# 6. MODERN ASPECTS OF LABORATORY DIAGNOSIS AND MONITORING OF DIABETES MELLITUS

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## 1.1. Introduction

Recently compiled data show that between 120 and 140 million people suffer from diabetes mellitus (DM) worldwide, and that this number may well double by the year 2025. Much of this increase will occur in developing countries and will be due to population aging, unhealthy diets, obesity and a sedentary lifestyle. By 2025, while most people with DM in developed countries will be aged 65 years or more, in developing countries most will be in the 45-64 year age range and affected in their most productive years.

DM is a metabolic disorder primarily characterized by elevated blood glucose levels and by microvascular and cardiovascular complications that substantially increase the morbidity and mortality associated with the disease and reduce the quality of life.

Type 1 DM is characterized by total reliance on exogenous insulin for survival and comprises approx.10% of all cases of DM. In Type 1 DM, the cause is an absolute deficiency of insulin secretion. Individuals at increased risk of developing this type of DM can often be identified by serological evidence of an autoimmune pathologic process occurring in the pancreatic islets and by genetic markers.

The more prevalent form of DM, called Type 2, comprising 90% of all people with DM, is characterized by insulin deficiency and/or insulin resistance to insulin action and an inadequate, compensatory, insulin-secretory response. In the latter category, a degree of hyperglycaemia sufficient to cause pathologic and functional changes in various target tissues, but without clinical symptoms, may be present for a long period of time before DM is detected. During this asymptomatic period, it is possible to demonstrate an abnormality in carbohydrate metabolism by measurement of plasma glucose in the fasting state or after a challenge with an oral glucose load.

Gestational DM (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. The definition applies regardless of whether insulin or only diet modification is used for treatment, or whether the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy. In the majority of cases of GDM, glucose regulation will return to normal after delivery. GDM complicates ~4% of all pregnancies.

## 1.2. Laboratory data for the diagnostic criteria of diabetes mellitus

The new criteria for DM mellitus have been modified from those previously recommended by WHO. Three ways to diagnose DM are possible, and each must be confirmed, on a subse-

quent day.

For example, one instance of symptoms with casual plasma glucose >11.1 mmol/l, confirmed on a subsequent day by:

- Fasting plasma glucose (FPG) >7.0 mmol/l,
- An oral glucose tolerance test (OGTT) with the 2-h postload value >11.1 mmol/l, or
- Symptoms with a casual plasma glucose >11.1 mmol/l warrants the diagnosis of DM.

An intermediate group of subjects, whose glucose levels, although not meeting criteria for DM, are nevertheless too high to be considered altogether normal. This group is defined as having FPG levels >6.1 mmol/l but <7.0 mmol/l or 2-h values in the OGTT of >7.8 mmol/l but <11.1 mmol/l. Thus, the categories of FPG values are as follows:

- FPG <6.1 mmol/l = normal fasting glucose;
- FPG >6.1 mmol/l and <7.0 mmol/l = impaired fasting glucose (IFG);
- FPG >7.0 mmol/l = provisional diagnosis of DM (the diagnosis must be confirmed, as described above).

The corresponding categories when the OGTT is used are the following:

- 2-h postload glucose (2-h PG) <7.8 mmol/l = normal glucose tolerance;
- 2-h PG >7.8 mmol/l and <11.1 mmol/l) = impaired glucose tolerance (IGT);
- 2-h PG >11.1 mmol/l = provisional diagnosis of DM (the diagnosis must be confirmed, as described above).

Since the 2-h OGTT cutoff of 7.8 mmol/l will identify more people as having impaired glucose homeostasis than will the fasting cutoff of 6.1 mmol/l, it is essential that investigators always report which test was used.

### 1.3. Rationale for the revised criteria for diagnosing DM

The revised criteria are still based on measures of hyperglycaemia. The metabolic defects underlying hyperglycaemia, such as islet cell autoimmunity or insulin resistance, should be referred to independently from the diagnosis of DM, i.e. in the classification of the disease. Plasma glucose concentrations are distributed over a continuum, but there is an approximate threshold separating those subjects who are at substantially increased risk for some adverse outcomes caused by DM (e.g., microvascular complications) from those who are not. Based in part on estimates of the thresholds for microvascular disease, the previous WHO criteria defined DM by FPG >7.8 mmol/l, 2-h PG >11.1 mmol/l in the OGTT, or both. These criteria effectively defined DM by the 2-h PG alone because the fasting and 2-h values are not equivalent. Almost all individuals with FPG >7.8 mmol/l have 2-h PG >11.1 mmol/l if given an OGTT, whereas only about one-fourth of those with 2-h PG >11.1 mmol/l and without previously known DM have FPG >7.8 mmol/l. Thus, the cut-off point of FPG >7.8 mmol/l defined a greater degree of hyperglycaemia than did the cut-off point of 2-h PG >11.1

mmol/l.

Under the previous WHO criteria, the diagnosis of DM is largely a function of which test is performed. Many individuals who would have 2-h PG >11.1 mmol/l in an OGTT are not tested with an OGTT because they lack symptoms or because they have an FPG <7.8 mmol/l. Thus, if it is desired that all people with DM be diagnosed and the previous criteria are followed, OGTTs must be performed periodically in everyone. However, in ordinary practice, not only is the OGTT performed infrequently, but it is usually not used even to confirm suspected cases. In summary, the diagnostic criteria are now revised to avoid the discrepancy between the FPG and 2-h PG cut-off point values and facilitate and encourage the use of a simpler and equally accurate test—fasting plasma glucose—for diagnosing DM.

HbA1c measurement is not currently recommended for diagnosis of DM, although some studies have shown that the frequency distributions for HbA1c have characteristics similar to those of the FPG and the 2-h PG. Moreover, these studies have defined an HbA1c level above which the likelihood of having or developing macro- or microvascular disease rises sharply. Furthermore, HbA1c and FPG (in type 2 DM) have become the measurements of choice in monitoring the treatment of DM, and decisions on when and how to implement therapy are often made on the basis of HbA1c.

While there are many different methods for the measurement of HbA1c and other glycosylated proteins, and standardization of the HbA1c test has just begun. In most clinical laboratories, a "normal" HbA1c is usually based on a statistical sampling of healthy, ‘presumably nondiabetic’ individuals. In conclusion, HbA1c remains a valuable tool for monitoring glycaemia, but it is not currently recommended for the diagnosis of DM.

### 1.4. Laboratory testing for diabetes mellitus in presumably healthy individuals

Type 1 DM is usually an autoimmune disease, characterized by the presence of a variety of autoantibodies to protein epitopes on the surface of or within the ß-cells of the pancreas. The presence of such markers before the development of overt disease can identify patients at risk. For example, those with more than one autoantibody (i.e., ICA, IAA, GAD, IA-2) are at high risk. At this time, however, many reasons preclude the recommendation to test individuals routinely for the presence of any of the immune markers. First, cutoff values for some of the assays for immune markers have not been completely established for clinical settings. Second, there is no consensus yet as to what action should be taken when a positive autoantibody test is obtained. Thus, autoantibody testing may identify people at risk of developing type 1 DM without offering any proven measures that might prevent or delay the clinical onset of disease. Last, because the incidence of type 1 DM is low, routine testing of healthy children will identify only the small number (<0.5%) who at that moment may be "prediabetic." Thus, the cost-effectiveness of such screening is questionable. Similarly, antibody testing of high-risk individuals (e.g., siblings of type 1 patients) is also not recommended until the efficacy and safety of therapies to prevent or delay type 1 DM have been demonstrated. On the other hand, the autoantibody tests may be of value to identify which newly diagnosed patients have immune-mediated type 1 DM in circumstances where it is not obvious, particularly when therapies become available to preserve ß-cell mass.

Undiagnosed type 2 DM is extremely common. As many as 50% of the people with the disease, are undiagnosed. Of concern, there is epidemiological evidence that retinopathy begins to develop at least 7 years before the clinical diagnosis of type 2 DM is made. Because hyperglycaemia in type 2 DM causes microvascular disease and may cause or contribute to macrovascular disease, undiagnosed DM is a serious condition. Patients with undiagnosed type 2 DM are at significantly increased risk for coronary heart disease, stroke, and peripheral vascular disease. In addition, they have a greater likelihood of having dyslipidaemia, hypertension, and obesity. Thus, early detection, and consequently early treatment, might well reduce the burden of type 2 DM and its complications. However, to increase the cost-effectiveness of testing undiagnosed, otherwise healthy individuals, testing should be considered in the high-risk populations only.

Suggested criteria for testing:

- The steep rise in the incidence of the disease after age 45 years.
- The negligible likelihood of developing any of the complications of DM within a 3-year interval of a negative screening test.
- Knowledge of the well-documented risk factors for the disease.

Although the OGTT and FPG are both suitable tests, in clinical settings, the FPG is strongly recommended because it is easier and faster to perform, more convenient and acceptable to patients, more reproducible, and less expensive. The best screening test for DM, the fasting plasma glucose (FPG), is also a component of diagnostic testing.

Laboratory measurement of plasma glucose concentration is performed on venous samples with enzymatic assay techniques, and the above-mentioned values are based on the use of such methods. HbA1c values remain a valuable tool for monitoring glycaemia, but it is not currently recommended for the screening or diagnosis of DM. Pencil and paper tests do not perform well as stand-alone tests. Capillary blood glucose testing using a reflectance blood glucose meter has also been used but because of the imprecision of this method, it is better used for self-monitoring rather than as a screening tool.

### 1.5. Laboratory screening in the community

Although there is ample scientific evidence showing that certain risk factors predispose individuals to development of DM, there is insufficient evidence to conclude that community screening is a cost-effective approach to reduce the morbidity and mortality associated with DM in presumably healthy individuals. While community-screening programs may provide a means to enhance public awareness of the seriousness of DM and its complications, other less costly approaches may be more appropriate, particularly because the potential risks are poorly defined. Thus, based on the lack of scientific evidence, community screening for DM, even in high-risk populations, is not recommended.

### 1.6. Laboratory tests of glycaemia in diabetes mellitus

#### 1.6.1. Self-monitoring of blood glucose

Within only a few years, self-monitoring of blood glucose (SMBG) by patients has revolu-

tionized management of DM. Using SMBG, patients with DM can work to achieve and maintain specific glycaemic goals. There is broad consensus on the health benefits of normal or near-normal blood glucose levels and on the importance, especially in insulin-treated patients, of SMBG in treatment efforts designed to achieve such glycaemic goals. It is recommended that most individuals with DM should attempt to achieve and maintain blood glucose levels as close to normal as is safely possible. Because most patients with type 1 DM can achieve this goal only by using SMBG, all treatment programs should encourage SMBG for routine daily monitoring. Daily SMBG is especially important for patients treated with insulin or sulphonylureas to monitor for and prevent asymptomatic hypoglycaemia. Frequency and timing of glucose monitoring should be dictated by the needs and goals of the individual patient, but for most patients with type 1 DM, SMBG is recommended three or more times daily. The optimal frequency of SMBG for patients with type 2 DM is not known, but should be sufficient to facilitate reaching glucose goals. When adding to or modifying therapy, type 1 and type 2 diabetic patients should test more often than usual. Because the accuracy of SMBG is instrument and user dependent, it is important for health care providers to evaluate each patient's monitoring technique, both initially and at regular intervals thereafter. In addition, because laboratory methods measure plasma glucose, many blood glucose monitors approved for home use and some test strips now calibrate blood glucose readings to plasma values. Plasma glucose values are 10–15% higher than whole blood glucose values, and it is crucial that people with DM know whether their monitor and strips provide whole blood or plasma results. Continuous ambulatory blood glucose monitoring may be also be used to determine 24-h blood glucose patterns and to detect unrecognised hypoglycaemia; however, its role in improving DM outcomes remains to be established.

### 1.6.2. Bedside monitoring of hospitalized patients with diabetes mellitus

The modern management of hospitalized patients with diabetes includes capillary blood glucose determinations at the bedside. This measure is analogous to an additional "vital sign" for people with diabetes. The rapidity with which results can be obtained, and therapeutic decisions made, can improve management and conceivably can shorten hospital stays. Replacing venepunctures with finger punctures enhances patient comfort. Bedside glucose determinations can be performed by adequately trained personnel. Use of bedside blood glucose monitoring requires:

- clear administrative responsibility for the procedure,
- a well-defined policy/procedure manual,
- a training program for those personnel doing the testing,
- quality control procedures, and
- regularly scheduled equipment maintenance.

## 1.7. Day-to-day management with laboratory methods: urine glucose and ketone testing

SMBG has supplanted urine glucose testing for most patients. Urine ketone testing remains an important part of monitoring, particularly in patients with type 1 DM, pregnancy with preexisting DM, and gestational DM. Urine glucose testing by patients in the home setting consists of semiquantitative measurements based on single voidings or, less often, by

more quantitative "blocks" collected over 4–24 h. The rationale is that urinary glucose values reflect mean blood glucose during the period of urine collection. However, despite the relatively low cost and ease of specimen collection, the well-described limitations of urine glucose testing make SMBG the preferred method of monitoring glycaemic status day-to-day.

For patients who cannot or will not perform SMBG, urine glucose testing can be considered an alternative that can provide useful, albeit limited information. Patients should be taught that urine glucose testing provides no information about blood glucose levels below the renal threshold, which for most patients is 10 mmol/l. Test strips that quantify urinary glucose specifically rather than reducing sugars are recommended because of fewer drug and other interferences. Second-voided specimens do not appear to offer any appreciable advantage over first-voided specimens.

Urine ketone testing is an important part of monitoring in type 1 patients. The presence of urine ketones may indicate impending or even established ketoacidosis, a condition that requires immediate medical attention. All people with DM should test their urine for ketones during acute illness or stress or when blood glucose levels are consistently elevated (e.g., >16.7 mmol/l), during pregnancy, or when any symptoms of ketoacidosis, such as nausea, vomiting, or abdominal pain, are present. Ketones are normally present in urine, but concentrations are usually below the limit of detectability with routine testing methods. However, positive ketone readings are found in normal individuals during fasting and in up to 30% of first morning urine specimens from pregnant women. Urine ketone tests using nitroprusside-containing reagents can give false-positive results in the presence of several sulfhydryl drugs, including the antihypertensive drug captopril. False-negative readings have been reported when test strips have been exposed to air for an extended period of time or when urine specimens have been highly acidic, such as after large intakes of ascorbic acid. Health care professionals should be aware, however, that currently available urine ketone tests are not reliable for diagnosing or monitoring treatment of ketoacidosis. Blood ketone testing methods that quantify ß-hydroxybutyric acid, the predominant ketone body, are now available and are preferred over urine ketone testing for diagnosing and monitoring ketoacidosis. Home tests for ß-hydroxybutyric acid are now available.

### 1.8. Long-term monitoring: glycated protein testing

Blood and urine glucose testing and urine ketone testing provide useful information for day-to-day management of DM. However, these tests cannot provide the patient and health care team with a quantitative and reliable measure of glycaemia over an extended period of time. Measurements of glycated proteins, primarily hemoglobin and serum proteins, have added a new dimension to assessment of glycaemia. With a single measurement, each of these tests can quantify average glycaemia over weeks and months, thereby complementing day-to-day testing.

#### 1.8.1. Glycosylated hemoglobin (HbA1c)

GHb, commonly referred to as glycated hemoglobin, glycohaemoglobin, glycosylated hemoglobin, or HbA1, is a term used to describe a series of stable minor hemoglobin components formed slowly and nonenzymatically from hemoglobin and glucose. The rate of forma-

tion of GHb is directly proportional to the ambient glucose concentration. Since erythrocytes are freely permeable to glucose, the level of GHb in a blood sample provides a glycaemic history of the previous 120 days, the average erythrocyte life span. GHb most accurately reflects the previous 2–3 months of glycaemic control.

Many different types of GHb assay methods are available to the routine clinical laboratory. Methods differ considerably with respect to the glycated components measured, interferences, and nondiabetic range. HbA1c has become the preferred standard for assessing glycaemic control. The HbA1c value has been shown to predict the risk for the development of many of the chronic complications in DM. However, optimal use of HbA1c testing for this purpose requires the standardization of HbA1c assays. Since HbA1c reflects a mean glycaemia over the preceding 2–3 months, measurement approximately every 3 months is required to determine whether a patient's metabolic control has reached and been maintained within the target range. Thus, regular measures of HbA1c permit detection of departures from the target range in a timely fashion. For any individual patient, the frequency of HbA1c testing should be dependent on the treatment regimen used and on the judgment of the clinician. In the absence of well-controlled studies that suggest a definite testing protocol, expert opinion recommends HbA1c testing at least two times a year in patients who are meeting treatment goals (and who have stable glycaemic control) and more frequently (quarterly assessment) in patients whose therapy has changed or who are not meeting glycaemic goals.

Proper interpretation of HbA1c test results requires that health care providers understand the relationship between test results and average blood glucose, kinetics of HbA1c, and specific assay limitations. HbA1c values in patients with DM are a continuum; they range from normal in a small percentage of patients whose average blood glucose levels are in or close to the normal range to markedly elevated values, e.g., two- to threefold increases, in some patients, reflecting an extreme degree of hyperglycaemia. One must take into account the results of studies showing a direct relationship between HbA1c values and the risk of many of the chronic complications of DM. The goal of therapy should be an HbA1c of <7% and that physicians should reevaluate the treatment regimen in patients with HbA1c values consistently >8%.

### 1.8.2. Glycated serum proteins (GSP):

Because the turnover of human serum albumin is much shorter (half-life of 14–20 days) than that of hemoglobin (erythrocyte life span of 120 days), the degree of glycation of serum proteins (mostly albumin) provides an index of glycaemia over a shorter period of time than does glycation of hemoglobin. Measurements of total GSP and glycated serum albumin (GSA) correlate well with one another and with measurements of HbA1c. In situations where HbA1c cannot be measured or may not be useful (e.g., hemolytic anemia), the GSP assay may be of value in the assessment of the treatment regimen. Several methods have been described that quantify either total GSP or total GSA. One of the most widely used is called the fructosamine assay. Values for GSP vary with changes in the synthesis or clearance of serum proteins that can occur with acute systemic illness or with liver disease. In addition, there is continuing debate as to whether fructosamine assays should be corrected for serum

protein or serum albumin concentrations.

A single measurement of GSP provides an index of glycaemic status over the preceding 1–2 weeks, while a single measurement of HbA1c provides an index of glycaemic status over a considerably longer period of time, 2–3 months. Measurement of GSP (including fructosamine) has been used to document relatively short-term changes (e.g., 1–2 weeks) in glycaemic status, such as in diabetic pregnancy or after major changes in therapy. However, further studies are needed to determine if the test provides useful clinical information in these situations. Simultaneous measurements of GSP and HbA1c might complement one another and provide more useful clinical information than measurement of HbA1c alone.

Measurement of GSP, regardless of the specific assay method, should not be considered equivalent to measurement of HbA1c, since it only indicates glycaemic control over a short period of time. Therefore, GSP assays would have to be performed on a monthly basis to gather the same information as measured in HbA1c three to four times a year. Unlike HbA1c, GSP has not yet been shown to be related to the risk of the development or progression of chronic complications of DM.

### 1.9. Laboratory diagnosis and monitoring of hyperglycaemic crises

Ketoacidosis and hyperosmolar hyperglycaemia are the two most serious acute metabolic complications of DM, even if managed properly. These disorders can occur in both type 1 and type 2 DM. The mortality rate in patients with diabetic ketoacidosis (DKA) is <5% in experienced centers, whereas the mortality rate of patients with hyperosmolar hyperglycaemic state (HHS) still remains high at 15%. The initial laboratory evaluation of patients with suspected DKA or HHS should include determination of plasma glucose, blood urea nitrogen/creatinine, serum ketones, electrolytes (with calculated anion gap), osmolality, urinalysis, urine ketones by dipstick, as well as initial arterial blood gases, and complete blood count with differential. HbA1c may be useful in determining whether this acute episode is the culmination of an evolutionary process in previously undiagnosed or poorly controlled DM or a truly acute episode in an otherwise well-controlled patient.

The majority of patients with hyperglycaemic emergencies present with leukocytosis proportional to blood ketone body concentration. Serum sodium concentration is usually decreased because of the osmotic flux of water from the intracellular to the extracellular space in the presence of hyperglycaemia, and less commonly, serum sodium concentration may be falsely lowered by severe hypertriglyceridaemia. Serum potassium concentration may be elevated because of an extracellular shift of potassium caused by insulin deficiency, hypertonicity, and acidaemia. Patients with low serum potassium concentration on admission have severe total-body potassium deficiency and require very careful cardiac monitoring and more vigorous potassium replacement, because treatment lowers potassium further and can provoke cardiac dysrhythmia.

The occurrence of stupor or coma in diabetic patients in the absence of definitive elevation of effective osmolality (>320 mOsm/kg) demands immediate consideration of other causes of mental status change. Effective osmolality may be calculated by the following formula: 2[measured Na+ (mEq/l)] + glucose (mg/dl)/18. Amylase levels are elevated in the ma-

jority of patients with DKA, but this may be due to nonpancreatic sources, such as the parotid gland. A serum lipase determination may be beneficial in the differential diagnosis of pancreatitis. However, lipase could also be elevated in DKA. Abdominal pain and elevation of serum amylase and liver enzymes are noted more commonly in DKA than in HHS.

### 1.10. Laboratory diagnosis and follow-up of diabetic nephropathy

DM has become the most common single cause of end-stage renal disease (ESRD). About 20–30% of patients with type 1 or type 2 DM develop evidence of nephropathy, but in type 2 DM, a considerably smaller fraction of these progresses to ESRD. However, because of the much greater prevalence of type 2 DM, such patients constitute over half of those diabetic patients currently starting on dialysis. The earliest clinical evidence of nephropathy is the appearance of low, but abnormal levels (>30 mg/day or 20 µg/min) of albumin in the urine, referred to as microalbuminuria, and patients with microalbuminuria are referred to as having incipient nephropathy. In addition to its being the earliest manifestation of nephropathy, albuminuria is a marker of greatly increased cardiovascular morbidity and mortality for patients with either type 1 or type 2 DM. Thus, the finding of microalbuminuria is an indication for screening for possible vascular disease and aggressive intervention to reduce all cardiovascular risk factors (e.g., lowering of LDL cholesterol, antihypertensive therapy, cessation of smoking, institution of exercise, etc.). In addition, there is some preliminary evidence to suggest that lowering of cholesterol may also reduce the level of proteinuria.

A routine urinalysis should be performed at diagnosis in patients with type 2 DM. If the urinalysis is positive for protein, a quantitative measure is frequently helpful in the development of a treatment plan. If the urinalysis is negative for protein, a test for the presence of microalbumin is necessary. Microalbuminuria rarely occurs with short duration of type 1 DM or before puberty; therefore, screening in individuals with type 1 DM should begin with puberty and after 5 years' disease duration. However, some evidence suggests that the prepubertal duration of DM may be important in the development of microvascular complications; therefore, clinical judgment should be exercised when individualizing these recommendations. Because of the difficulty in precise dating of the onset of type 2 DM, such screening should begin at the time of diagnosis. After the initial screening and in the absence of previously demonstrated microalbuminuria, a test for the presence of microalbumin should be performed annually.

- Screening for microalbuminuria can be performed by three methods:
- Measurement of the albumin-to-creatinine ratio in a random, spot collection.
- 24-h collection with creatinine, allowing the simultaneous measurement of creatinine clearance.
- Timed (e.g., 4-h or overnight) collection.

The first method is often found to be the easiest in an office setting and generally provides accurate information. First-void or other morning collections are preferred because of the known diurnal variation in albumin excretion, but if this timing cannot be used, uniformity of timing for different collections in the same individual should be employed. The role of annual urine protein dipstick testing and microalbuminuria assessment is less clear after diagnosis of microalbuminuria and institution of ACE inhibitor therapy and blood pressure con-

trol. Many experts recommend continued surveillance both to assess response to therapy and progression of disease. In addition to assessment of urinary albumin excretion, assessment of renal function is important in patients with diabetic kidney disease.

### 1.11. Laboratory diagnosis of dyslipidaemia and coronary heart disease in diabetes mellitus

Type 2 DM is associated with a two- to fourfold excess risk of coronary heart disease (CHD). The most common pattern of dyslipidaemia in type 2 diabetic patients is elevated triglyceride levels and decreased HDL cholesterol levels. The concentration of LDL cholesterol in type 2 diabetic patients is usually not significantly different from non-diabetic individuals. Diabetic patients may have elevated levels of non-HDL cholesterol (LDL plus VLDL). However, type 2 diabetic patients typically have a preponderance of smaller, denser LDL particles, which possibly increases atherogenicity even if the absolute concentration of LDL cholesterol is not significantly increased. The median triglyceride level in type 2 diabetic patients is <2.30 mmol/l, and 85–95% of patients have triglyceride levels below 4.5 mmol/l.

Because of frequent changes in glycaemic control in diabetic patients and their effects on levels of lipoprotein, levels of LDL, HDL, total cholesterol, and triglyceride should be measured every year in adult patients. If values fall in lower-risk levels, assessment may be repeated every 2 years. Optimal LDL cholesterol levels for adults with DM are <2.60 mmol/l, optimal HDL cholesterol levels are >1.15 mmol/l, and desirable triglyceride levels are <2.30 mmol/l. Type 1 diabetic patients who are in good control, tend to have normal levels of lipoprotein.

### 1.12. Laboratory diagnosis diabetic retinopathy:

Diabetic retinopathy is a highly specific vascular complication of both type 1 and type 2 DM. The prevalence of retinopathy is strongly related to the duration of DM. After 20 years of DM, nearly all patients with type 1 DM and >60% of patients with type 2 DM have some degree of retinopathy. In the younger-onset group, 86% of blindness was attributable to diabetic retinopathy. In the older-onset group, where other eye diseases were common, one-third of the cases of legal blindness were due to diabetic retinopathy. Overall, diabetic retinopathy is estimated to be the most frequent cause of new cases of blindness among adults aged 20–74 years.

It seems clear that proteinuria is associated with retinopathy. High blood pressure is an established risk factor for the development of macular edema and is associated with the presence of PDR. Observations indicate an association of serum lipid levels with lipid in the retina (hard exudates) and visual loss. Thus, systemic control of blood pressure and serum lipids may be important in the management of diabetic retinopathy.

**Recommended literature:**

1. Jeppsson JO, Kobold U, Barr J, Finke A, Hoelczel W, Hoshino T, Miedema K, Mosca A, Paroni R, Thienpont L, Umemoto M, Weykamp C. IFCC reference method for meas-

urement of HBA1C in human blood. JIFCC, 2001.06.20.
2. Coordinated performance measurement for the management of adult diabetes. A consensus statement from the AMA, JCAHO and NCQA. 2001.
3. Diabetic retinopathy. Position statement of ADA. Diabetes Care 2001; 24: Suppl.1.
4. Report on the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2001;24: Suppl.1.
5. Gestational diabetes mellitus. Diabetes Care 2001;24: Suppl.1.
6. Management of dyslipidemia in adults with diabetes. Diabetes Care 2001;24: Suppl.1.
7. Diabetic nephropathy. Diabetes Care 2001;24: Suppl.1.
8. Standards of medical care for patients with diabetes mellitus. Diabetes Care 2001;24: Suppl.1.
9. Tests of glycaemia in diabetes. Diabetes Care 2001; 24: Suppl.1.
10. Screening for diabetes. Diabetes Care 2001;24: Suppl.1.
11. Hyperglycaemic crises in patients with diabetes mellitus. Position statement of ADA. Diabetes Care 2001;24:154-61.
12. Bedside blood glucose monitoring. Position statement of ADA. Diabetes Care 2001;24: Suppl.1.
13. World Health Organization: Diabetes mellitus: report of WHO study group. Geneva, WHO. 1985 (Techn.Rep. 727).