Diabetes Mellitus

The term diabetes mellitus described as a clinical syndrome of multiple etiologies with disordered metabolism and inappropriate hyperglycemia due to either an absolute deficiency of insulin or to a combination of insulin resistance and inadequate insulin secretion to compensate. It affects the metabolism of carbohydrate, fat, and protein. The effect of this disease includes long term damage, dysfunction and failure of various organs with characterized common symptoms such as polyuria, polydipsia, polyphagia, weight loss etc. In its more severe forms keto acidosis or non- ketotic hyperosmolar state may developed and may leads to stupor, coma and in the absence of effective treatment causes death.

India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the "diabetes capital of the world". The so called "Asian Indian Phenotype" refers to certain unique clinical and biochemical abnormalities in Indians which include increased insulin resistance, greater abdominal adiposity i.e., higher waist circumference despite lower body mass index, lower adiponectin and higher high sensitive C-reactive protein levels. This phenotype makes Asian Indians more prone to diabetes and premature coronary artery disease. At least a part of this is due to genetic factors. However, the primary driver of the epidemic of diabetes is the rapid epidemiological transition associated with changes in dietary patterns and decreased physical activity as evident from the higher prevalence of diabetes in the urban population. Even though the prevalence of microvascular complications of diabetes like retinopathy and nephropathy are comparatively lower in Indians, the prevalence of premature coronary artery disease is much higher in Indians compared to other ethnic groups. The most disturbing trend is the shift in age of onset of diabetes to a younger age in the recent years. This
could have long lasting adverse effects on nation's health and economy. Early identification of at-risk individuals and appropriate lifestyle intervention would greatly help in preventing or postponing the onset of diabetes and thus reducing the burden on the community and the nation as a whole.

**Classification**

Several pathological processes involved in the development of diabetes. These range from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. Several distinct types of diabetes mellitus exist and are caused by complex interaction of genetics, environmental factors and life style choices. There are three main type of Diabetes:

- Type 1 diabetes
- Type 2 diabetes
- Gestational diabetes

Further Type 1 diabetes mellitus is divided in to Immune-mediated and Idiopathic (unknown mechanism). In immune-mediated Type 1 diabetes mellitus autoimmune Beta cell destruction leads to absolute insulin deficiency. Type 1 diabetes mellitus usually develops in childhood and adolescence and patients require lifelong insulin injection for survival.

Type 2 diabetes mellitus is divided in to obese and non-obese. It is caused predominantly due to obesity induced insulin resistance with insulin deficiency in late stage of the disease. Type 2 diabetes mellitus (T2DM) usually develops in adulthood and is related to obesity, lack of physical activity and unhealthy diets.

Gestational diabetes - Diabetes developed due to carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognized during pregnancy" is named as gestational diabetes (GDM).

**Epidemiology**

Diabetes the fourth or fifth leading cause of death in most high-income countries and there is substantial evidence that it is epidemic in many
economically developing and newly industrialized countries. The epidemiological evidences suggest that the incidence of diabetes is increasing worldwide.

According to the International Diabetic Federation (IDF) as on 2013, about 382 million people worldwide, or 8.3% adults, are estimated to have Diabetes. About 80% live in low-and middle-income countries. If these trends continue, by 2035, some 592 million people, or one adult in 10, will have Diabetes. This equates to approximately three new cases every 10 seconds or almost 10 million per year. Diabetes causes one death in every six seconds.

According to the Indian Council of Medical Research-Indian Diabetes study (ICMR-INDIAB), a national diabetes study - 2013, India has 62.4 million people with diabetes. This is set to increase to over 100 million by 2030. The majority of people with diabetes (>90%) have Type 2 diabetes (T2DM).

Diabetes is increasingly afflicting young and affluent urban people in India, reveals a survey of the diseases in 6 metros. The survey found that almost one in every eight person living in a metro is diabetic. The prevalence of diabetes was the highest in the urban (12.4%) areas, followed by the midland (8.1%), highland (5.8%) and coastal division (2.5%).

**Diagnosis**

In the recent era more importance are giving towards the diagnostic criteria of diabetes. All three tests – fasting plasma glucose (FPG), 2-hour plasma glucose (2-hour PG) and Glycosylated hemoglobin (HbA1c) – are able to predict the glucose levels that are diagnostic of diabetes. Furthermore, there is a relationship between elevated levels of all three markers and cardiovascular diseases, although the relationship is generally stronger for HbA1c.

The patient who have fasting blood sugar ≥126 mg/dl or PPBS ≥200 mg/dl or random blood sugar ≥200 mg/dl in two different occasion are diagnosed as diabetic patient, and/or elevated Glycosylated hemoglobin % (HbA1c) ≥6.5%.

"Study of Lagerstroemia speciosa (L.) Pers as a Hypoglycemic Agent" Page 140
FBS between 110-126 mg/dl and PPBS 140-200 mg/dl have been termed as impaired fasting glucose and impaired glucose tolerance respectively are at substantial risk for developing Type 2 DM and cardiovascular diseases.

**Screening**

All those who are above 40 years of age, obese, have family history of diabetes, hypertensive, female with PCOS or diagnosed as GDM, Impaired glucose tolerance, or impaired fasting glucose on previous testing, history of cardio-vascular diseases, other clinical conditions associated with insulin resistance elevated TG ≥150 mg/dl and reduced HDL <35 mg/dl, should be advised for screening test of diabetes time to time.

**Pathogenesis**

**Type 1 DM**

Type 1 DM develops as a result of the synergistic effects of genetics, environmental and immunologic factors that ultimately destroy the pancreatic beta cells. Type 1 diabetes mellitus is divided in to Immune-mediated and Idiopathic (unknown mechanism). In immune-mediated Type 1 diabetes mellitus autoimmune Beta cell destruction leads to absolute insulin deficiency. Type 1 diabetes mellitus usually develops in childhood and adolescence and patients require lifelong insulin injection for survival.

**Type 2 DM**

Type 2 DM is characterized by three pathological abnormalities.

a) **Impaired insulin secretion:** Insulin secretion and sensitivity are interrelated. In Type 2 DM, insulin secretion initially increases in responses to insulin resistance to maintain normal glucose tolerance. Eventually, the insulin secretory defects progresses to a state of grossly inadequate insulin secretion.

b) **Insulin resistance:** The decreased ability of insulin to act ineffectively on peripheral target tissues (especially muscle and liver) is a prominent feature of Type 2 DM and results from a combination of genetic susceptibility and obesity. Obesity particularly visceral or central (as evidenced by hip-waist ratio), is very common in Type 2 DM.
c) Excessive hepatic glucose production: In Type 2 DM, insulin resistance in the liver reflects the failure of hyperinsulinemia to suppress gluconeogenesis, which results in fasting hyperglycemia and decreased glycogen storage by the liver in the postprandial state. Increased hepatic glucose production occurs early in the course of diabetes, though likely after the onset of insulin secretory abnormalities and insulin resistance in skeletal muscle.

Prevention

Type 2 DM is preceded by a period of IGT, and a number of lifestyle modifications and pharmacologic agents prevent or delay the onset of DM. The diabetes prevention program demonstrated the intensive changes in lifestyle (diet and exercise for 30 minutes per day at least 5 days in a week) in individuals with IGT prevented or delayed the development of Type 2 DM. This effect was seen in individuals regardless of age, sex, or ethnic group. Metformin also helps in preventing or delaying diabetes. Individuals with a strong family history, those at high risk of developing DM, or those with IFG and IGT should strongly encouraged to maintain a normal body mass index (BMI) and engage in regular physical activity.

Management of Type 2 DM

Essential elements in comprehensive diabetes care of type 2 diabetes:

❖ Glycemic control
  ➢ Diet/lifestyle
  ➢ Exercise
  ➢ Medication

Oral Glucose Lowering Therapies in Type 2 DM

1. Insulin secretagogues: Increase insulin secretion
  ➢ Sulfonylureas
    • First generation: Chlorpropamide, tolazamide, tolbutamide
    • Second generation: Glimeoride, glipizide, glyburide
Non-Sulfonylureas

- Repaglinide, Nateglinide

2. Biaguanides: Metformin - Decreased hepatic glucose production, weight loss, increased glucose utilization, decreased insulin resistance.

3. α-Glucosides inhibitors: Decreased glucose production
   - Acarbose
   - Miglitol

4. Thiazolidinediones: Decreased insulin resistance, increased glucose utilization.
   - Rosiglitazone
   - Pioglitazone

5. Medical nutrition therapy and physical activity: Decreased insulin resistance, increased glucose utilization.

6. Insulin: Insulin plays an important role in the management of longstanding Type 2 DM. Insulin can be used in combination with any of OHA in patients who fails to reach the glycemic target.

Ayurvedic literature review

In Ayurvedic literature review, it can be inferred that Prameha is likely to be synonymous of diabetes mellitus. Basically Prameha seems to be one disease, of course due to vitiation in the aetiological factors Dosa and Dushya, the clinical manifestation differs, giving rise to three different types of Prameha i.e. Vataja, Pittaja, Kaphaja, which is further sub divided in to 20 sub types –
   ❖ 10 Kaphaja,
   ❖ 6 Pittaja and
   ❖ 4 Vataja.

20 subtypes of Prameha are not associated with diabetes. Most of them can be found independently in various systemic and metabolic disease or they can be attributed to different urological or nephrological problems.

In Ayurveda almost all the diseases are arranged or divided in the following sequence i.e. Vataja, Pittaja and Kaphaja. But Prameha is in

"Study of Lagerstroemia speciosa (L.) Pers as a Hypoglycemic Agent" Page 143
exception because this disease is arranged in the sequence of Kaphaja, Pittaja 
and Vataja. Prameha is Kapha oriented disease and whatever the aetiological 
factors described in general all aggravated Kapha first followed the other dosas. 
Vagabhatta also clearly mentioned that Paittik and Vatik Prameha occur when 
there will be relative predominance of these two dosas and Kapha diminished 
due to progression of the disease.

Classification of Prameha was found to have striking similarly towards 
the recent aetiopathological classification. For example Prameha has been said 
to be of two types –

1. Sahaja (Hereditary) 
2. Apathyanimitija (Acquired).

The Sahaja or Beejadosaja Prameha manifest due to the defects in the 
Beeja (sperm or ovum), Beejabhaga (chromosome) and Beejabhagaababayaba 
(genes). This disease may be manifest from birth (congenital) or may develop 
later on i.e. Hereditary. So this version indicated that the insulin dependent 
(Type 1) diabetes in modern science same as that of Sahaja Prameha. 
However the Apathyanimitija Prameha are caused due to indulgence of 
excessive Madhur, Singdhadravya along with sedentary life style which results 
dosadusti and Medadhatudusti after Ama formation and simultaneously it also 
vitiates the other dhatus and produce the disease Prameha by creating 
excessive urination and turbidity in urination. In specific aetiopathogenesis of 
Kaphaja Prameha, it has mentioned that due to the above causative factors 
Kaphadosa gets vitiates, spread throughout the body and effect the Medadhatu 
(BadhaMedadhatu) transferred to Abadhameda. The vitiated dosa is 
Bahudravyasleshma. If we go back through the modern review, it has cleared 
that obese patient are in a state of hyperinsulinemia which is future responsible 
for insulin resistance and causes hyperglycemia. As the disease progress 
insulin secretion is decreases, simultaneously fats and protein breakdown starts 
to supply the energy to the tissue because glucose cannot penetrate to the 
tissue. So that excessive free fatty acid, amino acid cholesterol, triglyceride etc. 
will be accumulated in the blood and plasma. This entire process is similar as

"Study of Lagerstroemia speciosa (L.) Pers as a Hypoglycemic Agent" Page 144
pathogenesis of Type 2 diabetes comparing Bahudravasleshma with hyperinsulinemia, Badhamedadhatu with the fat depots, dushitakle다 with the F.F.A, Mamsadusti as protein breakdown, dushitakle다 with the increased glucose level in blood along with the fats and protein bi-product. Pitta Prameha causes due to hyper activation of adrenal, cortisol, glucagons and thyroid hormone as well as Vatik Prameha causes due to the absolute lack of insulin.

As Charaka, Sushruta and Vagabhatta all of them mentioned that if all the Prameha remains untreated then it transformed to Madhumeha. This view directly indicates or support with the modern medicine where some of the type 2 patient needs insulin to control their blood sugar. The main dosa of Prameha is bahudravasleshma and dushyas are meda, mamsa, kleda. So while treating a patient with Prameha (on later stage DM) he advised to choose drugs having qualities opposite to dhusyas.

Prognostic classification also support that Vatik Prameha is Asadhya as the patient is asthenic along with faster deep seated dhatu vitiation.

Most of the diabetic patient diagnosed after developing of complication. So our ancient author includes the presenting pre diagnostic symptoms as premonitory sign and symptoms. In this era also it has been observed that so many patient developed neuropathy, repeated infection etc. and diagnosis made when they were checked for that above complains. In complication point of view Ayurveda says all of the complication whatever described by modern science after various experiment, except retinopathy. Even in relation to dushya of Prameha indicating vitiation of all the dhatus along with Ojas except Asthidhatu. In modern science it has been observed that diabetes does not spares any system except bony structure. Ayurveda emphasized all of the minor complications up to the serious complications i.e. Hridsula (angina or, IHD), Swas (diabetic keto acidosis induced dyspnea, Murcha (syncope or, coma) and may be developed Hridgraha (cardiac arrest) which leads to death.

Madhumeha is the progressive stage of all these Prameha and may also manifest as a single disease due to excessive Vatavridhi. So that
dhatukshayajanna Mahumeha is nothing but the complicated type 2 diabetes or other specific type 2 diabetes, Avritavatajanna may be purely type 2 diabetes and vataprakaopajanna purely insulin deficient state or type 1 diabetes.

Vagabhatta nicely mentioned that all the Prameha possess sweetness all over the body (hyperglycemia) followed by Madhumeha (glycosuria) in its complicated course.

In the management point of view also all the text have given more importance on diet, exercise, lifestyle modification and medicine as like as modern medicine today. In classics it has been mentioned that one should treat the patient according to their built and strength of the body i.e. for obese patients one should go for purification i.e. samsodhanachikitsa to remove the toxins and for the lean and weak patients the physician should do treatment with Brimhana therapy i.e. anabolic treatment with caution.

Sodhanachikitsa re-establishes the basic hormonal metabolism which are disarrange in diabetes. By sodhanachikitsa functional and structural inhibition such as insulin resistance, insulin insufficiency and obstructive pathology in hyperglycemia is being corrected. With these peripheral utilization of glucose is enhanced and the deranged lipid metabolism and excessive storage of fat is corrected to re-establish the functional equilibrium of tridoshas. Moreover, the neuroendocrine functions controlled by Vata. By Vasti the deranged functions of vata are corrected and re-establish the glucose and lipid metabolism. By Vamana also, the obstruction due to kapha, which is a predominant factor in this pathological condition, is corrected.

Madhumeha is a progressive stage of all Prameha and may manifest as a single disease as a sub-type of vatic Prameha. As vata increases mainly due to dhatukshya and vataavarana. Dhatukshayajanya vatic Prameha can be compared with type 1 DM, where the patients become emaciated due to dhatukshaya and tarpana (anabolic therapy) is indicated. It can be compared to insulin therapy, which is an anabolic hormone. Type 2 DM is similar to avaranjanya vatic Prameha, due to hyperinsulinemia and can be said to be due
to kaphavritavata and treated life-style modifications and medications where needed.

For the study, Lagerstroemia speciosa (Jarul/ Tinish/ Ajhar) leaves powder was taken whose taste (rasa) is Kasaya and Katu, which can decreased Kapha. This drug has Laghu and Rukshaguna which also helps in suppression of kaphadosa. This drug has been also mentioned in BhavaprakashNighantu (Ayurvedic classic of 16 century) in Vatadivarga and which have hypoglycemic action. So that to see the dravyapravaba, gunapravaba and dravyagunapravaba this plant has been selected.

The active principles of the plant which act as insulin like action is Corosolic Acid and others active principles are lagerostromin and Lagertannins. Corosolic acid activates the transport of glucose across the cell membrane, resulting blood sugar reduction. It has inhibitory effects on post prandial hyperglycemia by inhibiting alpha-amylase and alpha-glycosidase. Lagerstroeminis an ellagitannin works as insulin receptor activator by increasing tyrosine- phosphorylation of the sub-unit of insulin receptor. Lagertannins stimulates glucose transport and adipocyte differentiation inhibitory activity in 3T3 – L1 cells as adipogenesis, the differentiation and proliferation of adipocytes is a major mechanism leading to weight gain and obesity. On the other hand the above plant have the capacity to decreased obesity and increased insulin sensitivity of the tissue along with blood glucose lowering effect, seen after various experiment mentioned in the drug review.

100 patients of type 2 diabetes mellitus were selected from Govt. Ayurvedic College & Hospital, Guwahati and North Eastern India Ayurveda Research Institute, Bhetapara, Guwahati, Assam, which have fulfilled the inclusion criteria. An open non-comparative clinical trial was done with Lagerstroemia speciosa leaves powder in the dose of 12 grams daily in two divided dose ½ hour before breakfast and dinner with warm water for 3 months. Every one month interval patient was advised to come for the follow-up up to 3 consecutive occasions. In each follow-up FBS, PPBS done routinely and Glycosylated hemoglobin (HbA1C) tested before and after completion of
treatment. All the patients are advised for diet control and exercise described in literary review.

The assessment of the result of the clinical trial was determined by the significant changes in FBS, PPBS and HbA1c.

In the general clinical profile shows the whole demographic, clinical and laboratorial status of the patients.

The present clinical study of Age and Sex incidence in patients of Type 2 Diabetes mellitus revealed maximum number of patients reported in between 41 – 50 years (41%) and 51 – 60 years (40%) followed by 61 – 70 years (13%).

This indicates that Type 2 Diabetes mellitus is due to faulty dietary habit and ultra-modern lifestyle. Incidence of Type 2 Diabetes mellitus in India is higher in female than male. The study of sex incidence revealed that the maximum number of patients are female (52%) followed by male (48%).

Study of socioeconomic status showed that incidence of maximum number of Type 2 Diabetes mellitus cases from the higher income group (44%) followed by middle income group (40%), and hence least from the lower income group (16%).

This shows the prevalence of Type 2 Diabetes mellitus in the higher section of society due to their sedentary habit.

Among the 100 cases of Type 2 Diabetes mellitus more patients are from urban (72%) area followed by rural area (28%). The habitat shows that maximum urban people were affected has because of sedentary and stressful life style.

Findings of the present study have shown that the incidence of this diseases is more in graduate/ P.G. (62%) followed by secondary educated people (20%) and illiterate people (3%) as high educated people maintained their sedentary and stressful lifestyle. In present study in 100 cases of Type 2 Diabetes mellitus shows servicemen (38%), housewife (30%) are highly affected due to their low physical activity similarly of businessman (29%), so that excess fat deposition may triggered to the development of diabetes.
In this area more patients are non-vegetarian, so our studies also shows that incidence are more among non-vegetarian (94%) followed by vegetarian (6%). Non-vegetarian is highly affected because of high intake animal fats and low intake dietary fibers.

Regarding the addiction in Type 2 Diabetes mellitus 30% patient having no addiction, where maximum number betel/ tobacco (33%) followed by smoker patient (25%) and alcohol (12%). Alcohol and smoking both of these factors are the most risk factors to develop Type 2 Diabetes mellitus, have been already established.

Regarding incidence in physical activities more patients are mild active (60%) followed by moderate active (32%) and severe active (8%).

Similarly BMI of the 100 patient more are in over weight group (52%) followed by non-obese (40%) and obese (8%). These all factors increase insulin resistance leading to developing diabetes.

Among 100 patients in our study (38%) patient have positive family history and rest (62%) were negative family history.

Statistical evaluation was done in laboratorial parameters after calculating mean, SD, SE, Z and P value.

Effect of the drugs has been observed by calculating the Z value of mean difference between before after treatment.

Effect of treatment on fasting blood sugar (FBS) is shows statistically highly significant. FBS values before treatment i.e. Mean ± SD is 168 ± 36 and values after treatment are: Mean ± SD is 135 ± 19.5, SE value is 4.09 and Z value is 7.33 which is highly significant (P< 0.01).

Similarly effect of treatment on post prandial blood sugar (PPBS) is shows statistically highly significant. PPBS values before treatment i.e. Mean ± SD is 202 ± 44.4 and values after treatment are: Mean ± SD is 166 ± 26.4, SE value is 5.16 and Z value is 6.97 which is highly significant (P< 0.01).

Effect of treatment on HbA1c is as follows, before treatment: Mean ± SD is 7.3 ± 0.76, and after treatment: Mean ± SD is 6.5 ± 0.41, SE value is 0.086 and Z value is 9.3 which is also very highly significant (P< 0.01).
From the above observation regarding effect of treatment on FBS and PPBS, it have seen that decreasement of blood sugar is more in PPBS comparing to that of FBS. So we can conclude that the effect the drug is most in PPBS not only in terms of increased peripheral glucose utilization but we cannot denied the drugs have also some role in insulin secretion and by decreasing glucose absorption from the GIT. As it also decreases the FBS significantly, so it has also effect on hepatic glucose metabolism, like enhancing glycogen formation & storage and reducing glycogenolysis and gluconeogenesis.

In all cases blood sugar falls in sequential manner and not showed any unwanted hypoglycemic effect even the blood sugar may be slightly in a high range before treatment. This study directly support that the trial drugs has no any unwanted hypoglycemic affect.

Effect of treatment on Glycosylated hemoglobin (HbA1c) is shown statistically highly significant after 3 months of treatment (P<0.01). That means our trial drugs can control the blood sugar for longer duration.

In study it has been observed that our trial drugs act as a mild purgative.