

# IEQAS 11<sup>th</sup> Participants' Conference

Merrion Suite, Red Cow Moran's Hotel, Naas Road, Dublin 22

Thursday, October 16, 2003

## Clinical Impact of Laboratory Medicine on Treatment of Diabetes

### An IEQAS Workshop

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Faculty of Pathology



**RCPIonline**  
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**IEQAS** *Laboratory Medicine*

Irish External Quality Assessment Scheme

11:40 TEA/COFFEE/BI SCUITS

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11:55

IEQAS WORKSHOP PROGRAMME

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## CLINICAL IMPACT OF LABORATORY MEDICINE ON TREATMENT OF DIABETES

Introduction to laboratory services for diabetes – Gerard Boran

Clinical Impact of laboratory tests – John Nolan

Improvements through HBA1c standardisation – Ned Barrett

Reporting Conventions for HBA1c results – time for change? – Des Kenny

Round Table Discussion

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13:10 – 14:30 LUNCH

Laboratory Medicine  
plays an important role in the  
management of diabetes

## Presenting Symptoms

- § Thirst, polyuria, weight loss
- § Many are asymptomatic
- § May be discovered incidentally
- § Type 1 DM may present in ketoacidosis

## Comparison of Type 1 and Type 2 DM

|                             | <b>Type 1</b>          | <b>Type 2</b>       |
|-----------------------------|------------------------|---------------------|
| <b>Age of onset</b>         | Children, Young adults | Middle age, elderly |
| <b>Onset</b>                | Acute                  | Gradual             |
| <b>Body habitus</b>         | Lean                   | Often obese, Lean   |
| <b>Weight Loss; Ketosis</b> | Usual                  | Unusual             |
| <b>Serum Insulin Conc.</b>  | Low/absent             | Normal, High        |
| <b>Family History</b>       | Uncommon               | Common              |
| <b>HLA association</b>      | HLA DR3, DR4           | None                |

### Diagnostic Criteria

- § Demonstration of hyperglycaemia is essential to confirm the diagnosis, using the WHO 1999 guidelines.
- § At least two diagnostic blood glucose measurements are required in asymptomatic individuals.
- § Diagnostic criteria vary depending on the type of blood sample (e.g. venous plasma glucose, whole blood glucose, capillary blood glucose)
- § The Glucose Tolerance Test (GTT) should be reserved for a minority of patients who have borderline results (e.g. random glucose in the range 7.8-11.1 mmol/L, etc)

*Diabetes is indicated if\*:*

- § Fasting venous plasma glucose  $\geq 7.0$  mmol/L
- § 2-hour GTT glucose  $\geq 11.1$  mmol/L
- § Random venous plasma glucose  $\geq 11.1$  mmol/L

(\* In asymptomatic individuals, at least two glucose results in the diabetic range are required, either from a GTT or other fasting/random specimens)

*Impaired glucose tolerance is indicated if:*

§ Fasting venous plasma glucose < 7.0 mmol/L

**and**

§ 2-hour GTT glucose 7.8 - 11.1 mmol/L

Table 1: Values for diagnosis of diabetes mellitus and other categories of hyperglycaemia

|                                   | Glucose concentration, mmol l <sup>-1</sup> (mg dl <sup>-1</sup> ) |                                    |                                    |
|-----------------------------------|--|------------------------------------|------------------------------------|
|                                   | Whole blood<br>Venous  | Capillary                          | Plasma*<br>Venous                  |
| Diabetes Mellitus:                |  |                                    |                                    |
| Fasting <i>or</i>                 | ≥ 6.1 (≥ 110)  | ≥ 6.1 (≥ 110)                      | ≥ 7.0 (≥ 126)                      |
| 2-h post glucose load             | ≥ 10.0 (≥ 180)   | ≥ 11.1 (≥ 200)                     | ≥ 11.1 (≥ 200)                     |
| Impaired Glucose Tolerance (IGT): |  |                                    |                                    |
| Fasting (if measured) <i>and</i>  | < 6.1 (< 110) and  | < 6.1 (< 110) and                  | < 7.0 (< 126) and                  |
| 2-h post glucose load             | ≥ 6.7 (≥ 120)  | ≥ 7.8 (≥ 140)                      | ≥ 7.8 (≥ 140)                      |
| Impaired Fasting Glycaemia (IFG): |  |                                    |                                    |
| Fasting                           | ≥ 5.6 (≥ 100) and<br>< 6.1 (< 110)                                 | ≥ 5.6 (≥ 100) and<br>< 6.1 (< 110) | ≥ 6.1 (≥ 110) and<br>< 7.0 (< 126) |
| and (if measured)                 |  |                                    |                                    |
| 2-h post glucose load             | < 6.7 (< 120)  | < 7.8 (< 140)                      | < 7.8 (< 140)                      |

\* Corresponding values for capillary plasma are: for Diabetes Mellitus, fasting ≥ 7.0 (≥ 126), 2-h ≥ 12.2 (≥ 220); for Impaired Glucose Tolerance, fasting < 7.0 (< 126) and 2-h ≥ 8.9 (≥ 160) and < 12.2 (< 220); and for Impaired Fasting Glycaemia ≥ 6.1 (≥ 110) and < 7.0 (< 126) and if measured, 2-h < 8.9 (< 160).

For epidemiological or population screening purposes, the fasting or 2-h value after 75 g oral glucose may be used alone. For clinical purposes, the diagnosis of diabetes should always be confirmed by repeating the test on another day unless there is unequivocal hyperglycaemia with acute metabolic decompensation or obvious symptoms.

Glucose concentrations should not be determined on serum unless red cells are immediately removed, otherwise glycolysis will result in an unpredictable under-estimation of the true concentrations. It should be stressed that glucose preservatives do not totally prevent glycolysis. If whole blood is used, the sample should be kept at 0–4 °C or centrifuged immediately, or assayed immediately.

## Initial Investigations

Once the diagnosis is confirmed, other initial investigations may be carried out to:-

- § Identify the cause
- § Exclude secondary causes where appropriate
- § Quantify insulin reserves
- § Detect complications present at presentation (e.g. renal disease)
- § Detect hyperlipidaemia

# Laboratory Investigations in Diabetes

## Classification

### 1. Type 1.

Due to  $\beta$ -cell destruction, usually leading to absolute insulin deficiency.

### 2. Type 2.

Ranges from predominantly insulin resistance (most cases) to a predominant insulin secretory defect.

### 3. Other specific types.

A wide range of conditions can lead to secondary DM, e.g.

- § Endocrine disorders (acromegaly, cushings syndrome, etc)
- § Diseases of the exocrine pancreas (pancreatitis, haemochromatosis, etc)
- § Drugs (e.g. glucocorticoids, etc)
- § Genetic causes (rare)

### 4. Gestational DM.

# Laboratory Investigations in Diabetes

## Causes

### Type 1.

Many cases are due to autoimmune destruction of the  $\beta$ -cells of the islets of langerhans. Autoimmune form is associated with HLA DR3 and DR4. Islet-cell autoantibodies, insulin autoantibodies, autoantibodies to glutamic acid decarboxylase (GAD 65) are found. Some cases are idiopathic. Viruses may play a role in some cases.

### Type 2.

There are likely to many causes of Type 2 DM. Genetic factors are much more important than in Type 1 DM. Autoimmune destruction does NOT occur. Common patterns are:-

- § Overweight or obese patients. Most type 2 DM patients are in this category. Predominantly insulin resistance, possibly with some secretory defect.
- § "Lean" Type 2 DM patients. Predominant defect is in insulin secretion

# Laboratory Investigations in Diabetes

## Treatment

### Type 1

- § Insulin replacement is essential
- § Diabetic diet must also be followed

### Type 2

- § Cornerstone of treatment is the Diabetic Diet
- § Lean patients → sulphonylureas may be added (e.g. gliclazide, glibenclamide, etc)
- § Overweight, obese patients → biguanides may be added (e.g. metformin)
- § Insulin may also be added to the above if necessary

In addition to metabolic control, rigorous attention to and treatment of hypertension, hyperlipidaemia and complications at an early stage is essential to reduce morbidity and mortality.

# Laboratory Investigations in Diabetes

## Acute Metabolic Complications

All of the following conditions can lead to coma and death

### 1. Diabetic Ketoacidosis (DKA)

Absence of circulating insulin causes:

- § ↓ tissue glucose uptake; ↑ glycogenolysis; ↑ gluconeogenesis; ↑ proteolysis/amino acids;  
→ marked hyperglycaemia and glycosuria  
→ osmotic diuresis → hypovolaemia → pre-renal uraemia  
→ risk of acute renal failure
- § ↑ lipolysis → ketosis (acetoacetate,  $\beta$ -hydroxybutyrate, acetone) → metabolic acidosis  
→ vomiting →  
hyperventilation
- § Hyponatraemia
- § Hyperkalaemia in the face of total body potassium deficiency

# Laboratory Investigations in Diabetes

## 2. Diabetic HyperOsmolar Non-Ketotic state (HONK)

- § Marked hyperglycaemia/glycosuria occurs → hypovolaemia, pre-renal uraemia
- § ↑ lipolysis does NOT occur due to the presence of small amounts of insulin which inhibit lipolysis. Hence, no ketosis.

# Laboratory Investigations in Diabetes

## 3. Lactic acidosis

- § Uncommon now in isolation diabetes (used to be related to phenformin - not used now).
- § Seen in DKA where tissue hypoxia develops

# Laboratory Investigations in Diabetes

## 4. Hypoglycaemia

- § Very common problem - due to insulin accidental insulin overdose
- § Also seen in sulphonylurea therapy
- § Rebound hyperglycaemia occurs after episodes of hypoglycaemia

# Laboratory Investigations in Diabetes

## Longer Term Complications

### Macrovascular diseases (Affects large and medium arteries)

- § Coronary Heart Disease is the major cause of death in DM, due to atherosclerosis
- § Atherosclerosis also causes Peripheral Vascular disease which affects circulation in large vessels in the feet (leads to claudication, gangrene, etc). Cerebrovascular disease (strokes) is also more common
- § Aggressive treatment of risk factors is essential

### Microvascular diseases (affects small arteries, arterioles and capillaries)

- § Retinopathy
- § Nephropathy
- § Neuropathy

## Laboratory Monitoring

### Markers of glycaemic control

#### 1. HbA<sub>1c</sub>

- § Glucose reacts in its free aldehyde form with amino groups of Haemoglobin A (nonenzymatic glycation, a covalent reaction) to form an unstable schiff base (aldimine) which undergoes an Amadori re-arrangement to form stable HbA<sub>1c</sub> (a ketamine).
- § HbA<sub>1c</sub> reflects glycaemic control over the previous 8 weeks
- § Values are unaffected by day-to-day fluctuations in blood glucose
- § Hypoglycaemia may lead to lower than expected values
- § Values are reduced if red cell survival is reduced (120d normally)
- § The DCCT trial demonstrated that improvements in glycaemic control (assessed by HbA<sub>1c</sub> measurement) led to reduced microvascular complications in Type 1 DM patients
- § Measurement has become more reliable. Standardisation is being introduced.

## 2. Fructosamines

- § Nonenzymatic attachment of glucose to amino groups other than haemoglobin (e.g. serum proteins mainly albumin, membrane proteins, etc)
- § Reflects glucose control over 2-3 weeks
- § Initially attracted interest - was easier to measure than glycated haemoglobin
- § Falling into oblivion now!

## 3. Other glycated proteins

e.g. glycated albumin. No role. Fructosamines measure principally glycated albumin

#### 4. Serum 1,5-anhydroglucitol (AG)

- § This is a naturally occurring analogue of glucose, mostly derived from food
- § Circulating levels are 90-200  $\mu\text{mol/L}$  in health
- § AG is reduced in diabetics because of competition with glucose for urinary excretion
- § AG levels may reflect excursions of blood glucose over the renal threshold.
- § Still being investigated

## Microalbuminuria

- § Microalbuminuria is defined as an Albumin Excretion Rate in the range 20-200  $\mu\text{g}/\text{min}$  in an overnight or 24 hour sample
- § Corresponds to an Albumin/Creatinine ratio of 3-30  $\text{mg}/\text{mmol}$  – no need for timed collection with this measurement
- § Microalbuminuria must be confirmed in at least 2 of 3 specimens taken within a 6 month period
- § Urine albumin dipstick tests (Albustix) usually become positive around 200-300  $\text{mg}/\text{L}$  or 30  $\text{mg}/\text{mmol}$
- § Microalbuminuria is a marker for nephropathy in Type 1 Dm, and for macrovascular disease in type 2 DM
- § Early intervention with ACE inhibitors can reverse microalbumuria

## Lipids

- § Lipid abnormalities in diabetes contribute significantly to macrovascular disease
- § Poorly controlled DM can lead to raised VLDL-triglycerides, sometimes with massively elevated serum triglyceride
- § Low HDL-cholesterol, High Triglyceride syndrome is common in Type 2 DM
- § Isolated elevated (LDL-)cholesterol is less common but deserves aggressive treatment

### Renal function

- § The presence of persistent proteinuria/albuminuria progresses gradually to renal failure.
- § Urine protein/albumin and serum creatinine should be determined at least annually to detect early renal failure

### Thyroid function

### Home Glucose Monitoring

Most patients with DM monitor glycaemic control with either home blood glucose or urine glucose monitoring. Type 1 DM patients should use a blood glucose meter if possible. Many Type 2 DM patients can monitor satisfactorily with urine tests only.

## 8.1 Definition: Metabolic Syndrome

### No internationally agreed definition

The following, which does not imply causal relationships, is suggested as a working definition to be improved upon in due course: glucose intolerance, IGT or diabetes mellitus and/or insulin resistance together with two or more of the other components listed below:

- Impaired glucose regulation or diabetes
- Insulin resistance (under hyperinsulinaemic euglycaemic conditions, glucose uptake below lowest quartile for background population under investigation)
- Raised arterial pressure  $\geq 140/90$  mmHg
- Raised plasma triglycerides ( $\geq 1.7$  mmol l<sup>-1</sup>; 150 mg dl<sup>-1</sup>) and/or low HDL-cholesterol ( $< 0.9$  mmol l<sup>-1</sup>, 35 mg dl<sup>-1</sup> men;  $< 1.0$  mmol l<sup>-1</sup>, 39 mg dl<sup>-1</sup> women)
- Central obesity (males: waist to hip ratio  $> 0.90$ ; females: waist to hip ratio  $> 0.85$ ) and/or BMI  $> 30$  kg m<sup>-2</sup>
- Microalbuminuria (urinary albumin excretion rate  $\geq 20$  g min<sup>-1</sup> or albumin:creatinine ratio  $\geq 30$  mg g<sup>-1</sup>)
- Several other components of the Metabolic Syndrome have been described (e.g. hyperuricaemia, coagulation disorders, raised PAI-1, etc.) but they are not necessary for the recognition of the condition.

