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UTILITY OF ADVANCES IN BIOCHEMISTRY IN CLINICAL REALITY OF DIABETES MELLITUS

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Diabetes is characterized by chronic hyperglycemia and disordered carbohydrate, lipid and protein metabolism and is associated with the development of specific microvascular complications and of non specific macrovascular diseases.

Early detection and improvement in monitoring allow diabetic patients to lead normal lives. Clinical chemistry plays an important role in the diagnosis and treatment of diabetes.

Two decades back, the prevaling scientific view was that diabetes had a single cause which was failure of pancreatic β cells to produce insulin; and it was believed to produce single metabolic effect i.e. the presence of excessive glucose in the blood. Sole test for diagnosis was blood glucose (and glucose tolerance) and for monitoring two semiquantitative tests, urine glucose and ketone bodies were available. In light of knowledge that diabetes is a multifactorial disease with a variety of causes: genetic, environmental, immunological, impaired insulin receptor number and response etc. new test were developed in 1970s and 1980s that are important tools in 1990s for a more precise way to diagnose and monitor diabetes. these test may be clasified in the following four categories.

I. TESTS FOR THE DIAGNOSIS OF DIABETES :

Blood glucose determination remains the mainstay for the diagnosis. The common glucose methodologies of 1960s, based on oxidoreduction principles, lack accuracy and precision and have been improved upon by introduction of automation and enzymatic methods. Glucose analysis is subject to pre-analytical inaccuracy in uncentrifuged blood specimens because of glycolysis. Blood should, therefore, be taken in tubes containing fluoride or iodoacetate.

A fasting plasma glucose, or if necessary, 2 hours post-prandial plasma glucose is estimated. If results are inconclusive two hours, 75gm oral glucose tolerance (OGTT) may be performed.

WHO criteria reported in 1980, consider a fasting plasma glucose less than 10mg\dl (6.0 mmol\L) as normal and two values above 140mg\dl (7.8 mmol\L) is diagnostic of diabetes.

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In patients with values in the intermediate zone, OGTT is performed with 75gm oral glucose load. If the plasma glucose exceeds 200 mg% (11 mmol\L) on at least two occasions, the test is diagnostic of diabetes[1,2].

II. TEST FOR MONITORING DIABETES

Reflectometer glucose level : Portable glucometers provide the capability to measure capillary blood glucose levels at any time or place with instant availability of results. To adjust the daily dose of insulin. they can be used by the nursing staff or patients themselves. In doubtful cases, a specimen should be sent to the laboratory for conformation, to establish and monitor a quality control programme.

Glycated Haemoglobin (HbA1) is an index of long term diabetic control. Glycation of haemogloibn occurs by a slow enzymatic process, solely dependent on blood glucose concentration and is stable over 120 days life span of RBCs. Thus compared with plasma glucose levels that reflect immediate control, HbA1, indicates average long term control over preceding 6-8 weeks and is uesful in monitoring effectiveness of therapy during that period. On chomatography HbA1 itself shows 3 fractions : HbA1a, HbA1b and HbA1c of which HbA1c is most predominant and is measured by ion exchange chomatography or lately by affinity chomatography[3]. HbA1c estimation is particularly useful in unstable insulin dependent diabetes mellitus, childhood diabetes, and in 1st trimester of pregnancy where high values indicate risk of foetal congenital malformations. Reference values for non-diabetics are 3-6% of haemoglobin. In diabetic individuals higher values, depending on degree of glycaemic control, are found[4].

Measurement of glycated albumin or glycated total proteins, commonly referred to as the fructosamine assay, may be used in a manner analogous to the determination of glucose in the blood during the preceeding 2-3 weeks[5]. A clinical advantage is that it responds quickly to change in therapy. The method is simple and rapid. Fructosamine assay had been proposed as a screening test for the diagnosis of diabetes but recent studies have demonstrated it not to be appropriate for this purpose.

III. TESTS FOR THE IDENTIFICATION OF THE CAUSE OF DIABETES :

a) **Serum insulin level** is used in the investigation of diabetes demonstrating apparent insulin resistance, in differentiating between type I and type II diabetes, and in the investigation of hypoglycemia. The test is done by radio-immunossary.

b) **Insulin tolerance test** is useful in the evaluation of patients with insulin resistance. Following insulin injection, plasma glucose levels are measured at 30, 45, 60, 90 and 120 minutes. Normally it falls by 50% within 30 minutes and returns tonormal by 120 minutes. Insulin resistant diabetic individuals demostrate a slight or delayed devrease of glucose[6].

c) **Serum C peptide** is useful in the evaluation of endogenous secretion of insulin in patients with circulating insulin antibodies. The test is performed by radio-immunoassay[7].

Many diabetes related tests have been developed in the past 20 years: insulin, insulin tolerance, glucagon, anti Islet cell antibody (ICA) etc. though still research

procedures, these tests hold promise for future.

IV. TESTS FOR DIABETIC COMPLICATIONS :

If uncontrolled, diabetes may result in devastating complications like retinopathy nephropathy, neuropathy and accelerated atherosclerosis. Biochemical basis of these complications are enhanced polyol pathway and altered anti-oxidant status[8]. It is, therefore, mandatory that such patients are followed up by a full lipid profile including apolipoprotein levels, if possible. Periodic serum urea, calcium and creatinine and 24 hours urine protein determinations are mandatory for early detection of renal insufficiency.

Microalbumin is the newest test for monitoring diabetes to aid in the detection of early diabetic nephropathy. The test should be carried out annually, starting from the time of diagnosis in type II diabetic patients and 5 years after dignosis in type I diabetes. A positive test should encourage out to strive for better control of blood and to repeat monitoring at 6 monthbs intervals. Values between 30-140 mg\L on two occasions are considered significant[9].

These test have integrated recent advances in basic physiological mechanisms in glucose metabolism with clinical reality of diavetes and have enhanced the role of clinical labs in utilizing such knowledge to improve clinical outcome.

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CLUSTERING OF XEROPHTHALMIA AND VITAMIN A DEFICIENCY WITHIN COMMUNITIES AND FAMILIES

BACKGROUND :

In multiple studies in Indonesia, Nepal, Malawi, Zambia and Bangladesh, it has been demonstrated that vitamin A deficiency and Xerophthalmia cluster within families, neighbourhoods, and villages. A national survey of xerophthalmia in Indonesia in the 1970s demonstrated that Bitot's spots clustered in village within each of the region surveyed. A study from West Java, Indonesia children without xerophthalmia who were from neighbourhoods with xerophthalmic children had lower serum retinol levels than those from neighbourhoods without xerophthalmia. Xerophthalmia surveys done in Sumatra, Nepal, Malawi an Zambia showed that if one child in a household had xerophthalmia, the risk of another child in the same household having xerophthalmia was between 7.3 and 13.2 times higher than if the index child did not have xerophthalmia. This increased risk was not entirely explained by siblings being more likely to have the same infectious diseases that predispose children to xerophthalmia. Furthermore, mothers of xerophthalmic children in Bangladesh were 5 to 10 times more likely to have night blindness than mothers of children without xerophthalmia. In terms of community risk if one child in a village had xerophthalmia, the likelihood that another child in that village had xerophthalmia was between 1.2 and 2.3 times greater than if the index child did not have xerophthalmia.

Although xerophthalmia is not an infectious disease, children in the same household and same community share common socio-economic and sociocultural conditions that result in similar exposure to frequent bouts of infectious disease, food availability, and dietary habits that predispose them to xerophthalmia. The increased risk of xerophthalmia in some household and some communities is important in improving understanding of the underlying causes of vitamin A deficiency. It also provides us with an efficient way of improving vitamin A status by targeting siblings, mothers, and neighbours of children with xerophthalmia for vitamin A prophylaxis. Health workers in areas where vitamin A deficiency is endemic should be aware that behind every child they see with xerophthalmia are siblings, mothers, and neighbours with xerophthalmia or those who are vitamin A deficient and, therefore, at high risk of developing it in the near future.

International Vitamin A Consultative Group (IVACG) Statement on clustering of Xerophthalmia

Vitamin A deficiency is known to affect specific regions of the world and areas wtihin high-risk countries. It is now recognized that vitamin A deficiency also concentrates within high risk families and copmmunities. Siblings of xerophthalmic children are 10 times more likely to have xerophthalmia than siblings of children who do not have xerophthalmia. Mothers of xerophthalmic

children are 5 to 20 times more likely to be night blind (vitamin A deficient) than mothers of nonxerophthalmic children. In addition, neighbourng children of a xerophthalmic child are twice as likely to have or develop xerophthalmia than children in neighbourhoods where xerophthalmia has not been seen.

The fact that xerophthalmia "clusters" has clear relevance and application for treatment and prevention. Children presenting with xerophthalmia should be treated according to the World Health Organisation's WHO/UNICEF/IVACG guidelines. Their preschool siblings should be supplemented prophylactically with vitamin A according to the WHO/UNICEF/IVACG guidelines.

The family and especially the child's mother, should be provided appropriate counselling and other assistance to improve her dietary intakes of vitamin A as well as those of her children. Communities in which xerophthalmic children are present should be made aware of the problem, its consequences, and potential solutions. The local setting should be given special consideration in the context of population-based measures to prevent Vitamin A deficiency.

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MALARIA PROBLEM AND DRUG POLICY IN NEPAL

Global Problem

Malaria is probably the second most common infectious cause, after tuberculosis, of morbidity and mortality all over the World. It has been estimated that 300-500 million new clinical cases of malaria occur every year worldwide (more than 90% of which occur in tropical Africa), causing 1.5 to 2.7 million deaths, the great majority being recorded in African children.

Of the 1.4 billion population of the South-East Asia Region, it is estimated that 1.2 billion people live in malarious areas. Of the 10 countries in the Region, only DPR Korea and Maldives are free from indegenous cases of malaria.

In 1995, malaria cases in the Region were estimated at 21.9 million, with almost 32,000 deaths. Outside of Africa, two thirds of all the reported cases are concentrated in just six countries, of which two - India and Sri Lanka - are in the South-East asia Region. India accounted for more than 85% of the cases in the Region in the same year.

Problem in Nepal

In Nepal it was estimated that 2 million cases of malaria occured annually and 10-15% of them resulted in death before 1950. Not strange enough that the malarious areas of Terai and Inner Terai were stamped as "Kalapani". There was a phenomenal decline in the incidence during the malaria eradication era of the late 1950s and 1960s and the malaria cases came down to such a low level that the problem was erroneously thought to have been eradicated. But the truth was that with the resurgence of malaria inn the South-East Asia Region. Nepal also experienced malaria reappearing in epidemic proportions in the seventies, which reached a peak in 1974. since then the dynamics of malaria in Nepal has been characterised by periodic increase or decrease in the incidence over the years and occurence of epidemic every 7-8 years. From 1994 to 1997 the total cases recorded in th country were below 10,000 annually, out of which 10% were by *P. falciparum*. The low incidence rates of malaria may seem to be a very good achievement, but one should not be complacent only with these records. The incidence recorded could be a tip of an iceberg due to gross under-reporting of the malaria cases, which is evidenced by the gradual increase of slide positivity rate and recent outbreaks of *P. falciparum* malaria in Kanchanpur (1996) and Nawalparasi (1997) districts.

The burden of malaria is mainly in the forested areas. these areas produce more than 60% of the total malaria cases and 75% of the total *P. falciparum* cases of the country. Presently malaria problem districts in Nepal are Kanchanpur, Kailali, Dadeldhura, Nawalparasi, Mahottari, Dhanusha, Sindhuli, Morang, Jhapa, Kabhrepalanchowk and Sindhupalchowk.

Chloroquine resistance to imported *P. falciparum* was first reported in 1972. Indig-

enous *P. falciparum* resistantto chloroquine was detected in 19484 (micro *in-vitro* method). the areas affected are Jhapa, Morang, Udayapur, shanusha, Mahottari, Sindhuli, Makawanpur, Nawalparasi, Kailali, Kanchanpur and Dadeldhura.

Resistance of *P. falciparum* to sulfadoxine-pyrimethamine was suspected in 1993 and confirmed in 1996/97. Parasan Health Post in Kanchanpur and Pratappur Health Post in Nawalparasi are the facilities where such a resistance has been encountered.

The use of Anti-malaria in Nepal

In many instances the prescribing of anti-malarials in Nepal is not consistent with the Malaria Drug Policy. Either expensive and inappropriate antimalarials are prescribed or rightly prescribed drugs do not conform to correct dosages and regimens. The problem is further compounded by the fact that many people generally do not know enough about how malaria is caused and spread, and how it can be prvented. Some do not come for treatment on time while others do not have access to proper health care services. This creates a haphazard pattern of use of antimalarials and poor coompliance. The proble is becoming more difficult to manage because of the continuous intensification and spread of resistance to antimalarial drugs among the parasites (especially *P. falciparum*).

Table - 1

Guidelines for the use of antimalarials as per the National Malaria Drug Policy

Type of Malaria	*Drugs, dosages, and routes of administration*
Clinical	Chloroquine total 1500 mg over 3 days orally
P. vivax	Chloroquine total 1500 mg over 3 days + primaquine total 75 mg over 5 days orally
P. falciparum	Sulfadoxine 1500 mg + pyrimethamine 75 mg + primaquine 45 mg in a single dose orally
Suspected treatment failure of clinical malaria	Sulfadoxine 1500 mg + Pyrimethamine 75 mg + primaquine 45 mg in a single dose orally
Severe and complicated malaria	Quinine dihydrochloride/sulphate with an initial loading dose of 20 mg/kg body weight in 500ml isotonic saline or 5% dextrose infused at a constant rate over 4 hours and then continued with 10 mg/kg body weight at the same infusion rate 8-hourly. However, parenteral quinine dihydrochloride/sulphate is replaced by oral quinine tablets 10 mg salt/kg body weight 8-hourly for 7 days as soon as the patient becomes conscious and is able to swallow the tablets
Malaria in pregnancy : P. vivax P. falciparum	 Chloroquine total 1500 mg over 3 days orally Sulfadoxine 1500 mg + pyrimethamine 75 mg a single dose orally
Malaria in infants and children below 2 years	Chloroquine total 25 mg/kg bosy weight over 3 days

National Malaria Drug Policy

The National Malaria Drug Policy of Nepal conforms to the National Drug Policy of 1995. Chloroquine, primaquine, sulfadoxiine, pyrimethamine and quinine are all listed in the National List of Essential Drugs and are supplied free of cost by the government. However, currently only chloroquine and primawuine are manufactured locally at the Royal Drugs Limited, kathmandu. Quinine is reserved for the management of complicated and severe malaria cases at Primary Health CAre Centres and Hospitals, which have provision for qualified medical graduates.

Standard treatments specifying indications of antimalarial drug regimens, dosage, and routes of administration are given in Table 1.

- The dosages shown in the table represent adults dosages (>15 years of age with an average body weight of 60 kg): the dose for lower age groupos should be adjusted accordingly.

Dose Calculations

- The standard total dose of chloroquine is 25 mgkg body weight over 3 days (Day 1-10 mg/kg, Day 2 - 10 mg/kg, Day 3 - 5 mg/kg).
- The standard total dose of primaquine is 1.25 mg/kg bosy weight over 5 days (15 mg daily for 5 days).
- The standard total dose of sulfadoxine + pyrimethamine is 25 mg/kg body weight in a single dose.
- The standard total dose of quinine is 2.10 mg/kg body weight over 7 days (10 mg/kg body weight 8-hourly).

Some points to consider

- The above dtrugs should not be given on empty stomach.
- Premaquine should not be given to pregnant women and children below 2 years.
- Sulfadoxie-Pyrimethamine has no effect on P. vivax malaria.
- Inadequate doses may lead to the development of drug resistance.

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PROTEASE INHIBITORS FOR AIDS

The last one year has seen tremendous progress in the fight against acquired immunodeficiency syndrome (AIDS) by the introduction of a new class of anti-retroviral drugs known as protease inhibitors. In the initial trials, protease inhibitors were being used as reserve drugs - to be used only in the