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Early metabolic abnormalities of NIDDM (Part I)

This is the first in a series of two articles on Early metabolic abnormalities of Non-Insulin Dependent Diabetes Mellitus (NIDDM)

NIDDM has reached epidemic proportions. The epidemic has affected developed and developing countries alike and the worldwide prevalence of diabetes is projected to increase dramatically by 2025. Increase in type 2 diabetes is related to lifestyle changes that have resulted in overweight, obesity and decreased physical activity levels. These changes, in combination with genetic predisposition, increased insulin resistance and progressive β-cell failure, results in rising glycemia in the nondiabetic range. In addition to the risk for diabetes, insulin resistance and impaired insulin secretion are accompanied by a host of major cardiovascular disease (CVD) risk factors including hypertension and dyslipidaemia. Further reduction in insulin secretion over time results in increasing glycaemia and the development of diabetes, which in turn is associated with the development of microvascular and cardiovascular complications.

The transition from the early metabolic abnormalities that precede diabetes-i.e. impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) to diabetes-may take many years. However, current estimates indicate that most individuals (perhaps up to 70%) with these pre-diabetic states eventually develop diabetes. During the pre-diabetic state, the risk of a CVD event is modestly increased. With the development of diabetes, however, there is a large increase in risk for CVD as well as for long-term complications affecting eyes, kidneys and nervous system. Complications of diabetes are related to its duration, chronic level of glycemia and other risk factors.

Although clinical trials have demonstrated the effectiveness of intensive glycaemic and blood pressure control in reducing the long-term complications of diabetes, public health burden of the disease remains enormous. Magnitude of the epidemic, coupled with complex treatment requirements that are difficult and costly to implement, makes the prevention of diabetes a critical public health goal.

IFG and IGT

Isolated IFG = FPG of 100–125 mg/dl with the 2h OGTT value <140 mg/dl; isolated IGT = 2h OGTT value of 140–199 mg/dl with the fasting level <100 mg/dl. The combined characteristics of IFG and IGT have been studied by identifying populations that fulfill both criteria (FPG = 100–125 mg/dl and 2h OGTT value = 140–199 mg/dl). Conversely, normal glucose tolerance (NGT) is defined as FPG <100 mg/dl and 2h OGTT plasma glucose <140 mg/dl.

Prevalence of IFG and IGT varies widely with ethnicity, age and sex; prevalences of both metabolic disorders increase with advancing age. IGT is more frequent in women than in men.

The natural history of both IFG and IGT is variable, with ~25% progressing to diabetes, 50% remaining in their abnormal glyceamic state and 25% reverting to NGT over an observational period of 3 –5 years. Individuals who are older, overweight and have other diabetes risk factors are more likely to progress. Moreover, low insulin secretion and severe insulin resistance identify individuals more likely to progress to diabetes. With longer observation, majority of individuals with IFG or IGT appear to develop diabetes.

Both IFG and IGT have a heterogeneous pathogenesis and this may contribute to different rates of progression to diabetes. Also, the poor precision and accuracy of glucose measurements and the poor reproducibility of the glucose tolerance test itself contribute to the difficulty of defining the natural history of IFG/IGT in any one individual. Individuals with both IFG and IGT have approximately double the rate of developing diabetes compared with individuals with just one of them.

Numerous longitudinal studies indicate that both IFG and IGT are associated with a modest increase in the hazard ratio (~1.1–1.4) for CVD, with IGT

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being a slightly stronger risk predictor. Majority of this risk appears to be conferred by progression to diabetes, when the risk of CVD increases two- to fourfold. Many cardiovascular risk factors (e.g., low HDL cholesterol, hypertension and elevated triglycerides) are prevalent in IFG and IGT, but it is unclear whether they occur more frequently in one state than the other. However, after adjusting for known cardiovascular risk factors, both IFG and IGT remain independent, albeit weak, risk factors for CVD in some studies but not in others. Even so, it is unclear whether the CVD risk associated with IFG or IGT can be attributed to the development of diabetes during follow-up or whether these states per se convey such risk.

Pathogenesis of IFG and IGT

The epidemiologic differences between IFG and IGT suggest that different pathophysiological mechanisms contribute to these disturbances in glucose homeostasis. During a standard 75g OGTT, people with isolated IGT have, by definition, FPG levels that are similar to those with NGT. However, following glucose ingestion, plasma glucose concentration rises excessively at all time points and remains elevated (by definition ≥140–199 mg/dl) after 120 min. On the other hand, in isolated IFG, the FPG is higher (by definition 100–125 mg/dl) than in NGT and isolated IGT and the plasma glucose concentrations at 30–60 min in the OGTT are greater than in both NGT and isolated IGT. Thereafter, the plasma glucose concentration in IFG declines to near-baseline values at 120 min. These two very distinct oral glucose tolerance curves reflect different pathophysiologic disturbances in glucose homeostasis in isolated IFG and isolated IGT. The plasma glucose curves in people with both IFG and IGT reflect the characteristics of both.

Although both isolated IFG and isolated IGT are insulin-resistant states, they differ in their site of insulin resistance. People with isolated IFG predominantly have hepatic insulin resistance and normal muscle insulin sensitivity, whereas individuals with isolated IGT have normal to slightly reduced hepatic insulin sensitivity and moderate to severe muscle insulin resistance. Not surprisingly, individuals with both IFG and IGT manifest both muscle and hepatic insulin resistance.

Pattern of insulin secretion also differs between IFG and IGT. People with isolated IFG have a decrease in first-phase (0–10 min) insulin secretory response to intravenous glucose and a reduced early-phase (first 30 min) insulin response to oral glucose. However, the late-phase (60–120 min) plasma insulin response during the OGTT is normal in isolated IFG. Isolated IGT also has a defect in early-phase insulin secretion in response to an oral glucose load and in addition has a severe deficit in late-phase insulin secretion.

Combination of hepatic insulin resistance and defective insulin secretion in isolated IFG results in excessive fasting hepatic glucose production accounting for fasting hyperglycaemia. The impairment in early insulin response in combination with hepatic insulin resistance results in excessive early rise of plasma glucose in the 1st hour of the OGTT. However, preservation of late insulin secretion combined with normal muscle insulin sensitivity allows glucose levels to return to the preload value in isolated IFG. In contrast, in isolated IGT, defective late insulin secretion combined with muscle and hepatic insulin resistance results in prolonged hyperglycemia after a glucose load.

Alteration of natural history of IFG/IGT

At the simplest level, the natural history of both IFG and IGT can be defined in terms of progression to diabetes.

A wide variety of interventions have been shown to alter the natural history of IFG/IGT progression to diabetes. All of the controlled clinical trials to date have measured changes in glycaemia as their primary outcome. None of the completed studies determine definitively whether the interventions "reset the clock" or altered the rate of progression. Results of published studies support a beneficial effect on the underlying pathophysiology, specifically a reduction in insulin resistance and an improvement in relative insulin secretion.

Prevention or delay of diabetes should lead to a decrease in duration dependent diabetes related microvascular complications; however, direct data are not available to determine whether this occurs. Published trials do not have sufficient power to show a reduction in these hard outcomes. One of the other major reasons to recommend therapeutic interventions for individuals with IFG/IGT is the potential to reduce the long-term increased risk of CVD associated with diabetes. Potential for achieving this goal can be assessed by evaluating three distinct outcomes: cardiovascular risk factors, surrogate markers of atherosclerosis or clinically significant cardiovascular events. Interventions that similarly reduce the progression from IFG/IGT to diabetes may have different effects on the CVD outcomes above. An example of dissociation between diabetes delay/prevention and reduction in CVD risk factors is seen by comparing the effects on blood pressure of intensive lifestyle change versus metformin, both of which reduced diabetes development in the Diabetes Prevention Program (DPP). Intensive lifestyle change was associated with no increase in incident hypertension compared with a significant increase in the metformin and placebo arms. On the other hand, in the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial, rosiglitazone both decreased the development of diabetes and reduced blood pressure.

Of the usual surrogate measures of atherosclerosis, only carotid intima-media thickness has been studied in diabetes prevention trials. In STOP-NIDDM (Study to Prevent Non–Insulin-Dependent Diabetes Mellitus) trail, treatment with acarbose was associated with a reduced rate of increase in carotid intima-media thickness over time compared with placebo.

The only study to show a significant beneficial effect of an intervention on CVD events was the STOP-NIDDM study. Acarbose treatment was associated with a 49% relative risk reduction of the composite CVD outcome (P = 0.03), an unexpected finding given the relatively small number of CVD events (15 in the treated group, 32 in the placebo group).

In summary, intensive lifestyle interventions can have substantial effects on diabetes delay/prevention and modest, albeit statistically significant, effects on CVD risk factors. Whether these changes will translate into meaningful reductions in CVD events remains to be demonstrated. The impact on CVD risk factors or events when pharmacologic agents are used to prevent/delay diabetes is even less clear and may differ depending on the medication used.

Clearly there is a need for further studies that quantify changes in β-cell function/mass and insulin sensitivity over time in response to interventions. Such studies may discover specific effects of different interventions on the underlying pathogenesis of the disease.

Source

Impaired Fasting Glucose and Impaired Glucose Tolerance-Implications for care-available from
http://care.diabetesjournals.org/content/30/3/753.full

Compiled by Dr. Madhava Gunasekera of the Epidemiology Unit

Table 1: Vaccine-preventable Diseases & AFP

06th – 12th April 2013 (15th Week)

Disease	No. of Cases by Province									Number of cases during current week in 2013	Number of cases during same week in 2012	Total number of cases to date in 2013	Total number of cases to date in 2012	Difference between the number of cases to date in 2013 & 2012
	W	C	S	N	E	NW	NC	U	Sab					
Acute Flaccid Paralysis	00	00	00	02	01	00	00	00	00	03	01	19	25	- 24.0 %
Diphtheria	00	00	00	00	00	00	00	00	00	-	-	-	-	-
Measles	10	00	06	00	00	01	00	00	02	19	01	188	18	+ 944.4 %
Tetanus	00	00	00	00	00	00	00	00	00	00	00	06	03	+ 100.0 %
Whooping Cough	00	00	02	00	00	00	00	00	00	02	05	24	29	- 17.2 %
Tuberculosis	28	25	32	01	07	11	24	17	28	173	29	2507	2531	+ 0.94 %

Table 2: Newly Introduced Notifiable Disease

06th – 12th April 2013 (15th Week)

Disease	No. of Cases by Province									Number of cases during current week in 2013	Number of cases during same week in 2012	Total number of cases to date in 2013	Total number of cases to date in 2012	Difference between the number of cases to date in 2013 & 2012
	W	C	S	N	E	NW	NC	U	Sab					
Chickenpox	12	03	06	09	02	06	01	00	07	46	53	1305	1684	- 22.5 %
Meningitis	05 CB=3 GM=2	01 ML=1	05 GL=2 HB=1 MT=2	03 VU=1 JF=1 MU=1	00	00	00	00	03 RP=2 KG=1	17	05	303	204	+ 48.5 %
Mumps	03	03	01	01	03	01	06	01	06	25	66	479	1543	- 68.9 %
Leishmaniasis	00	00	01 MT=1	00	00	00	00	00	00	01	09	349	206	+ 69.41 %

Key to Table 1 & 2

Provinces: **W**: Western, **C**: Central, **S**: Southern, **N**: North, **E**: East, **NC**: North Central, **NW**: North Western, **U**: Uva, **Sab**: Sabaragamuwa.

DPDHS Divisions: **CB**: Colombo, **GM**: Gampaha, **KL**: Kalutara, **KD**: Kandy, **ML**: Matale, **NE**: Nuwara Eliya, **GL**: Galle, **HB**: Hambantota, **MT**: Matara, **JF**: Jaffna, **KN**: Killinochchi, **MN**: Mannar, **VA**: Vavuniya, **MU**: Mullaitivu, **BT**: Batticaloa, **AM**: Ampara, **TR**: Trincomalee, **KM**: Kalmunai, **KR**: Kurunegala, **PU**: Puttalam, **AP**: Anuradhapura, **PO**: Polonnaruwa, **BD**: Badulla, **MO**: Moneragala, **RP**: Ratnapura, **KG**: Kegalle.

Data Sources:

Weekly Return of Communicable Diseases: Diphtheria, Measles, Tetanus, Whooping Cough, Chickenpox, Meningitis, Mumps.

Special Surveillance: Acute Flaccid Paralysis.

Leishmaniasis is notifiable only after the General Circular No: 02/102/2008 issued on 23 September 2008. .

Dengue Prevention and Control Health Messages

You have a duty and a responsibility in preventing dengue fever. Make sure that your environment is free from water collections where the dengue mosquito could breed .

Table 4: Selected notifiable diseases reported by Medical Officers of Health

06th – 12th April 2013 (15th Week)

DPDHS Division	Dengue Fever / DHF*		Dysentery		Encephalitis		Enteric Fever		Food Poisoning		Leptospirosis		Typhus Fever		Viral Hepatitis		Human Rabies		Returns Received
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	%
Colombo	62	2352	2	42	0	9	1	41	1	11	8	85	1	4	2	28	0	0	**77**
Gampaha	28	1096	8	38	0	7	0	13	0	6	9	102	0	6+	3	75	0	0	**73**
Kalutara	15	508	0	47	0	8	1	28	0	7	6	154	0	1	0	5	0	0	**38**
Kandy	25	563	1	27	0	5	1	7	1	2	3	25	1	42	2	46	0	0	**70**
Matale	5	144	0	31	0	0	0	1	0	0	1	17	0	1	0	14	0	0	**38**
NuwaraEliya	1	75	1	25	0	2	0	2	0	2	0	8	1	27	0	3	0	0	**38**
Galle	10	226	0	29	1	8	0	1	0	4	6	84	2	19	0	4	0	1	**53**
Hambantota	4	116	1	18	0	2	0	5	0	9	4	104	1	30	0	53	0	0	**75**
Matara	8	193	0	18	0	7	0	6	1	5	5	82	1	29	6	80	0	1	**88**
Jaffna	37	314	5	64	0	3	8	158	0	7	0	0	21	247	2	8	0	0	**67**
Kilinochchi	0	17	0	10	0	0	0	5	0	1	0	6	0	9	0	0	0	0	**0**
Mannar	0	43	0	16	0	1	1	41	0	11	0	6	0	7	0	0	0	0	**20**
Vavuniya	0	31	0	19	0	9	0	4	0	4	3	27	0	1	0	0	0	0	**50**
Mullaitivu	3	40	0	3	0	1	0	3	0	1	0	9	0	3	0	0	0	0	**40**
Batticaloa	8	244	2	46	1	3	0	0	0	3	1	9	0	2	0	4	0	0	**57**
Ampara	1	48	0	35	0	0	0	1	0	0	0	6	0	0	0	1	0	0	**14**
Trincomalee	1	99	0	18	0	1	1	1	0	0	1	44	0	4	0	2	0	1	**42**
Kurunegala	29	1512	4	73	0	14	1	19	0	3	3	111	1	13	1	20	0	1	**58**
Puttalam	15	438	1	20	0	4	0	5	0	1	2	11	2	9	0	1	0	0	**67**
Anuradhapu	1	235	1	25	1	11	0	1	0	2	6	147	0	9	0	9	0	0	**47**
Polonnaruw	0	131	0	32	0	0	0	7	0	0	0	79	0	1	0	16	0	1	**29**
Badulla	5	145	0	38	0	0	0	5	0	1	0	13	0	23	0	15		0	**41**
Monaragala	2	87	0	30	0	3	0	6	0	18	11	91	0	19	1	28	0	0	**45**
Ratnapura	9	556	0	137	0	74	0	15	0	12	2	132	0	15	1	99	0	1	**33**
Kegalle	16	362	0	17	0	10	1	6	0	3	4	41	4	32	4	82	0	0	**64**
Kalmune	0	382	0	29	0	1	0	0	0	13	0	4	0	2	0	4	0	0	**23**
SRI LANKA	**285**	**9957**	**26**	**887**	**03**	**183**	**15**	**381**	**03**	**126**	**75**	**1397**	**35**	**555**	**22**	**597**	**00**	**06**	**52**

Source: Weekly Returns of Communicable Diseases WRCD).
***Dengue Fever / DHF** refers to Dengue Fever / Dengue Haemorrhagic Fever.
****Timely** refers to returns received on or before 12th April, 2013 Total number of reporting units 336. Number of reporting units data provided for the current week: 175
A = Cases reported during the current week. **B** = Cumulative cases for the year.

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Comments and contributions for publication in the WER Sri Lanka are welcome. However, the editor reserves the right to accept or reject items for publication. All correspondence should be mailed to The Editor, WER Sri Lanka, Epidemiological Unit, P.O. Box 1567, Colombo or sent by E-mail to **chepid@sltnet.lk.**

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