected which efficiently promote anabolism and store energy during periods of food availability. This stored energy is then used to tide over famine conditions. With progress, when food became available throughout the year, the 'thrifty genotype' became detrimental by promoting obesity, diabetes and other related disorders. Even though very attractive, till today no gene(s) has been identified with the thrifty genotype. Moreover, if these adaptive mechanisms are entirely genetic there is little hope of preventing diabetes in the near future.

THRIFTY PHENOTYPE

A new thought was introduced when Barker *et al*[9,10] showed that the high cardiovascular mortality in the socio-economically deprived areas of the UK (Scotland, Wales) was closely associated with high infant mortality in these areas. High infant mortality was related to poor intrauterine growth and low birth weight, possibly as a result of maternal malnutrition.

A series of studies by Barker's group showed an association of adult diabetes, hypertension, dyslipidemias and abnormal coagulation profile with low birth weight. These associations of birth weight with cardiovascular risk were independent of lifestyle factors and adult obesity. Further studies showed that low birth weight is associated with insulin resistance in adult life. The concept of *in utero* 'metabolic programming' was thus established. Barker proposed that adult diabetes and insulin resistance syndrome are related to a 'thrifty phenotype'(low birth weight). In this scheme, lifestyle factors take a backseat and early life environment rather than genetics is believed to have caused the present day epidemic of diabetes and cardiovascular disease. Accordingly, it might be possible to curtail the epidemic in future generations by improving mothers' nutrition. The implications of these findings for a developing country like India, where over a third of newborns have low birth weight, are enormous.

It is important to remember that most of the diabetic patients (NIDDM) in these studies are obese in adult life. Thus, the concept of foetal-infant origins of adult diabetes is not to be confused with the MRDM of WHO which refers to malnutrition (BMI<18 kg/m^2) at the time of diagnosis of diabetes.

STUDIES IN INDIAN CHILDREN

We collaborated with Barker's group to study the relationship between low birth weight and glucose-insulin metabolism in Indian children[11]. Birth weight data were available from the hospital register. Four hundred and four children were randomly selected from the labour ward register and invited for the study at four years of age. The study included anthropometric measurements and a glucose tolerance test. Two hundred and one children participated in the study. Plasma glucose and insulin concentrations 30 minutes after glucose were inversely related to birth weight (Table 4) but fasting and two-hour plasma glucose and insulin concentrations were not related. The relationship between glucose/insulin and birth weight was independent of current weight but current weight and skinfold thicknesses were directly related to 30 minutes glucose and insulin concentrations.

On the other hand, head circumference was inversely related to glucose and insulin concentrations. Thus, two parameters of poor intrauterine and early growth (birth weight and head circumference) were inversely related to plasma glucose and insulin concentrations while the parameters of current obesity (weight and skinfold thicknesses) were directly related. Thus *poor early growth but excess later growth ('obesity')* are associated with metabolic-endocrine abnormalities which could lead to diabetes in adult life. It is difficult to comment on the B-cell function and peripheral insulin resistance from glucose-insulin concentrations during an OGTT but higher glucose and insulin concentrations could be interpreted as an indicator of peripheral insulin resistance. A serial follow-up of these children is in progress.

Table 4
Birth weight, plasma glucose and insulin concentrations in 4-year-old urban children

Birthweight (Kg)	Number of children	Plasma glucose (mmol/L) at 30 min	Plasma insulin (pmol/L) at 30 min
≤2.4	36	8.1	321
-2.6	36	8.3	337
- 2.8	44	7.8	309
- 3.0	42	7.9	298
≥3.0	43	7.5	289
All	201	7.9	310
P for trend		**0.01**	**0.04**

STUDIES IN ADULT RURAL INDIANS

Excited by these results in young children, we decided to test the hypothesis of the association of growth with future diabetes and cardiovascular risk in a rural population in whom malnutrition is common.

We studied 321 adults above the age of 40 (out of a total population of 383, 85 per cent ascertainment) in Pimpale Jagtap, a rural village near Pune. As a group, this rural population is short and thin (Table 5). Since birth weight records were not available, we used head circumference and height as surrogates for growth and nutrition in early life. Head circumference reflects intrauterine and early childhood growth while height reflects childhood and pubertal growth. BMI and waist-hip ratio reflect recent nutrition.

We performed an OGTT and studied a range of cardiovascular risk factors in this population. There were two known diabetic men in this village, OGTT revealed 12 more diabetics and 13 subjects with impaired glucose tolerance (IGT, Table5). An interesting finding was a low two-hour plasma glucose (<70 mg %) in 21 per cent of these subjects, such 'reactive hypoglycaemia' could precede diabetes in susceptible subjects. Plasma IRI concentrations (two-hour post-glucose) followed the inverted U shaped curve (Starling's law of pancreas, Figure 2) suggesting that even in this population of thin rural subjects compensatory hyperinsulinaemia (insulin resistance) precedes the insulin deficiency of diabetes. Two-hour plasma glucose concentrations were related directly to BMI ($r=0.17$, $p<0.05$) but inversely to height ($r=-0.18$, $p<0.01$) and head circumference ($r=-0.12$, $p<0.05$). Plasma glucose and IRI concentrations and other cardiovascular risk factors (cholesterol, triglycerides, low HDL, blood pressure) were all interrelated, suggesting an association with insulin resistance. Ischaemic electrocardiograms (Minnesota code) were associated with increasing age (both sexes), smaller head circumference (men) and higher blood pressure (women).

Figure 2
Relation between 2-hr plasma glucose and immuroreaction insulin concentrations in the rural population (>40 years)

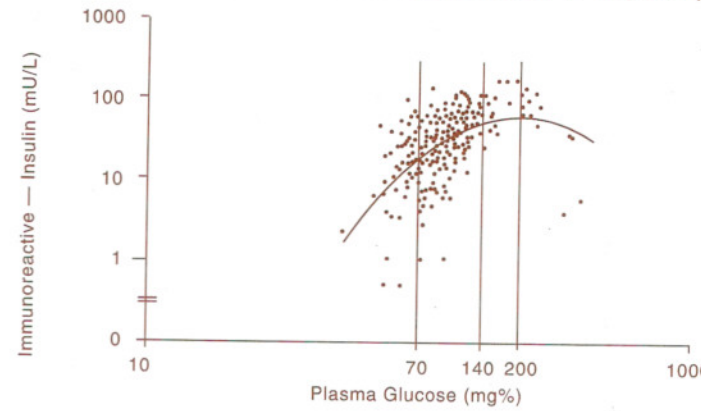


Table 5
Mean anthropometric characteristics of a rural population >40yrs

	Men (158)	Women (163)
Age (yrs)	58.5	53.2
Height (m)	1.63	1.50
Weight (kg)	52.0	44.5
BMI (kg/m^2)	19.5	19.8
Waist-Hip Ratio	0.88	0.78
Head Circumference (cms)	53.6	52.8

Table 6
Cardiovascular risk factors in a rural population >40 yrs

	Men (158)	Women (163)
Obese	2%	10%
Impaired Glucose Tolerant	3%	5%
Diabetic	4%	4%
Hypertensive	3%	4%
Cholesterol >240 mg%	nil	0.5%
Triglycerides >150 mg%	11%	15%
Ischaemic Electrocardiogram (Minnesota)	10%	22%

These results in an adult rural population support our preliminary results in four-year-old children that a combination of poor growth in early life with overgrowth in later years is associated with insulin resistance, diabetes and a detrimental cardiovascular risk profile.

We, therefore, propose a modification to Barker's 'thrifty phenotype' hypothesis to take into account the substantial contribution of later 'overgrowth' to adult cardiovascular risk. We suggest that adult insulin resistance syndrome and associated cardiovascular risk represent an *energy adaptation maladaptation syndrome (ENAMAS)*. Early life malnutrition (intrauterine and early childhood) leads to adaptation of the energy metabolism to help survive the 'famine' (meta-