An Update on the Available Diabetic Monitoring Tests

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Abstract- Diabetes mellitus is a common disorder affecting individuals of all ages. It is not a pathogenic entity but a group of aetiologically different metabolic defects. By the year 2025, there is predicted to be a 35 % increase in the world-wide prevalence of diabetes. The rising number of people with diabetes will occur mainly in populations of developing countries, leading to more than 300 million people with diabetes globally by 2025. Presently as many as 50 % of people with diabetes are undiagnosed.

Monitoring biomarkers associated with Diabetic Mellitus plays a key role in the assessment of glycemic control. Several studies have clearly shown that improved glycemic control is strongly associated with a decreased development and/or progression of diabetic complications. The basic laboratory test include detection of sugar in urine, fasting and post prandial glucose levels, Glucose Tolerance and Glucose Challenging Tests by giving 75 gms of glucose. Once diabetes is confirmed and treatment initiated, several laboratory tests are available to assess the diabetic control. While tests like fructosamine and Glycohemoglobin are used to assess short and long time diabetic control, there are some other special tests like microalbumin to assess progress to renal problem, C-peptide to assess Impaired glucose tolerance and proinsulin and Insulin to assess the degree of resistance in type 2 daibeties mellitus, insulin like growth factor-1 to assess insulin resistance, glycemic control and development of microvascular complications. Glucagon and Epinephrine measurement helps glucose recovery during times of hypoglycemia, cortisol to assess type 1 diabetes mellitus and Body Mass Index to link type 2 daibetes mellitus. This review paper presents an update on all available diagnostic tests, its merits and demerits.

Index Terms- DM , GTT, IGT, GCT, HbA1c, GDM, NIDDM

I. INTRODUCTION

Fructosamine

Fructosamine test measures glycemic control for a short period for 2-3 weeks. Fructosamine level was found to correlate well with HbA1c ($r = 0.82$, $p < 0.001$) and both HbA1c and fructosamine correlates well with the mean daily blood glucose value during the preceding week ($r = 0.45$, $p < 0.01$ and $r = 0.58$, $p < 0.01$) respectively. These data suggest that serum fructosamine is as effective as the HbA1C in correlating to mean blood glucose control in Insulin Dependent Diabetes Mellllitus (IDDM) patients. (1)

A study shows that a weak correlation between fructosamine and mean blood glucose suggesting that it is not a reliable marker of the short-term integrated glycemia. Therefore, frequent monitoring of fructosamine levels does not add to the management of the adolescent population. (2) In a study involving 30 diabetic and 61 non diabetic children, fructosamine level showed a significant correlation to HbA1c suggesting that fructosamine could be used instead of HbA1c to monitor short time Diabetic control (3)

Fructosamine correlated moderately well with HbA1c, (affinity; $r = 0.8$) and placed 71% of IDDM and 72% of Non Insulin Dependent Diabetes Mellitus (NIDDM) patients in the same clinical category of good, moderate, or poor control. Differences can probably be partly attributed to the different periods over which HbA1c, and fructosamine reflect average glycemia and partly to imprecision. (4)

In a study involving obese diabetic and non-diabetic subjects, fructosamine was markedly lower than for lean diabetic and non-diabetic subjects with similar glycaemic control. Stepwise multiple-regression analysis showed that fructosamine was associated with glycaemic control (as indicated by fasting plasma glucose and HbA1c) suggesting that serum fructosamine concentrations will decrease in obese diabetic and non-diabetic subjects with body mass index ≥ 30 kg m^{-2} giving rise to the underestimation of glycaemic control as indicated by fructosamine measurement. A change in the glycation reaction itself may be partly responsible for such decrease. (5)

Fructosamine appears to be as effective as HbA1c in its ability to correlate with mean blood glucose in a cross-sectional study in both type I and type II diabetic patients. However, due to the increased sensitivity of the fructosamine in detecting glycemic changes, caution must be taken in interpreting glycemic control from infrequent use of this assay, because it may not provide a reliable overview of glycemic control over a period such as 2-3 months as has been firmly established with HbA1c. (6)

The value of fructosamine measurement in the detection of diabetes in pregnancy was further tested in a group of high-risk patients for developing carbohydrate intolerance. It is concluded that fructosamine has limited value as a screening test for gestational diabetes mellitus (GDM), particularly for the mild form of glucose intolerance.(7) A second generation fructosamine test, corrected for total protein as a practical alternative to

glucose screening for GDM achieved 79.4% sensitivity and 77.3% specificity for the diagnosis of GDM confirmed by a glucose tolerance test using Carpenter's modified criteria. [8] Fructosamine concentration in serum of diabetics and healthy individuals generated a reference interval of 1.9 to 2.9mmol/L and correlated with HbA1c ($r=0.65$, $p<0.001$).[9]

Fructosamine was found to correlate only with post load glucose values in excess of 180 mg/dL at 2 hour ($r = 0.87$; $p = 0.01$), i.e. with the highest overall glucose values, but not with fasting glucose or milder postprandial hyperglycemia of under 180 mg/dL suggesting that quantification of fructosamine detects only the rather severe cases of gestational hyperglycemia, but is too insensitive to uncover mild asymptomatic GDM, and therefore fructosamine could not be considered as useful parameter for the diagnosis of this condition.[10]

Serum fructosamine levels did not differ significantly if measured at fasting or 2 h after ingestion of 75 g of glucose. [11]

II. Glycosylated Hemoglobin

The current recommended goal for glycosylated hemoglobin (HbA1c) in patients with diabetes is <7.0%, which is considered good glycemic control, although some guidelines are stricter (<6.5%). People with diabetes who have HbA1c levels within this range have a significantly lower incidence of complications from diabetes, including retinopathy and diabetic nephropathy.[12] The characteristics of several screening tests for NIDDM showed that Fasting Plasma Glucose (FPG) has the best screening properties, HbA1c and quantitative urine glucose also provide high specificity and approximately 80% sensitivity in detecting NIDDM. The choice of a particular method could depend on cost, convenience, and availability.[13] Determination of HbA1c or fasting plasma glucose concentrations alone may be acceptable alternatives to measuring glucose concentration 2 hrs after challenge with 75 g glucose for the diagnosis of diabetes.[14] The prevalence of diabetic retinopathy was much higher in the subgroup with elevated HbA1c levels and increased with increasing HbA1c level, and so no advantage over fasting or post challenge glucose levels in the diagnosis of diabetes.[15]

A significant correlation was observed between HbA1c values and fasting blood glucose ($r = 0.68$, $p < 0.01$) suggesting that HbA1c levels are influenced by slightly reduced carbohydrate tolerance. [16] A raised HbA1c is useful for confirming the diagnosis of diabetes mellitus in patients with long-standing hyperglycaemia but is within the reference range in many patients with newly developed diabetes or other minor abnormalities of glucose tolerance. The glucose tolerance test must remain the test of choice in these patients. [17]

Patients with risk factors for diabetes and FPG levels ≥99 mg/dLand in particular in patients with FPG 110 mg/dL but below the current diagnostic threshold—the HbA_{1c} level appears helpful in identifying those with early diabetes. Individuals with elevated HbA_{1c} values but nondiagnostic FPG levels are overwhelmingly likely to have diabetes and patients with a single FPG between 124 and 144 mg/dL, maintaining HbA1c within normal appears to be of greater value than repeat FPG testing in confirming the diagnosis of diabetes.[18]

GDM is a risk factor for delivering a large-for-gestational-age (LGA) babies. HbA1C for GDM diagnosis may not be linearly associated with LGA or macrosomia, possibly because of the mediating effect of strict glycaemic control in this clinical setting. [19]

Women with GDM not maintaining HbA1c within the normal range before delivery had a three-fold increased risk of having an LGA infant and a six-fold increased risk of neonatal hypoglycaemia.[20]

A study involving nonpregnant, early pregnant and late pregnant women has demonstrated a decline of the upper normal level of HbA_{1c} from 6.3 to 5.7% in early pregnancy and to 5.6% in the third trimester of pregnancy, indicating a reduction of HbA_{1c} during normal pregnancy that is of clinical importance when defining the goal for HbA_{1c} during pregnancy complicated with diabetes.[21]

III. Insulin and C – peptide

C-peptide is more reliable than insulin as a measure of endogenous insulin secretion, and is usually measured in insulin-treated patients. Fasting or stimulated serum or plasma C-peptide measurement is used as an index of endogenous insulin reserve in people with diabetes. Both C-peptide and insulin secretions reflects the metabolic needs of the body. C-peptide secretion by a healthy pancreas thus reflects the insulin requirement of the body .An insulin-insensitive individual will thus develop NIDDM despite increased insulin production ('high output failure'), whereas IDDM is associated with near-normal insulin sensitivity and 'low-output failure. This difference will be reflected in the levels of C-peptide at diagnosis.

Both plasma immunoreactive insulin and C-peptide concentrations from 0800-1600 h were higher ($P < 0.002$-0.001) in patients with either Imparied Glucose Tolerance (IGT) or NIDDM than in the group with normal glucose tolerance. [22]
As the clinical diagnosis is not always straightforward, a random C-peptide taken at diagnosis may help to classify diabetes. There is an obvious use for C-peptide determinations to evaluate beta-cell function in children with diabetes.[23]

C-peptide measurement has a key role in the correct diagnosis of the type of diabetes in adults. and in children and majority of patients become severely insulin deficient within 5 years of diagnosis (2–3 years in children), whereas in Maternity Onset Diabetes of the Young (MODY) and NIDDM, C-peptide persists. C-peptide testing is most useful beyond 2–3 years of diabetes and can not discriminate MODY from type 2 diabetes.[24]

C-peptide levels are lower in children compared with adults, and the speed of C-peptide decline is more rapid (particularly in children aged <5 years). Increasing use of sensitive C-peptide assays have demonstrated that IDDM patients may continue to secrete C-peptide at low levels, often for decades after diagnosis. [25]

It is therefore becoming increasingly clear that C-peptide has major functions in supporting insulin action with a multitude of beneficial effects on diabetic polyneuropathy and primary diabetic encephalopathy in IDDM.[26] Available data demonstrate that even relatively modest treatment effects on C-peptide will result in clinically meaningful benefits. The development of therapies for addressing this important unmet clinical need will be facilitated by trials that are carefully designed with β-cell

function as determined by C-peptide measurement as the primary efficacy outcome.[27]

The association between chronic complications and residual C-peptide levels was also analyzed. It is possible that this residual beta cell secretion is associated with a lower insulin requirement, a lower frequency of chronic complications and a higher frequency of other autoimmune diseases.[28]
Diabetic patients with high C-peptide levels (> 0.16 nmol/L) resemble type II diabetes. The small proportion of diabetic patients with basal serum C-peptide in the range of 0.17-0.32 nmol/L have indeterminate status.[29]

Cord blood samples showed parallel rises in blood glucose and plasma C-peptides in the newborns of women with GDM.[30] There was a significant difference in the levels of C – peptide and insulin as well as insulin resistance between the suspected latent autoimmune diabetes (LADA) group and classic NIDDM patients, which was maintained on and followed up. C-peptide could be used as an important screening tool for autoimmunity.[31] Cord levels of C peptide in infants of diabetic mothers were elevated at the earliest gestational age studied (<34 weeks) and were directly related to the severity of maternal diabetes, as assessed by the White classification.[32]

IV. Microalbumin

Microalbuminuria is an important clinical marker in patients with diabetes because of its well-established association with progressive renal disease.Around 10% to 42% of IDDM & NIDDM patients develop microalbuminuria, which is largely related to disease duration.[33] Microalbuminuria predicts early mortality in patients with diabetes and is an important cardiovascular risk factor. In IDDM patients with microalbuminuria, the relative risk of cardiovascular death is 1.2 times that of normoalbuminuric IDDM patients and in macroalbuminuria the risk is increased 10-fold. The risk of premature death from cardiovascular event in NIDDM patients with microalbuminuria is about 4 times that of patients with normoalbuminuria. This increased risk seems to start at relatively low levels of albuminuria.[34]

Microalbuminuria often progressed to proteinuria (6.3/100 person/year) in those who were treated. Poor glycemic control and elevated serum cholesterol were the major determinants/predictors of this progression. Although treatment with Acetyl Choline Esterase -1 increased during the past decade, it was not completely effective, because microalbuminuria progressed to proteinuria in many treated patients. [35]
Physicians should routinely measure urinary albumin excretion in patients with NIDDM and hypertension and be aggressive in treating this modifiable risk factor as they do blood pressure, cholesterol, or blood glucose.[36] Microalbuminuria is an early predictor of diabetic nephropathy and premature cardiovasculardisease. The higher rate of fatal cardiovascular events with olmesartan among patients with preexisting coronary heart disease is of concern.[37] High prevalence of microalbuminuria in diabetic patients and its positive association with blood pressure and altered lipid profile suggests that screening for microalbuminuria is essential.[38]

V. Proinsulin

GDM is not independently associated with hyperproinsulinemia as measured by the proinsulin–to–C-peptide ratio. Instead, in pregnant women, increased insulin resistance is associated with decreased proinsulin–to–C-peptide ratio, independently of glucose tolerance status. These data suggest that relative proinsulin secretion in late pregnancy is primarily related to insulin resistance and does not necessarily reflect β-cell function.[39] In adults with IGT and obesity (OB), an elevated proinsulin (PI) is predictive of NIDDM. [40]

PI, the precursor molecule of insulin, undergoes intra-cellular processing within beta-cells to form equimolar concentrations of insulin and C-peptide. In the healthy state, nearly all PI synthesized is processed to insulin and C-peptide, but this is not the case in diabetic patients where inefficiencies in PI processing are evident.[41]

The association between PI and Intima Media wall Thickness (IMT) appears to be stronger than that of insulin. The biological significance of the association between PI and IMT is unknown, and thus it is possible that the relation between PI and atherosclerosis may be an epiphenomenon. Further work on the biological basis of this association is necessary.[42]

VI. Insulin like Growth Factor I

Insuline Like Growth Factor – 1 (IGF-1) and its receptors share considerable homology with insulin and insulin receptors, and their respective signaling pathways interact at the post receptor level. While the growth hormone (GH)-IGF-1 axis principally regulates tissue growth and differentiation, insulin exerts its primary effects on fuel metabolism. However, these two endocrine systems interact at multiple levels and in diabetes mellitus the GH-IGF-1 axis is grossly disturbed, with increased secretion of GH, reduced plasma levels of IGF-1, and complex tissue-specific changes in IGF binding proteins (IGFBPs). These observations have given rise to the view that GH-IGF-1 axis dysfunction, particularly low plasma levels of circulating IGF-1, probably play a significant role in several aspects of the pathophysiology of diabetes mellitus, including insulin resistance and poor glycemic control, and may also influence the development of microvascular complications.[43]

Patients with NIDDM have a 2 to 3 fold increased risk for Alzheimer's disease (AD), the most common form of dementia. Vascular complications might explain partially the increased incidence of neurodegeneration in patients with NIDDM. Neuronal resistance for IGF- 1 might represent a molecular link between NIDDM and AD, characterizing AD as "brain-type diabetes".[44]

IDDM is a disease of insulin deficiency, resulting from the autoimmune-mediated destruction of pancreatic beta cells. However, as a likely consequence of intraportal insulin deficiency, patients with IDDM also exhibit abnormalities of the GH-IGF binding protein (IGFBP) axis, including GH hypersecretion, reduced circulating levels of IGF-I and IGFBP-3, and elevated levels of IGFBP-1. These abnormalities not only exacerbate hyperglycemia in patients with IDDM, but may contribute to the pathogenesis of diabetes-specific complications, including diabetic neuropathy, nephropathy, and retinopathy.[45]

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VII. Glucagon

The development of severe diabetic hyperglycemia requires the presence of glucagon, whether secreted by pancreatic or newly identified gastrointestinal A cells, as well as a lack of insulin. Glucagon suppression could improve therapeutic glucoregulation in diabetes.[47] The secretion of glucagon by pancreatic α-cells plays a critical role in the regulation of glycaemia. A better understanding of the α-cell physiology is necessary for an integral comprehension of the regulation of glucose homeostasis and the development of diabetes.[48] As a counter regulatory hormone for insulin, glucagon plays a critical role in maintaining glucose homeostasis in vivo in both animals and humans. Glucagon and glucagon receptor have been pursued extensively in recent years as potential targets for the therapeutic treatment of diabetes.[49]

VIII. Epinephrine

Epinephrine compensates largely for deficient glucagon secretion. Glucose recovery from hypoglycemia fails to occur only in the absence of both glucagon and epinephrine. The efficacy of glucose counter regulation in a given patient may determine the degree to which euglycemia can be achieved with aggressive insulin therapy in that patient.[50]

Children with IDDM showed a greater rise in plasma norepinephrine than did adults with IDDM ($P < 0.001$), and both diabetic groups failed to mount a glucagon response. GH and cortisol responses were unaffected by either childhood or diabetes. Enhanced secretion of epinephrine, induced by mild reduction in plasma glucose, may contribute to the management difficulties characteristically observed in young patients with diabetes.[51]

Despite equivalent epinephrine, insulin and glucose levels, changes in glucose flux, glucagon, and cardiovascular responses were greater in healthy subjects compared with NIDDM. However, NIDDM patients had greater lipolytic responses and there is a spectrum of significant in vivo physiological differences of epinephrine action on the liver, muscle, adipose tissue, pancreas and cardiovascular system between NIDDM and healthy subjects.[52]

Enhanced glycemic responsiveness of patients with IDDM to epinephrine is not the result of increased sensitivity of adrenergic receptor-effector mechanisms per se nor of their increased glucagon secretory response; rather, it is the result of their inability to augment insulin secretion. Augmented insulin secretion, albeit restrained, normally limits the glycemic response, but not the lipolytic or ketogenic responses to epinephrine in humans.[53]

Elevations of plasma epinephrine comparable to those observed in physiologic stress, cause a sustained 20--35 mg/dL elevation of plasma glucose in normal humans. In diabetes, the hyperglycemic effect of epinephrine is markedly accentuated. [54]

IX. Cortisol

In NIDDM subjects, hypothalmic-pituitary-adrenal activity is enhanced in patients with diabetes complications and the degree of cortisol secretion is related to the presence and number of diabetes complications.[55] Plasma HbA1c levels of NIDDM patients with elevated cortisol levels were found to be significantly higher than NIDDM patients with normal cortisol levels.[56]The consistent presence of normal cortisol secretion rate in diabetic children without acidosis argues against the contention that increased cortisol secretion is a factor in the pathogenesis of juvenile diabetes mellitus.[57] The degree of severity of several clinical measures of NIDDM correlates with cortisol concentrations. Moreover, the results provide evidence for a positive relationship between metabolic disturbances and cortisol concentrations that are within the accepted normal range.[58]

Altered cortisol action occurs not only in obesity and hypertension but also in glucose intolerance, and could therefore contribute to the link between these multiple cardiovascular risk factors.[59]In NIDDM subjects, Hypothalamic-Pituitary-Adrenal (HPA) activity is enhanced only in patients with chronic complications and the degree of cortisol secretion is directly associated with the presence and the number of diabetes complications.[60]An increase in basal cortisol level in the blood plasma or the adrenal cortex reaction to insulin hypoglycemia was seen in patients in the early periods of diabetes mellitus (latent, initial manifest type).[61]

X. Body Mass Index (BMI)

Obesity contributes to the development of NIDDM, and weight control efforts are an important component of the clinical management of diabetes. Although epidemiological studies have examined weight change as a predictor of diabetes and intervention studies have shown that weight loss produces short-term improvements in glycemic control in people with NIDDM and few data exist on how body weight changes longitudinally in relation to the development of diabetes.[62]

Weight gain after age 18 was a major determinant of risk. For an increase of 20–35 Kg, the relative risk was 11.3, and for an increase of more than 35 Kg, the relative risk was 17.3.[63]Waist circumference may be a better indicator than Weight to Height Ratio (WHR) to establish the of the relationship between abdominal adiposity and risk of diabetes. Although early obesity, absolute weight gain throughout adulthood, and waist circumference were good predictors of diabetes, attained BMI was the dominant risk factor for NIDDM; even men of average relative weight had significantly elevated Relative Risk.[64]

Obesity and increases in body weight in adults are considered to be among the most important risk factors for NIDDM.[65]Weight maintenance and prevention of weight gain during adulthood are necessary to decrease the risk of NIDDM.[66]

Increases in obesity and diabetes among US adults continue in both sexes, all ages, all races, all educational levels, and in all smoking levels. Obesity is strongly associated with several major health risk factors.[67]Subclinical hypercortisolism (SH) may play a role in several metabolic disorders, including diabetes.[68]

XI. Conclusion

This review aritcel has brought together the various laboratory tests available to screen and monitor diabetic control and the following are the conclusions arrived.

Traditional screening tests like urine sugar, FPG, 2hr Post glucose load PG, GGT, GCT are all still being used in all clinical laboratories as all the tests are cost effective and serve as first line of Diabetes detection. Contraversy is still prevalent about the use of Frustosamine to monitor short time diabetic control during the preceeding 2-3 weeks. The Gold standard to monitor long term diabetic control during the preceeding 2-3 months is HbA1c and the test could also be used to screen for diabetes.C-peptide is considered as a better marker than pro insulin and isnulin to monitor diabetic control in IDDM patients, particularly in children as it is a major regulator of Insulin action. The hyperglycemic hormones viz GH, glucagon, epinephrine and cortisol also play a major role in maintaing plasma glucose during times of hypoglycemia. Microalbuminuria tests is very useful to monitor complications arising out of uncontrolled DM and is a very useful marker to assess the development of neuropathy, retinopathy and nephropathy in diabetic patients. IGF-1 test is of research interest and available data suggests that its measurement may be useful to elucidate the molecular link between DM an AD while tests like urine sugar, FPG, 2hr PG, Fructosamine and HbA1c could be routinely done in any clinical laboratory, as all these tests are cost effective, other tests like insulin, C-peptide, IGF-1 and hyperglycemic hormones are recommended only under extreme special situations.

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