

Clinical Practice

Investigation for Diabetes mellitus-an insight

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Diabetes mellitus has emerged as the leading non-communicable disease affecting the whole globe in epidemic proportions. Besides, it plays a significant role in the causation and / or progression of other communicable and non-communicable diseases. The classification of the disease is an expression of its heterogeneity. Further, its major categories- the Type 1 and Type 2 Diabetes are themselves a large heterogenic groups, and the clear cut differentiation is essential to mandate accurate treatment strategies.

A detailed clinical history and a thorough examination is essential to have an insight of the disease and its progression and also for assessing the involvement of other systems. A well planned investigation work-up is vital for diagnosis and progression. The aim of the investigative work-up should be-

1. To establish the broad diagnosis of Diabetes mellitus as per the guidelines
2. To sub-categorize the disease
3. To evaluate the immediate and acute complications of the disease
4. To evaluate the chronic complications
5. To evaluate the involvement of other organ systems
6. Possible prevention of the disease

Criteria for the diagnosis of diabetes in non-pregnant individuals

A1C $\geq 6.5\%$ (≥ 48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay. OR

FPG ≥ 126 mg/dL (≥ 7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h

OR

2-h PG ≥ 200 mg/dL (≥ 11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water

OR

In an individual with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (≥ 11.1 mmol/L). Random is any time of the day without regard to time since previous meal.

A. Fasting, Post-prandial and Random

Fasting blood glucose levels is useful in the screening of Diabetes mellitus in the population. Impairment of the FBG is the primary defect in Type 1 DM, this appear a little later in Type 2 DM. This is why nearly 30% Type 2 Diabetics are missed with only FBG. However, it is useful in adjusting the fasting dose of insulin. Impaired FBG levels ranges form 100-125 mg/dl (5.7-6.4 mmol/L). The best time to measure it is before 7:30 am as it correlates best with the sunrise and has less Dawn's phenomenon. **Post-prandial blood glucose (PPG)** values are evaluated 2 hours after the meals (preferably the first meal). It is preferred for screening of Type 2 DM and people with pre-diabetes. It is further used to adjust the doses of OHAs and insulin. Its determination is helpful in identifying individual who are missed on screening with FBG. Besides, it is a better predictor of the progression of diabetes and is an independent CV risk factor. **Random blood glucose levels (RBG)** gives information about day to day or hour to hour monitoring of blood sugar levels.

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- B. Continuous glucose monitoring:** It provides instantaneous real time display of glucose levels and rate of change of glucose, alerts and alarms for actual or impending hypo or hyperglycemia, 24/7 coverage and ability to characterize glycemic variability. However, its use is limited due to cost, need for recalibration, need for replacement of sensors, time and inconvenience to retrieve old data etc.
- C. Flash glucose monitoring:** The device is small, lightweight and relatively inexpensive, does not require calibration and has 2-week period use, and has excellent accuracy.
- D. Beta cell directed auto-antibodies:** Some of the common autoantibodies include GAD-65 (Glutamic acid decarboxylase), Insulinoma associated antigen-2/islet tyrosine phosphatase 2A (IA2), ZnT8, ICA, IAA etc.
- E. C-peptide levels:** C-peptide is a pro-insulin which is cleaved prior to co-secretion with insulin and is a measure of pancreatic beta cell function. It is produced in equimolar amounts to endogenous insulin but is excreted at a more constant rate over a longer time. Indications for measuring C-peptide levels include fasting hypoglycemia and assessment of insulin secretory reserve in patients with diabetes. In patients with fasting hypoglycemia with concomitant hyperinsulinism, one needs to consider a differential diagnosis of insulinoma, exogenous insulin administration (factitious), sulfonylurea therapy (factitious), insulin autoimmune syndrome due to endogenous anti-insulin antibodies (Hirata disease).
- F. Glycosylated Hemoglobin:** Glycated hemoglobin comes from post translational alteration of HbA caused by non-enzymatic covalent bonding of glucose to the beta globin's chain N terminal valine. This process is called glycation, and the circulating and structural proteins having free amino acids are consequently affected. HbA1c concentration reflects the concentration of glucose to which erythrocytes are exposed over their lifespan (that is approximately 3-4 months). Approximately 50% of HbA1c reflects blood glucose in the past 1 month, 25% for the past 1 to 2 months, and 25% for the past 2 to 4 months.
- G. Serum Fructosamine:** Compared to haemoglobin, which has a half-life of around 90 days-120 days in red blood cells, non-immunoglobulin type serum proteins have a half-life of about 14 days to -21 days. This implies that, although HbA1c offers a long-term assessment of glycaemic control (i.e., over two to three months), Fructosamine testing only gives data on glucose control for the past two weeks.

Fructosamine blood levels fluctuate more than HbA1c, enabling timely identification of rapid fluctuations in blood glucose. As a consequence, Fructosamine estimation is advantageous not just as a secondary glycaemic control indication in instances when HbA1c is inconsistent but also for diagnosing impaired glycaemic control prior to apparent increases in HbA1c. It is particularly useful in Diabetes in pregnancy where short term fluctuations are needed to be corrected and also in the first degree non-diabetic relatives of diabetics.

- H. Lipid profile:** Non glycaemic parameters play an important role in the glycaemic control and long term complications. LAI guidelines provides a useful range for these parameters. These targets are based upon the risk factor/markers.
- I. Renal function tests:** Kidneys bear the brunt of diabetes. They include Bun, Serum creatinine, Urinary albumin creatinine ratio (UACR) and estimation of e-GFR. The normal GFR for an adult male is 90 to 120 mL/min. However, this number varies significantly by age.

The calculated creatinine clearance is used to provide an indicator of GFR. The urine is collected over 24 hours or over the fixed period of time. It is calculated using the equation:

$$C = (U_{Cr} \times V) / P_{Cr}$$

C=clearance, U=urinary concentration (mg/dL), V=urinary flow rate (volume/time in mL/min), and P=plasma concentration (mg/dL)

Kidney Disease Improving Global Outcomes (KDIGO) stages of CKD are as follows:

- Stage 1: GFR greater than 90 mL/min/1.73 m²
 - Stage 2: GFR 60 to 89 mL/min/1.73 m²
 - Stage 3a: GFR 45 to 59 mL/min/1.73 m²
 - Stage 3b: GFR 30 to 44 mL/min/1.73 m²
 - Stage 4: GFR 15 to 29 mL/min/1.73 m²
 - Stage 5: GFR less than 15 mL/min/1.73 m² (end-stage renal disease)
- J. Anthropometry:** BMI, Waist circumference, waist to hip ratio, neck hump measurements are markers of insulin resistance.
- K. Liver Function Tests:** Long standing or chronic diabetes due to its multisystem affection can adversely affect liver functions. NAFLD is the manifestation of metabolic syndrome.
- L. Thyroid function test:** Assessment of thyroid functions may be important for the control of diabetes and also, there may be an aetiological correlation.

M. ECG: A resting ECG should be done in all cases and further cardiac evaluation is mandated depending upon the clinical scenario. It should be remembered that in diabetics, the ischemic symptoms may be masked.

N. Ultrasonography: NAFLD is the hepatic component of metabolic syndrome, and hence, needs to be screened.

O. Vitamin B12 levels especially in those taking metformin

Besides, Ultrasonography should be done for the evaluation of NAFLD and periodic eye check-up for Diabetic retinopathy and ECG should be done.

Referrals

1. Ophthalmologist for dilated fundus examination
2. Dietician and nutritionist for dietary planning
3. Family planning for child bearing potential
4. Self-management and education
5. Behavioural health professional, if indicated
6. Audiology if indicated
7. Rehabilitation medicine if indicates, especially diabetic foot and post-amputation

There can be number of more investigations depending on the clinical requirement. The investigations are like chords of a piano-should be planned and synchronised to the clinical needs to give a beautiful melody.

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