DIABETES MELLITUS. A REVIEW.

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Summary

Diabetes mellitus is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action or both. In 2006, according to the World Health Organization, at least 171 million people world wide suffer from diabetes mellitus and is estimated that by the year 2030, this number will double. The major symptom of diabetes mellitus includes excessive thirst, frequent urination, increased appetite, weakness, fatigue and weight loss. Insulin is the principal hormone that regulates uptake of glucose into most cells from the blood and deficiency of insulin or insensitivity of its receptor cells plays a central role in all forms of diabetes mellitus. There are two major types of diabetes mellitus namely type 1 diabetes and type 2 diabetes. The complication of diabetes mellitus includes long-term damage, dysfunction and failure of various organs of the body. Some risk factors of diabetes mellitus include genetic predispositions, obesity and age. The primary goal in the management of diabetes is to control blood sugar levels. In the type 1 Diabetics, this requires regular insulin injections whereas in type 2 diabetes dietary modification is required. Breastfeeding has been documented to decrease the risk of type 1 diabetes while type 2 diabetes risks can be reduced by making changes in diet and increasing physical activity. To stem the economic, social and health implications of diabetes mellitus, the government of member nations of the United Nations should encourage more research on diabetes mellitus especially researches exploiting different treatment options like herbal medicine. It is also necessary to subsidies the cost of oral hypoglycaemic drugs and insulin injections used by diabetics especially in developing countries so that diabetics can easily afford them.

Keywords: Diabetes mellitus, Diagnosis, Complications, Management, Risk factors

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Introduction

The term diabetes mellitus describes a metabolic disorder of multiple etiologies characterized by chronic hyperglycaemia (high blood sugar) with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both (1). The effect of diabetes mellitus includes long-term damage, dysfunction and failure of various organs of the body. Diabetes mellitus may present characteristic symptoms such as thirst, polynuria, blurring of vision and weight loss (1). In its most severe forms, ketoacidosis or non-ketotic hyperosmolar state may develop and lead to stupor, coma and in absence of effective treatment death (1). Diabetes mellitus is characterized by recurrent or persistent hyperglycaemia and other signs, as distinct from a single illness or condition.

Epidemiology and Statistics of Diabetes Mellitus

In 2006, according to the World Health Organization, at least 171 million people world wide suffer from diabetes mellitus (2). Its incidence is increasing rapidly and it is estimated that by the year 2030, this number will double (2). Diabetes is a common and very prevalent disease affecting the citizens of both developed and developing countries (3). The greatest increase in prevalence is however expected to occur in Asia and Africa, where more patients will likely to be found by 2030. In 2005, there are about 20.8 million people with diabetes in the United States alone. (2) reported that there are about 6.2 million people undiagnosed and about 41 million people that would be considered prediabetic. The national diabetes information clearing house estimates that diabetes costs $132 billion in the United States alone every year. (2) pointed out that 1 in 3 Americans born after year 2000 will develop diabetes in their lifetime. Statistical projections from India suggested that the number of diabetes will rise from 15 million in 1995 to 57million in the year 2025 making India the country with the highest number of diabetics in the world (4; 5). Although there is a paucity of data on the prevalence of diabetes in Nigeria and other African countries, available data suggested that diabetes was emerging as a major health problem in Africa (6). The prevalence of diabetes in Nigeria was estimated to be between (1.4 to 2.7) % of the population (7, 8, 9) and over 90% of these are non–insulin dependent diabetes mellitus (10). Diabetes mellitus has been reported to be the major cause of blindness, kidney failure, lower-extremity amputation, cardiovascular diseases and premature mortality (11).

Diagnosis of Diabetes Mellitus

The major symptoms of diabetes mellitus include excessive thirst, frequent urination, increased appetite, weakness, fatigue and weight loss (in Type 1) (12). Other symptoms may include muscle cramps, impaired vision, poor wound healing and in women itching due to vaginal yeast infection (12). (1) reported that diabetes mellitus can be diagnosed by demonstrating any one of the following:

i. fasting plasma glucose level at or above 126mg/dl (7.0mmol/l).
ii. plasma glucose at or above 200mg/dl or 11.1mmol/l two hours after a 75g oral glucose load as in a glucose tolerance test.

iii. random plasma glucose at or above 200mg/dl or 11.1mmmol/l.

When the glucose concentration in the blood is high (above the renal threshold) re-absorption of glucose in the proximal renal tubules is incomplete and part of the glucose remains in the urine (glycosuria). This increases the osmotic pressure of the urine and thus increases the reabsorption of water by the kidney resulting in an increased urine production (polyuria) and an increased fluid loss. Lost blood volume will be replaced osmotically from water held in body cells, causing dehydration and increased thirst. Prolonged high blood glucose causes glucose absorption and so leads to changes in the shape of the lenses of the eyes, leading to vision changes (1). Blurred vision is a common complaint leading to diabetes mellitus diagnosis. Type 1 diabetes should always be suspected in cases of rapid vision changes whereas Type 2 is generally more gradual, but still can be suspected (1). One can frequently make a diagnosis of Type 1 diabetes mellitus simply by smelling acetone on the breath of a patient (13). Also ketoacid can be detected by chemical means in the urine and their quantitation aids in determining the severity of the diabetes (13).

Insulin and Diabetes Mellitus

Insulin is the principal hormone that regulates the uptake of glucose into most cells from the blood (especially muscle and fat cells but not central nervous system cells) (14). Deficiency of insulin or insensitivity of its receptor cells plays a central role in all forms of diabetes mellitus (14). Insulin is a hormone secreted by the beta cells of the pancreas and is a small soluble protein which contains 51 amino acids residues arranged in two chains (A and B) (15). The A chain contains 21 and the B chain 30 acid residues. The chains are cross linked by two sulphur bridges between cytosine residues. The insulin molecule has been synthesized from its constituent amino acids. The molecular weight of insulin is 6000. Insulin is formed by proteolytic cleavage of its 84 amino acid precursor, pro-insulin, which has very little biological activity. There are small differences in amino acid composition among the insulin obtained from different species of animal (15). This does not affect their characteristic biological activity but it does account for the fact that insulin from one animal species may promote antibody formation when injected into another species (15). Insulin from cattle or sheep is for this reason liable to produce allergic reactions in some diabetic patients, where as pig insulin which has more close resemblance to human insulin in structure, is much better tolerated (15)

Insulin and Blood Glucose Regulation

Immediately after a high carbohydrate meal, the glucose that is absorbed into the blood causes rapid secretion of insulin (13). The insulin in turn causes rapid uptake, storage and use of glucose by almost all tissues of the body but especially by the muscle, adipose tissue and liver. Insulin promotes muscle glucose uptake and metabolism, storage of glycogen in muscle and facilitates glucose transport through the muscle cell membrane (13). Insulin production is more or less constant within the beta cells, irrespective of blood glucose levels. It is stored within vacuoles pending release, via exocytosis, which is triggered by increased blood glucose levels. If the amount of insulin available is insufficient and cells respond poorly to the effects of insulin (insulin insensitivity) or the insulin itself is defective, glucose will not be handled properly by body cells as much as stored appropriately in the liver and muscles (14). The net effect is persistent high levels of blood glucose, poor protein

and other metabolic derangement, such as acidosis (14). The maintenance of blood glucose homeostasis is a particularly important function of the pancreas (16). Circulating glucose concentrations are determined by the balance that exists among the following processes (Figure 1): glucose absorption from the digestive tracts, transport of glucose into cells, cellular (primary hepatic) glucose production and abnormal urinary excretion of glucose (16)

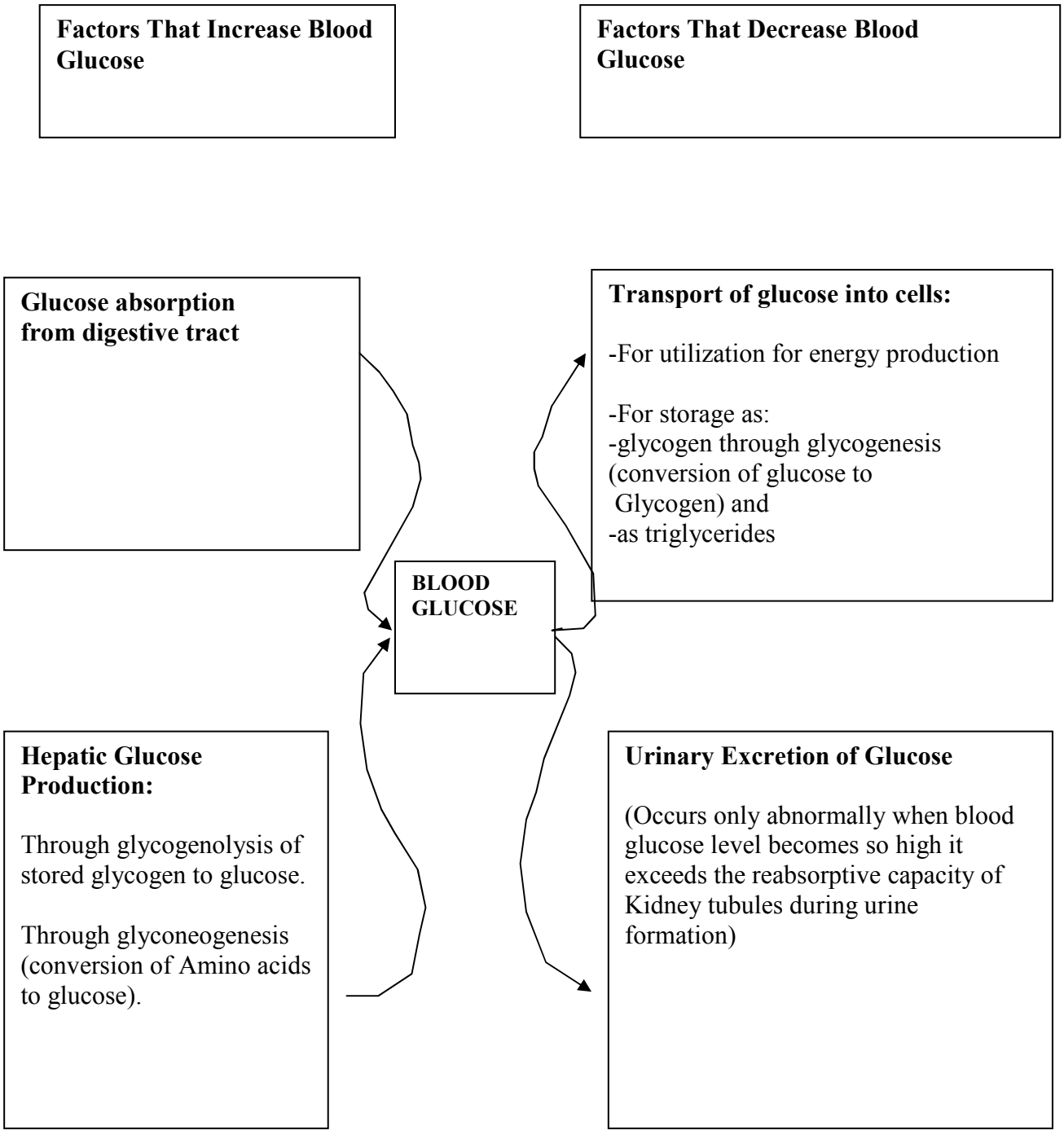

Figure 1: Factors affecting blood glucose concentration. Source: (16).

(13) explained the mechanism for achieving high degree of blood glucose control as follows:

1. The liver functions as an important blood glucose buffer system. When the blood glucose level rises to a high concentration after a meal and the rate of insulin secretion also increases as much as two thirds of the glucose absorbed from the gut and is almost immediately stored in the liver in the form of glycogen. Then during the succeeding hours, when both the blood glucose concentration and the rate of insulin secretion fall, the liver releases the glucose back into the blood.
2. Both insulin and glucagons function as important feed back control systems for maintaining a normal glucose concentration. When the glucose concentration rises too high, insulin is secreted, the insulin in turn causes the blood glucose concentration to decrease toward normal. Conversely, a decrease in blood glucose levels stimulates glycogen secretion, the glycogen then functions in the opposite direction to increase the glucose toward normal.
3. In severe hypoglycemia, a direct effect of low blood glucose on the hypothalamus stimulates the sympathetic nervous system. In turn, the epinephrine from the adrenal glands causes further release of glucose from the liver. Thus helps protect against severe hypoglycemia.
4. Over a period of hours and days, both growth hormone and cortisol are secreted in response to prolonged hypoglycemia and they both decrease the rate of glucose utilization by most cells of the body, converting instead to greater amount of fat utilization.

It is important to maintain a relatively constant blood glucose concentration because glucose is the only nutrient that is normally used by the brain, retina and germinal epithelium of the gonads in sufficient quantities to supply them optimally with their required energy (13).

Action of Insulin on Fat metabolism

(16) explained that insulin exerts multiple effects in the lowering of blood fatty acids levels and promote triglyceride storage thus:

1. It increases the transport of glucose into adipose tissue cells by means of GLUT- 4 recruitment. Glucose serves as a precursor for the formation of fatty acids and glycerol, which are the raw materials for triglyceride synthesis.
2. It activates enzymes that catalyze the production of fatty acids from glucose derivatives.
3. It promotes the entry of fatty acids from the blood into adipose tissue cells.
4. It inhibits lipolysis (fat breakdown), thus reducing the release of fatty acids from adipose tissue into the blood.

Collectively, these actions favor removal of glucose and fatty acids from the blood and promote their storage as triglycerides.

Action of Insulin on Protein Metabolism

(16) explained that insulin lower blood amino acid levels and enhances protein synthesis through several effects:

1. It promotes the active transport of amino acids from the blood into muscles and other tissues. This effect decreases the circulating amino acid level and provides the building blocks for protein synthesis within the cells.
2. It increases the rate of amino acid incorporation into protein by stimulating the cells protein synthesizing machinery.
3. It inhibits proteins degradation.

To cap it up, insulin stimulates biosynthetic pathways that lead to increased glucose utilization, increased carbohydrate and fat storage and increased protein synthesis (16). In so doing, insulin lowers the blood glucose, fatty acid and amino acid levels.

Types of Diabetes Mellitus

(17) reported that there are two major types of diabetes mellitus:

1. Type 1 Diabetes, also called insulin dependent diabetes mellitus (IDDM), is caused by lack of insulin secretion by beta cells of the pancreas.
2. Type 2 Diabetes, also called Non-insulin Dependent Diabetes Mellitus (NIDDM), is caused by decreased sensitivity of target tissues to insulin. This reduced sensitivity to insulin is often called insulin resistance.

Type 1 Diabetes Mellitus (IDDM)

Type 1 diabetes mellitus – formerly known as insulin dependent diabetes (IDDM), childhood diabetes or juvenile diabetes, is characterized by loss of the insulin producing beta cells of the islets of langerhans of the pancreas leading to a deficiency of insulin (14). There is no known preventive measure that can be taken against Type 1 diabetes. Most people affected by Type 1 diabetes are otherwise healthy and of a healthy weight when onset occurs. The main cause of beta cell loss leading to Type 1 diabetes is a T-cell mediated autoimmune attack (14). The principal treatment of Type 1 diabetes is replacement of insulin. The average glucose level for the Type 1 patient should be as close to normal (80 – 112mg/dL or 4 – 6mmol/L) as possible. Values above 200mg/dL (10mmol/L) are often accompanied by discomfort and frequent urination leading to dehydration (18). The usual onset of Type 1 diabetes occurs at about 14years of age in the United States and for this reason it is often called juvenile diabetes mellitus. (13) reported that Type 1 diabetes may develop very abruptly, with three principal sequelae:

1. increased blood glucose (hyperglycaemia)
2. increased utilization of fat for energy and for formation of cholesterol by the liver.
3. depletion of the body's protein

There is a world wide increase in the incidence of Type 1 diabetes and it is estimated to be 40% higher in 2010 than in 1998 (19).

Type 2 Diabetes Mellitus (NIDDM)

Type 2 diabetes mellitus – previously known as adult – onset diabetes, maturity onset diabetes mellitus is due to a combination of defective insulin secretion and insulin resistance or reduced insulin sensitivity (defective responsiveness of tissues to insulin), which almost certainly involves the insulin receptors in cell membranes (18). The cause and mechanism of insulin resistance are:

i. Central obesity (fat concentrated around the waist in relation to abdominal organs and not subcutaneous fat) is known to predispose individuals for insulin resistance possibly due to its secretion of adipokines that impair glucose tolerance. Obesity is found in approximately 55% of patients diagnosed with Type 2 diabetes (18).

ii Aging (about 20% of elderly patients are diabetic in North America).

iii Family history (Type 2 is much more common in those with close relatives who have had it). Type 2 diabetes is usually first treated by attempts to change physical activity, the diet (generally to decrease carbohydrate intake) and weight loss (14). These can restore insulin sensitivity, even when the weight loss is modest. The usual next step is treatment with oral antidiabetic drugs (sulfonylurea, metformin, and thiazolidinediones). Present modality of treatment only prevents some of its devastating complication and does not eliminate all the adverse consequences (19). Lack of exercise and obesity are considered major contributors to Type 2 diabetes, roughly 90% of individuals with Type 2 diabetes are obese (12). Obesity, insulin resistance and metabolic syndrome usually precede development of Type 2 diabetes. Insulin resistance results in increased fasting and postprandial beta cell synthesis which leads to beta cell burn out and eventually, diabetes (12). The condition of insulin resistance may exist for many years before pancreatic beta cell function actually becomes impaired. In addition to diabetes, insulin resistance and the resultant hyperinsulinemia are associated with an increased risk for coronary artery disease and high blood pressure (12). Insulin resistance is part of a cascade of disorders that is often called the metabolic syndrome. (13) reported some of the features of the metabolic syndrome which includes:

1. Obesity, especially accumulation of abdominal fat.
2. insulin resistance
3. fasting hyperglycaemia
4. lipid abnormalities, such as increased blood triglycerides and decreased blood high density lipoprotein cholesterol
5. Hypertension.

Complications of Diabetes Mellitus

Diabetes is the seventh leading cause of death in the United States (12).Unfortunately, it can go undiagnosed until one of its life threatening complications develops. The acute consequences of diabetes mellitus can be grouped according to the effects of inadequate insulin action on carbohydrate, fat and protein metabolism. These effects ultimately cause death through various pathways. Numerous long term complications of diabetes mellitus frequently occur after 15 to 20 years despite treatment to prevent the short-term effects (16). Chronic elevation of blood glucose level leads to damage of blood vessels (angiopathy) (20). The endothelial cells lining the blood vessels take in more glucose than normal, since they don't depend on insulin. They then form

more surface glycoproteins than normal and cause the basement membrane to grow thicker and weaker. In diabetes, the resulting problems are grouped under micro vascular disease and macro vascular disease. (20) reported that damage to small blood vessels leads to a microangiopathy causing the following:

(i) Diabetic retinopathy- growth of friable and poor-quality new blood vessels in the retina which can lead to severe vision loss or blindness.

(ii) Diabetic neuropathy progressive damage to the nerves. It most commonly affects the legs, causing pain or numbness working up from the feet.

(iii) Diabetic nephropathy – progressive damage to the kidney. It is manifested as an excessive linkage of protein into the urine followed by gradual decline of the kidney function and even kidney failure.

(20) explained that macrovascular disease leads to cardio-vascular diseases such as:

i. Coronary artery disease, leading to angina or myocardial infarction (heart attack).
ii. Stroke (mainly the ischemic type)
iii. Peripheral vascular disease, which contributes to intermittent claudicating as well as diabetic foot.
iv. Diabetic myonecrosis (muscle wasting).

About 85% of all diabetics develop retinopathy, 25-50% develops kidney disease and 60-70% has mild to severe forms of nerve damage (12). Diabetics are also 2 to 4 times more likely to develop cardiovascular disease and 2 to 4 times more likely to suffer a stroke (12).

Some Risk Factors of Diabetes Mellitus

1. Genetic factors

Both type 1 and type 2 diabetes are at least partly inherited. Type 1 diabetes appears to be triggered by some (mainly viral) infections or in a less common group by stress or environmental exposure (such as exposure to certain chemicals or drugs). There is a genetic element in individual susceptibility to some of these triggers which has been traced to particular HLA genotypes (the genetic self identifiers relied upon by the immune system). However, even in those who have inherited this susceptibility, type 1 diabetes mellitus seems to require an environmental trigger. A small proportion of people with type 1 diabetes carry a mutated gene that causes maturity onset diabetes of the young. Wolfram's syndrome – wolfram's syndrome is an autosomal recessive neurodegenerative disorder that first becomes evident in childhood. It consists of diabetes insipidus, diabetes mellitus, optic atrophy, and deafness, hence the acronym DIDMOAD (21). There is a stronger inheritance pattern for type 2 diabetes. Those with first degree relatives with type 2 diabetes have a much higher risk of developing type 2 diabetes, increasing with the number of those relatives. Concordance among monozygotic twins is close to 100% and about 25% of those with the disease have a family history of diabetes. Candidate genes include KCNJ11 (potassium inwardly rectifying channel, subfamily J, member 11), which encodes the islet ATP sensitive potassium channel KIR6.2 and TCF7L2 (transcription factor 7 – like 2), which regulates proglucagon gene expression and thus the production of glucagons like peptide-1 (14).

2. Obesity

Obesity is another risk factor of diabetes mellitus, particularly central obesity (that is in and around abdominal organs), which is found in approximately 85% of North American Patients diagnosed with diabetes, most experts believe that inheriting a tendency toward obesity also contributes to developing diabetes mellitus..

3. Aging

According to the American Diabetes Association, approximately 18.35% (8.6 million) of Americans aged 60years and older have diabetes. Diabetes mellitus prevalence increases with age and the numbers of older persons with diabetes are expected to grow as the elderly population increases in number. The National Health and Nutrition Examination Survey (NHANES III) demonstrated that, in the population over 65 years old, almost 18% to 20% have diabetes. Regarding another study more than 40% 0f Americans 65 years and older meet diagnostic criteria for type 2 diabetes or IGT impaired glucose tolerance (22). Older Americans are also more likely to have complicating conditions such as retinopathy, hypertension, and kidney problems. The way diabetes is managed changes with age. Insulin production decreases because of the age- related impairment of pancreatic beta cells. Insulin resistance increases due to the loss of lean tissue and the accumulation of fat, particularly intra-abdominal fat and the decreased tissue sensitivity to insulin. Glucose tolerance progressively declines with age and there is a high prevalence of type 2 diabetes in the older population (22). Age – related glucose intolerance in humans is often accompanied by insulin resistance but circulating insulin levels are similar to those of younger people. (23). Researchers and clinicians agree that treatment goals for older patience with diabetes need to be individualized and take into account health status, as well as life expectancy, level of dependence and willingness to adhere to a treatment regimen. (24).

Management of Diabetes Mellitus

Diabetes mellitus is currently a chronic disease, without a cure and medical emphasis must necessarily be on managing and avoiding possible short terms as well as long term diabetes – related problems. The primary goal in the management of diabetes is to control blood sugar levels (12).

Management of Type 1 diabetes mellitus

.Type 1 Diabetes management requires regular insulin injections. The theory of treatment of Type 1 diabetes mellitus is to administer enough insulin so that the patient will have carbohydrate, fat and protein metabolism that is as normal as possible (13). When blood glucose homeostasis, is not maintained, pathological complications begins to manifest.

Management of Type 2 diabetes mellitus

Type 2 diabetes management requires dietary modification including the strict control of simple carbohydrate intake and increasing the percentage of complex carbohydrate as well as fiber (12). (13) stated that in persons with Type 2 diabetes, dieting and exercise are usually recommended in an attempt to induce weight loss and reverse the insulin resistance. (12) reported that for people with Type 2 diabetes the use of insulin and oral hypoglycaemic drugs such as sulphonylureas and biguanidines are necessary to help keep blood glucose at a normal level. Additionally, dietary supplements such as chromium may provide benefit to diabetic individuals. The benefits of vitamin E,

magnesium and other nutrients are well documented. In recent years, several plant extracts have been examined for antidiabetic activity in an effort to identify alternative treatment strategies that pose less of risk for diabetes (25, 26, 27).

Prevention of Diabetes Mellitus

Type 1 diabetes risk is known to depend upon a genetic predisposition based on HLA types (particularly types DR3 and DR4), an unknown environmental trigger and an uncontrolled autoimmune- response which attacks the insulin producing beta cells (28). Research from the 1980s suggested that breastfeeding can prevent the risk of type 1 diabetes (29), various other nutritional risk factors are being studied, but few have a strong link with the development of type 1 diabetes (30).Type 2 diabetes risk can be prevented in many cases by making changes in diet and increasing physical activity (31, 32). Maintaining a healthy weight, getting at least two and half hours of exercise per week (marathon intensity or duration is not needed; a brisk sustained walk appears sufficient at present), have a modest fat intake and eating a good amount of fiber and whole grains. Magnesium may play a significant role in preventing type 2 diabetes (33). Although they do not recommend alcohol consumption as preventive, they noted that moderate alcohol intake (at or below one ounce of alcohol per day depending on body mass) may reduce the risk. They stated that there is not enough consistent evidence that eating foods of low glycemic index is helpful, but nutritious, low glycemic-index (low carbohydrate0 foods are encouraged. Some studies have shown delayed progression to diabetes in predisposed patients through the use of metformin, rosiglitazone, (34) or valsartan, (35). In patients on hydroxychloroquine for rheumatoid arthritis, incidence of diabetes was reduced by 77% (36). Breastfeeding might also be correlated with the prevention of type 2 diabetes in mothers (37).

Conclusions and Recommendations

In view of the fact that at least 171 million people world wide suffer from diabetes mellitus as at 2006 and this figure estimated to double by the year 2030, there is no doubt that diabetes mellitus remains a major health concern of our time and demands urgent measures to reduce its incidence. The high cost of managing diabetes today ($132 billion in the United States alone every year) points to the fact that if we don't invest on a cure for diabetes now, we may have to spend most of our national income in the management of diabetes mellitus in the nearest future, which will be counter - productive and disastrous especially for the developing countries of the world. To stem the economic, social and health implications of diabetes mellitus we therefore make the following recommendations:

1. The government of member nations of the United Nations should encourage more research on diabetes mellitus especially researches exploiting different treatment options like using herbal medicine etc.
2. There should be more awareness on the disease especially in the developing countries like Nigeria so that diabetics understand their illness properly and how to manage themselves properly.
3. The government of member nations of the United Nations should subsidies the cost of oral hypoglycaemic drugs and insulin injections used by diabetics especially in developing countries so that diabetics can easily afford them.
4. The government of member nations of the United Nations should invest in the training of more specialized medical doctors to manage diabetic cases and employ them in government hospitals so that diabetics can afford the costs of consulting them.

REFERENCES

1. WHO. (1999). Definition, diagnosis and classification of diabetes mellitus and its complications. World Health Organization Department of Nonncomunicabl Disease Surveillance. (http://whglibdoc.who.int/hg/1999/WHO-NCD-NCS-99.2pdf). 60 pp. Retrieved on 7/6/2007
2. ADA. (2005).Total prevalence of diabetes and pre-diabetes 15 pp. American Diabetes Association, (http://www.diabetes.org/diabetes - statistics/prevalence's). Retrieved on 07/06/2007.
3. Erasto, P., Adebola, P. O., Grierson, D. S. and Afolayan, A. J. (2005). An ethanobotanical study of plants used for the treatment of diabetes in the eastern cape province, South Africa. *African Journal of Biotechnology*, 4(2): 1458 – 1460.
4. King, H., Aubert, R. E. and Herman, W. H. (1998). Global burden of diabetes 1995 – 2005: Prevalence, numerical estimates and projections. *Diabetes Care*, 21: 1414 – 1431.
5. Boyle, J. P., Honeycutt, A. A., Narayam, K. M., Hoerger, T. J., Geiss, L. S., Chens, H. and Thompson, T. J. (2001). Projection of diabetes burden through 2050: impact of changing demography and disease prevalence in the United State. *Diabetes Care*, 24: 1936 – 1940. *Clinical Nutrition*, 6: 8 – 12.
6. Mbanya, J. C., Bonicci, F. And Nagan, K. (1996). *Guideline for management of NIDDM in Africa. A concensus documemt,* Novo Nordisk, Greece.
7. Erasmus, R.T., Ebonyi, E. and Fakeye, T. (1988). Prevalence of diabetes Mellitus in rural Nigerian population. *Nigerian Medical Practitioners*, 15: 22-26.
8. Ngumah, Q. C. (1995). The role of optometrists in screening for diabetes in Nigeria. *International Diabetic Digest,* 6: 37 -38.
9. Bakari, A. G., Onyemelike, G. C., Sani, B. G., Hassan, S. S. and Aliyi, T. M. (1999).Relevance of diabetes in suburban northern Nigeria: result of a public screening survey. *Diabetes International,* 9: 59 - 60.
10. Ohwworiole, A. E., Kuti, J. A and Kabiawu, S. D. (1988). Casual blood glucose levels and prevalence of undiscovered diabetes mellitus in Lagos metropolis, Nigeria. *Diabetes*, 5(2): 56 – 60.
11. Gohdes, D. (1995). Diabetes in North American Indians and Alaska natives. Pages 561 – 582. *In*: Harris, M. I., Cowie, C. C., Stem, M. P., Boyko, E. J., Reiber, G. E., and Berineth, P. H. (Eds*), Diabetes in America*. 8th Edition. United States Department of Health and Human Services, Public Health Services, National Institute of Health, Washington, DC. DHHS Publication Number (NIH) 95 – 1468.
12. Kaczmar, T. (1998). Herbal support for diabetes management. *Clinical Nutrition*, 6: 8 – 12.
13. Guyton, A. C. and Hall, J. E. (2006). *Textbook of Medical physiology*. 11th Edition. Elsevier Inc, New Delhi.
14. Rother, K. I. (2007). Diabetes treatment bridging the divide. *The New England Journal Medicine*, 356(15): 1499 – 1501.
15. Neil, E. and Keele, C. A. (1971). *Samson Wright's Applied Physiology.* Twelfth Edition, Oxford University Press, London.
16. Sherwood, L. (1997). *Human Physiology from cells to systems*. Third Edition. Wadsworth Publishing Company, New York,

17. James, W. P. and Pearson, W. M. (1998). Diabetes. Pages 529 – 533. *In:* Ganon, J. D. and James, W. P. (Eds*), Human Nutrition and Dietetics.* Churchill Living Stone, London.
18. Eberhart, M. S., Ogden, C., Engelgau, M., Cadwell, B., Hedley, A. A. and Saydah,
19. Osinubi, A. A., Ajayi, O. G. and Adesiyun, A. E. (2006). Evaluation of the anti-diabetic effect of aqueous leaf extracts of *Tripinanthus butungil* in male spragne Dawley rats. *Medical Journal of Islamic World Academy of Science*, 16(1): 41 – 47.
20. Weisis, J. and Sumpio, B. (2006). Review of prevalence and outcome of vascular disease in patients with diabetes mellitus. *European Journal of Endovascular surgery*, 31(2): 143 – 150.
21. AMN (2006). Diabetes Mellitus Classification and pathogenesis. Armenian Medical Network. (http://ww.health.am/db/diabetes-mellitus/) Retrieved on 06-6-08.
22. Harris, M.I., Flega, K.M, Cowie, C.C., Eberhardt, M.S., Goldstein, D. E., Little, R.R., Wiedmeyer,, H.S and Byrd – Holt, D.D. (1998). Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S adults: the third national and nutrition examination survey. *Diabetes Care*, 21: 518 – 524.
23. Annette, M. C. and Halter, J.B. (2003). Aging and insulin secretion. (http:// ajpendo. Physiology.org/cgi/content/full/284/1/E7?ck=nck) Retrieved on 06-6-08.
24. NIDDKD (2002). Diabetes and aging. National institute of diabetes and digestive and kidney diseases. (http:// diabetes.niddk.nih.gov/about/dateline/spri02/8) Retrieved on 06-6-08.
25. Ozougwu, J. C. (2011). Antidiabetic effects of *Allium cepa* (onions) aqueous extracts on alloxan – induced diabetic *Rattus novergicus*. *Journal of Medicinal Plant Research*, 5(7): 1134 – 1139.
26.Ozougwu, J. C., Nwachi, U. E. and Eyo, J. E. (2008). Comparative Hypolipidaemic effects of *Allium cepa, Allium sativum* and *Zingiber officinale* aqueous extracts on alloxan- induced diabetic *Rattus novergicus. Bio-Research, 6(2): 384 _ 391.*
27. Ozougwu, J. C. and Eyo, J. E. (2010). Studies on the anti diabetic activity of *Allium sativum* (Garlic) aqueous extracts on Alloxan – induced diabetic albino rats. *Pharmacologyonline*, 2: 1079 – 1088.
28 Daneman, D. (2006). Type 1 diabetes. *Lancet* 367 (9513): 847 – 858.
29. Borch-Johnsen, K., Joner, G., Mandrup-Poulsen, T., Christy, M., Zachau-Christiansen, B., Kastrup, K. and Nerup, J. (1984). Relation between breast feeding and incidence rates of insulin-dependent diabetes mellitus. A hypothesis. *Lancet*, 2 (8411) : 1083 1086
30. Virtanen, S and Knip, M. (2003). Nutritional risk predictors of beta cell autoimmunity and type 1 diabetes at a young age. *American Journal of Clinical Nutrition*, 78 (6): 1053 – 1067.
31. Lindstrom, J., Ilanne-Parikka, P., Peltonen, M., Aunola, S., Eriksson, J., Hemio, K., Hamalainen, H., Sundvall, J., Valle, T., Uusitupa, M and Tuomilehto, J. (2006). Sustained reduction in the incidence of type2 diabetes by lifestyle intervention: follow- up of the Finnish Diabetes Prevantion study. *Lancet*, 368 (9548): 1673 – 1679.
32. Knowler, W., Barrett-Connor, E, Fowler, S., Hamman, R., Lachin, J., Walker, E., and Nathan, D. (2002). Reduction in the incidence of type 2 diabetes with

lifestyle intervention or metformin. *New England Journal of Medicine*, 346(6): 393 – 403.

33. Van Dam, R. M., HU, F. B., Rosenberg, L., Krishnan, S., and Palmer, J. R. (2006). Dietary calcium and magnesium, major food sources, and risk of type 2 diabetes in U.S. black women. *Diabetes Care*, 29(10): 2238 – 2243
34. Gerstein, H., Yusuf, S., Bosch, J., Pogue, J., Sheridan, P., Dinccag, N., Hanefeld, M., Hoogwerf, B., Laakso, M., Mohan, V., Shaw, J., Zinman, B and Holman, R. (2006). Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial. *Lancet*, 368 (9541) : 1096 – 1105.
35. Kjelden, S.E., Julius, S., Mancia, G., Mclnnes, G.T., Hua, T., Weber, M.A., Coca, A., Ekman, S., Girerd, X., Jamerson, K., Larochelle, P., Macdonald, T.M., Schmieder, R.E.M, Schork, M.A., Stolt, P., Viskoper, R., Wildimsky, J and Zanchetti, A. (2006). Effect of valsartan compared to amlodipine on preventing type 2 diabetes in high risk hypertensive patients: the value trial. *Journal of Hypertension*, 24 (7): 1405 – 1412.
36. Wasko, M.C., Hubert, H.B., and Lingala, V.B. (2007). Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis. Journal of American Medical Association, 298 (2): 187 – 193.
37. Stuebe, A. M., Rich-Edwards, J. W., Willett, W.C., Manson, J. E. and Michels, K. B. 920050. Duration of lactation and incidence of type 2 diabetes. *Journal of American Medical Association*, 294 (20): 2601 – 2610.