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Diabetes mellitus – a devastating metabolic disorder

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Abstract
Diabetes mellitus is an endocrinological and/or metabolic disorder with an increasing global prevalence and incidence. High blood glucose levels are symptomatic of diabetes mellitus as a consequence of inadequate pancreatic insulin secretion or poor insulin-directed mobilization of glucose by target cells. Diabetes mellitus is aggravated by and associated with metabolic complications that can subsequently lead to premature death. This review explores diabetes mellitus in terms of its historical perspective, biochemical basis, economic burden, management interventions along with the future perspectives.

Keywords: Insulin, blood glucose levels, islets of langerhans, hyperglycemia.

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INTRODUCTION

Diabetes mellitus is a combination of heterogeneous disorders commonly presenting with episodes of hyperglycaemia and glucose intolerance, as a result of lack of insulin , defective insulin action, or both (Sicree *et al.,* 2006). Such complications arise due to derangements in the regulatory systems for storage and mobilization of metabolic fuels, including the catabolism and anabolism of carbohydrates, lipids and proteins emanating from defective insulin secretion, insulin action, or both (Shillitoe, 1988; Votey and Peters, 2004).

Classification of diabetes mellitus is based on its aetiology and clinical presentation. As such, there are four types or classes of diabetes mellitus viz; type 1 diabetes, type 2 diabetes, gestational diabetes, and other specific types (Sicree *et al.,* 2006). Type 1 diabetes is said to account for only a minority of the total burden of diabetes in a population although it is the major type of the diabetes in younger age groups at majority of well-to-do countries. The incidence of type 1 diabetes is increasing in both rich and poor countries. Furthermore, a shift towards type 1 diabetes occuring in children at earlier ages is imminent (Sicree *et al.,* 2006).

85 to 95% of all diabetes in high-income countries are of type 2 accounting for an even higher dominance in developing countries. It is intimately associated with improper utilization of insulin by target cells and tissues. It is currently a common and serious health concern globally. According to WHO, (1994), this problem has been aggravated by rapid cultural and social dynamics, ageing populations, increasing urbanization, dietary changes, reduced physical activity and other unhealthy lifestyle and behavioural patterns.

Diabetes mellitus and lesser forms of glucose intolerance, particularly impaired glucose tolerance, can now be found in almost every population in the world and epidemiological evidence suggests that, without effective prevention and control programmes, diabetes will likely continue to increase globally (WHO, 1994).

In 2010, about 285 million people in the age group 20-79 were envisaged to have diabetes worldwide, about 70% of whom live in developing nations. This estimate is expected to increase to about 438 million, by 2030. Further, by 2030, the number of people with IGT is projected to increase to 472 million, or 8.4% of the adult population (Sicree *et al.,* 2006).

The debilitating effects of diabetes mellitus include various organ failures, progressive metabolic complications such as retinopathy, nephropathy, and/or neuropathy (Piero, 2006). Diabetics are accompanied by risk of cardiovascular, peripheral vascular and cerebrovascular diseases. Several pathogenetic processes are involved in the development of diabetes, including destruction of pancreatic β-cells that lead to lowered sensitivity of insulin action (WHO, 1999; Votey and Peters, 2004).

ECONOMIC BURDEN OF DIABETES MELLITUS

Economic aspects of diabetes and diabetes care currently attract considerable attention as the world diabetes epidemic takes hold and the healthcare activities of countries come under pressure to accomplish more within constrained resources (Sobngwi *et al*., 2001). Diabetes mellitus is a very expensive disease and has profound implications in terms of long-term microvascular and macrovascular complications and their associated cost. These complications reduce both life expectancy and quality of life (Ashcroft and Ashcroft, 1992; Collins, 2002; Votey and Peters, 2004).

According to Kirigia *et al.* (2009), diabetes mellitus poses a big economic burden with regards to health system costs, indirect costs arising from losses occasioned by patient disability and premature mortality, time spent by family members accompanying patients when seeking care, and intangible costs in terms of psychological pain to the family and loved ones.

The prevalence of diabetes in the WHO African Region was estimated in 2000 to be at 7.02 million people. Of these, about 0.702 million had type 1 diabetes and 6.318 million had type 2 diabetes. In addition, close to 113,100 people died from diabetes related causes, 561,600 were permanently disabled, and 6,458,400 experienced temporary disability (WHO, 2008; Kirigia *et al.,* 2009).

Barcelo *et al*. (2003) estimated total annual cost associated with diabetes in Latin America and the Caribbean to be US$65.216 billion. With a prevalence of 200,000 type 1 diabetics in India, Shobhana *et al*. (2002) estimated that the cost of treatment could be as high as US$50 million. According to American Diabetes Association, the combined direct and indirect costs of diabetes in 1997 were estimated at US$98 billion in the United States of America. The estimated total direct costs of diabetes in Spain is over US$650 million where there were over 1.4 million known diabetics in 1994 (Hart *et al.,* 1997). In England and Wales, the estimated cost of type 1 diabetes is US$1.92 million (Gray and Fenn, 1995). Unfortunately, there is a dearth of similar evidence for the WHO African Region (Kirigia *et al.,* 2009).

The growing burden of diabetes and other non-communicable diseases is one of the major health challenges to economic developments bedeviling WHO African Region states. As Kirigia *et al.* (2009) indicate, the effectiveness of prevention and control of those illnesses rely largely on the performance of health systems, functions of leadership and governance; health workforce; medical products, vaccines and

technologies; information; financing; and services delivery.

ETYMOLOGY OF DIABETES MELLITUS

The terms "Diabetes" and “Mellitus” are derived from Greek. “Diabetes” denotes "a passer through; a siphon" whereas the "Mellitus" denotes "sweet". It is thought that the Greeks named it so due to the excessive amounts of urine produced by diabetics attracted flies and bees. The traditional way of diagnosing diabetes mellitus in ancient Chinese was by observing whether ants are attracted to a person's urine or not. In medieval ages, the European doctors tested for diabetes by tasting the urine themselves, a scene occasionally depicted in Gothic beliefs (Patlak, 2002).

HISTORY OF DIABETES MELLITUS

Diabetes mellitus has been known since antiquity, its treatments were known since the Middle Ages, and the elucidation of its pathogenesis occurred mainly in the 20th century. Non-progressing Type II diabetics almost went undiagnosed (Patlak, 2002). The discovery of the role of the pancreas in diabetes was made by Joseph Von Mering and Oskar Minkowski in 1889. They found that upon complete removal of the pancreas from dogs, the dogs exhibited all the signs and symptoms of diabetes and died shortly afterwards. In 1910, Sir Edward Albert Sharpey-Schafer of Edinburgh in Scotland suggested that diabetics lacked a single chemical which was normally produced by the pancreas. Name of this chemical was later proposed to be insulin (Himsworth, 1936).

In 1921, Frederick Grant Banting and Charles Herbert Best repeated the work of Von Mering and Minkowski but went a step further and managed to show that they could reverse the induced diabetes in dogs by giving them an extract from the pancreatic islets of Langerhans of healthy dogs. This was a step forward in elucidation of the endocrine role of pancreas in metabolism and existence of insulin (Banting *et al.,* 1922). These scientists proceeded on to isolate insulin from bovine pancreases at the University of Toronto in Canada, thereby leading to the availability of an effective treatment of diabetes mellitus, with the first clinical patient being treated in 1922. The distinction between what is now known as type I and type II diabetes was made by Sir Harold Percival (Harry) Himsworth in 1935 (Himsworth, 1936).

Following these discoveries, other landmark discoveries followed viz; identification of sulfonylureas in 1942, the radioimmunoassay for insulin, as discovered by Rosalyn Yallow and Solomon Berson, Reaven's introduction of the metabolic syndrome in 1988, and identification of thiazolidinediones as effective antidiabetics in the 1990s (Patlak, 2002).

BIOCHEMICAL BACKGROUND OF DIABETES MELLITUS

A regular energy source is a prerequisite for every cell to function in the human body. Glucose is the body’s primary energy source, which circulates in the blood as a mobilizable fuel source for cells (Piero, 2006; Kibiti, 2006; Njagi, 2006). Insulin is a pancreatic hormone responsible for blood glucose level regulation. The hormone binds to its receptor sites on peripheral side of the cell membranes. It affords entry of glucose into respiring cells and tissues via requisite channels. Insulin stimulates catabolism on glucose into pyruvate through glycolysis. It also upregulates glycogenesis from excessive cytosolic glucose and lipogenesis from excessive cytosolic acetyl-COA. These metabolic events are antagonistic to metabolic events triggered by the hormone glucagon. When glucose levels are at or below threshold, glucose stays in the blood instead of entering the cells (Belinda, 2004).

The body attempts to arrest hyperglycemia, by drawing water out of the cells and into the bloodstream. The excess sugar is excreted in the urine. This is why diabetics present with constant thirst, drinking large amounts of water, and polyuria as the cells try to get rid of the extra glucose. This subsequently leads to glucosuria (Piero, 2006).

As hyperglycemia prolongs, the body cells are devoid of glucose due to the lack of insulin. This forces the cells to seek alternative mobilizable energy sources. In this regard, the cells turn to fatty acids stored in adipose tissue. The fats are not fuel sources for the red blood cells, kidney cortex and the brain. The red blood cells lack mitochondria in which beta-oxidation pathway rests. The fatty acids cannot pass the blood-brain barrier. To avail energy to such cells and tissues, the acetyl-CoA arising from catabolism of fatty acids is diverted to ketogenesis to generate ketone bodies, which can serve as alternative fuel sources for such cells and tissues. These ketone bodies are also passed in the urine, thereby leading to ketonuria, which characterizes diabetes mellitus. Build up of ketone bodies in the blood produces ketosis. Ketone bodies are acidic in nature and therefore, their build up in blood lowers blood pH, leading to acidosis. A combination of ketosis and acidosis lead to a condition called ketoacidosis. If left untreated, ketoacidosis leads to coma and death (Belinda, 2004).

ROLE OF INSULIN IN DIABETES MELLITUS

Insulin is a polypeptide hormone synthesized in humans and other mammals within the beta cells of the islets of Langerhans in the pancreasThe islets of Langerhans form the endocrine part of pancreas, accounting for 2% of the total mass of the pancreas,

with beta cells constituting 60-80% of all the cells of islets of Langerhans (Anon, 2004).

Insulin exhibits a multitude of effects in many tissues, with liver, muscle, and adipose tissue being the most important target organs for insulin action. The basic physiological function of insulin is promoting the synthesis of carbohydrates, proteins, lipids, and nucleic acids. The effects of insulin on carbohydrate metabolism include stimulation of glucose transport across muscle and adipocyte cell membranes, regulation of hepatic glycogen synthesis, and inhibition of glycogenolysis and gluconeogenesis (Piero, 2006). The end result of these actions is a reduction in blood glucose concentration. With regard to protein metabolism, insulin promotes transfer of amino acids across membranes, stimulates protein synthesis, and inhibits proteolysis. Incorporation of fatty acids from circulating triglyceride into adipose triglyceride and lipid synthesis are stimulated by insulin; lipolysis is inhibited. Insulin contributes to nucleic acid synthesis by stimulating the formation of ATP, DNA, and RNA (Cahill, 1971).

Insulin initiates its physiological effects by binding to a high affinity specific receptor located on the plasma membrane. The receptor is saturable, and both the binding capacity and the biological activity of insulin are maximal at a plasma insulin concentration of 20 to 30 μU/ml. Insulin is not altered during the binding process, and reaction of the disulfide bonds is not involved. After binding to the receptor, insulin transmits its signal to the interior of the cell through a second messenger that influences enzymatic processes. Thus, the hormone probably carries out its actions without entering the cell (Kibiti, 2006). Two membrane-bound enzyme systems are associated with the insulin signal: the adenyl cyclase-cAMP and the Magnesium - activated Sodium – Potassium - ATPase systems. Insulin inhibits cAMP formation only in situations where it has been previously stimulated by catecholamines, glucagons, or other hormones. Stimulation of intracellular Potassium transport is one of the well-known effects of insulin (Steiner, 1977).

In turn, potassium is an important factor in membrane potential and enzymatic regulation. Magnesium is involved in the activation of many intracellular enzymes. Intracellular Magnesium accumulation is also promoted by insulin. It has been proposed that the insulin membrane receptor is located in the vicinity of the Magnesium-dependent Sodium-Potassium-ATPase system and that activation of the receptor modifies the activity of this system. The result is accumulation of Magnesium intracellularly with activation of critical intracellular enzymes. Following an overnight fast, the 8.00 am normal plasma insulin concentration is 5 to 15 μU/ml. Postprandial values, 100g glucose, can be 5 to 10 times higher than the baseline. Insulin output under basal condition approximates 0.5 to 1.0 U/h and increases about 5 times after food ingestion (Steiner, 1977).

The ability of insulin to mediate tissue glucose uptake is a critical step in maintaining glucose homeostasis and in clearing the postprandial glucose load (Ginsberg *et al.,* 1975; Reaven, 1983). The insulin production is directly proportional to the amount of sugar (carbohydrate) consumed. The more sugar one consumes, the more insulin the body will have to produce, but, the tiny pancreatic beta cells were never designed to produce this level of insulin. With a limited capacity to produce insulin, a capacity that is more than sufficient to last a lifetime under normal dietary conditions, the forced over-production of insulin will eventually exhaust that capacity and the cells will cease to operate (Robert, 2002).

However, insulin production does not always depend on blood glucose levels; insulin is stored in cells prior to its release. Insulin deficiency plays a central role in all forms of diabetes because it is the major hormone that enables cells (primarily muscle and fat cells) to uptake glucose from the bloodstream. Insulin makes it possible for most body tissues to remove glucose from the blood for use as fuel, for conversion to other needed molecules, or for storage. Furthermore, insulin is also the major regulatory signal for glycogenesis in the hepatocytes and myocytes (WHO, 1999).

Higher insulin levels upregulate various anabolic processes including cell growth, cellular protein synthesis, and fat storage. Insulin is more of an anabolic hormone rather than cataboli. Insufficient amounts of insulin or poor cellular response to insulin as well as defective insulin leads to improper handling of glucose by body cells or appropriate glucose storage in the liver and muscles. This ultimately leads to persistently high levels of blood glucose, poor protein synthesis, and other metabolic derangements (WHO, 1999). As a consequence of the widespread prevalence of diabetes and the severity of its complications, extensive research and treatment development efforts must be undertaken to identify and develop more effective remedies to improve the quality of life of those affected by the disease (John, 1998).

The chronic hyperglycemia arising from diabetes mellitus accompanies long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Pathogenesis of diabetes mellitus underlies autoimmune destruction of the pancreatic beta cells leading to insulin deficiency and biosignalling derangements that are consequent to insulin resistance or insensitivity. Defective insulin

secretion and defective insulin action frequently coexist in the same patient. It is still obscure which abnormality is the primary cause of the hyperglycemia (Anon, 2004). Hyperglycemia is characterized by polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Stunted growth and susceptibility to opportunistic infections may also be associated with chronic hyperglycemia. Uncontrolled diabetes mellitus leads to hyperglycemia with ketoacidosis as well as the nonketotic hyperosmolar syndrome. Long-term metabolic complications of diabetes mellitus include retinopathy, nephropathy, peripheral neuropathy, amputations, and Charcot joints as well as autonomic neuropathy causing gastrointestinal, genitourinary, cardiovascular symptoms and sexual dysfunction. Diabetics are also at a greater risk atherosclerotic, cardiovascular, peripheral arterial and cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism also accompany uncontrolled diabetes mellitus (Anon, 2004).

Insulin regulates blood glucose levels by its effects on the liver and skeletal muscles. Normal blood glucose levels are maintained by sustenance of balance between hepatic glucose production and glucose utilization by the peripheral tissues. Insulin regulates hepatic gluconeogenesis and promotes glucose catabolism by the skeletal muscles. In type 2 diabetes mellitus, postabsorptive hepatic glucose production is increased, which positively correlates with fasting plasma glucose concentration. Between gluconeogenesis and glycogenolysis, gluconeogenesis appears to be drastically increased in type 2 diabetes mellitus (Consoli, 1992).

It is postulated that an enhanced release of gluconeogenic precursors is annexed to increased total glucose output. Unnecessary glucose output can be ameliorated by inhibition of glycogenolysis and/or gluconeogenesis from endogenous precursors. Stimulation of intrahepatic disposal of neoformed glucose contributes to autoregulation. As Tappy, (1995) indicates, these observations support the concept that intrahepatic disposal of glucose-6-phosphate plays a major role in the control of endogenous glucose production.

Studies by Kahn and Porte, (1988) established that the degree of impaired beta-cell responsiveness to glucose is closely related to the degree of fasting hyperglycemia but in a curvilinear fashion. Decreased insulin secretion and defective cellular insulin action also compromises efficient glucose uptake by peripheral tissues. This derangement gets more predominant as the islet dysfunction declines. Management interventions improve islet function and raise plasma insulin levels, reduce hepatic gluconeogenesis, or improve the efficiency of tissue glucose uptake.

Halter *et al.* (1985) argue that even if fasting insulin levels are comparable between type 2 diabetics and normal subjects, insulin secretion is markedly impaired in type 2 diabetics in relation to the degree of hyperglycemia present. Furthermore, the degree of fasting hyperglycemia in a given patient with non-insulin-dependent diabetes mellitus is closely related to the degree of impaired pancreatic beta-cell responsiveness to glucose.

MANAGEMENT OF DIABETES MELLITUS

Life style management is apparently the cornerstone of management of diabetes mellitus. It is recognized as being an essential part of diabetes and cardiovascular disease prevention. Meta-analyses demonstrate that lifestyle interventions, including diet and physical activity, led to a 63% reduction in diabetes incidence in those at high risk. Lifestyle modification programs have demonstrated encouraging improvement in risk factors for diabetes; however, the effect on diabetes incidence has not been reported (Rebecca *et al.,* 2009). The dietary management of diabetes mellitus is a complement of lifestyle management. It has a positive effect on long term health and quality of life. Dietary management aims at optimal metabolic control by establishing a balance between food intake, physical activity, and medication to avoid complications. In type 2 diabetes, the dietary objective is for improved glycemic and lipid levels and weight loss as appropriate (Piero *et al.,* 2006).

In spite of the underscored importance of lifestyle measures in diabetes therapy, most diabetics cannot escape the value of pharmacotherapy to achieve target glucose concentrations. Different oral hypoglycemics have been in use to aid in maintenance of blood glucose level at the requisite threshhold in diabetics through distinct mechanisms (Inzucchi, 2002). Sulfonylureas and the nonsulfonylurea secretagogues establish normoglycemia by upregulating endogenous insulin secretion; alpha-glucosidase inhibitors work by delaying intestinal carbohydrate absorption; thiazolidinediones (TZDs) maintain normoglycemia by enhancing insulin sensitivity primarily by increasing peripheral glucose disposal, and suppressing hepatic glucose production. Metformin works by decreasing hepatic gluconeogenesis while at times also increasing peripheral glucose mobilization and disposal (Curtis, 2007). Synthetic insulin injections are also a therapy against type I diabetes mellitus.

Curtis,(2007) reports that despite many effective oral hypoglycemic agents available to manage type 2 diabetes, 5% to 10% of the population with diabetes experience secondary failure. This bottleneck can be

arrested if clinicians understand the limitations of some therapies currently in use. Secondary failure arises as a result of deteriorating beta cell function, poor compliance to treatment, weight gain, reduced exercise, dietary changes, or illness. A major drawback associated with hypoglycemic agents is that they are expensive and harbor adverse effects on patients

Plant derived medications have also found immense use in the management of diabetes mellitus. Piero *et al.* (2012) notes that there is a new trend in the world to turn to phytodrugs to avoid the adverse effects associated with conventional hypoglycemic agents. Many plant species have been used to treat life-threatening diseases including diabetes mellitus. A World Health Organization (WHO) study shows that 80% of the world population solely relies on medicinal plants for their primary health care needs (Njagi *et al.,* 2012).

To date, the catalogue of antidiabetic medicinal plants is growing at a pleasantly high rate particularly in the African continent. Perhaps this is advised by the economic situation in African, which has driven African diabetics to seek cheaper treatment and management options. This overreliance on antidiabetic medicinal plants has probably invoked scientists to bioassay these plants in an effort to elucidate more hypoglycemic medicinal plants. The antidiabetic potential of some medicinal plants extracts has been demonstrated in human and animal models of type II diabetes. However, more detailed research on the antidiabetic plants is inevitable to ameliorate the concerns of *in vivo* safety and efficacy (Piero *et al.,* 2012).

WHAT DOES THE FUTURE HOLD?

Currently, the management of type 2 diabetes focuses on glucose control via lowering of blood glucose (fasting and postprandial) and hemoglobin A(1c). The considered view is that the diabetes therapy should focus on delaying progression of the disease. Treatment options are supposed to be directed at the known pathogenetic disturbances of the disease. Recently, treatment and/or management strategies have been directed at the development of novel therapeutic options that are more efficacious in maintaining normoglycemia in type 2 diabetics and that provide durable glucose control (Defronzo, 2010).

The realization that diabetes mellitus is a "metabolic curse" should be a trigger for desire to seek understanding of the biochemical and molecular basis of this metabolic disorder. Such an understanding will inform efforts to elucidate more effective management interventions against diabetes mellitus. In this regard, more efficacious synthetic insulin with rapid actions, ability to traverse all body compartments, less adverse effects as well as longer durations of actions need to be designed. The oral hypoglycemic agents, which are apparently bedeviled by side effects, need to be optimized to mitigate these demerits. Lifestyle management needs to be optimized to achieve the intended goal of lowering the glycemic index in diabetics.

Gene therapy will doubtlessly address the complications of diabetes mellitus. The pioneering gene therapy approach to diabetes mellitus was occasioned by the cloning of the insulin gene. The strategy was based on the premise that non-insulin producing cells could be manipulated to produce insulin using a suitable promoter and insulin gene construct. It was thought that these substitute cells could reclaim insulin production diabetics. Advances in molecular biology have enabled unraveling of the human genome. This milestone can be exploited in order to characterize the insulin gene for its subsequent use in management of diabetes. The immunological concerns underlying gene therapy can also be addressed by the current advances in molecular biology. However, irrespective of all these concerns, it is imperative to always farthom that the merits of gene therapy of diabetes exceed the demerits and present advantages as compared with conventional treatment before this approach could gain widespread acceptance in general medical practice.

REFERENCES

1. American Diabetes Association, 1998. Economic consequences of diabetes mellitus in the United States in 1997. Diabetes Care, 21:296-309.
2. Anonymous. 2004. Diagnosis and Classification of Diabetes Mellitus – Position Statement.
3. Ashcroft, F.M. and S.J.H. Ashcroft, 1992. Insulin, Molecular Biology to Pathology. Oxford University Press. pp 266-284.
4. Banting, F.G., C.H. Best, J.B. Collip, W.R. Campbell, and A.A. Fletcher, 1922. Pancreatic extracts in the treatment of diabetes mellitus. preliminary report. Canadian Medical Association Journal, 145(10):1281-1286.
5. Barcelo A, Aedo C, Rajpathak S and Robles S. 2003. The cost of diabetes in Latin America and the Caribbean. Bulletin of the World Health Organization, 81(1):19-27.
6. Belinda R. 2004. Gale Encyclopaedia of Alternative Medicine. pp 2603-2605.
7. Cahill GF Jr and Boston MD. 1971. Physiology of insulin in man. Diabetes, 20(12):785-799.
8. Collins FM. 2002. Current treatment approaches to type 2 diabetes mellitus successes and shortcomings. American Journal of Managed Care, 8(16 suppl):S460-S471.
9. Consoli A. 1992. Role of liver in pathophysiology of NIDDM. Diabetes Care, 15(3):430-41.
10. Curtis LT. 2007. New technologies and therapies in the management of diabetes. American journal of managed care, 13(2 suppl): S47-S54
11. Defronzo RA. 2010. Current issues in the treatment of type 2 diabetes. Overview of newer agents: where treatment is going. Am J Med 123(3 Suppl):S38-48. doi: 10.1016
12. Gray A, McGuire A and Fenn P. 1995. The cost of insulin-dependent diabetes mellitus (IDDM) in England and Wales. Diabetic Med, 12(12):1068-1076

13. Halter JB, Ward WK, Porte D, Jr., Best JD and Pfeifer MA. 1985. Glucose regulation in non-insulindependent diabetes mellitus. Interaction between pancreatic islets and the liver. Am J
14. Med 79(2B):6-12.
15. Hart WM, Espinosa C and Rovira J. 1997. Cost of unknown diabetes mellitus in Spain. Med Clin (Barcelona*)*, 109:289-293.
16. Himsworth HP. 1936. Diabetes mellitus: its differentiation into insulin-sensitive and insulin-insensitive types. Lancet, 227(5864):127-130.
17. Hoppener JW and Lips CJ. 2006. Role of islet amyloid in type 2 diabetes mellitus. Int J Biochem Cell Biol, 38(5-6):726-36.
18. Inzucchi SE. 2002. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. JAMA, 287(3):360-372.
19. John C. 1998. Treatment of Diabetes Mellitus with Herbs. Annual Review of Pharmacology, 13: 35-43.
20. Kahn SE and Porte DJr. 1988. Islet dysfunction in non-insulin-dependent diabetes mellitus. AM J Med 85 (5A): 4-8
21. Kibiti CM. 2006. Hypoglycaemic potential of some Kenyan plants used in traditional medicine in Rift valley, Nairobi and Eastern provinces, Msc thesis, Kenyatta University.
22. Kirigia JM, Sambo HB, Sambo LG and Barry SP. 2009. Economic burden of diabetes mellitus in the WHO African region. BMC International Health and Human Rights, 9:6.
23. Njagi JM. 2006. Hypoglycemic effects of some Kenyan plants used traditionally in the management of diabetes mellitus in Gachoka division, Mbeere district, Msc thesis, Kenyatta University, Kenya, 2006.
24. Patlak M. 2002. New weapons to combat an ancient disease: Treating diabetes. Federation of American Society for Experimental Biology, 16(14):1853-1857.
25. Piero MN. 2006. Hypoglycemic effects of some Kenyan plants traditionally used in management of diabetes mellitus in eastern province, Msc thesis, Kenyatta University.
26. Piero MN, Njagi JM, Kibiti CM, Ngeranwa JJN, Njagi ANM, Njue WM and Gathumbi PK. 2012. Herbal management of diabetes mellitus: a rapidly expanding research avenue Int J Curr Pharm Res, 4 (2):1-4.
27. Piero MN, Njagi JM, Kibiti CM, Ngeranwa JJN, Njagi ENM and Miriti PM. 2012. The Role of Vitamins and Mineral Elements in Management of Type 2 Diabetes Mellitus: A Review South As. J. Biol.Sci., 2(Supp.1):107 – 115.
28. Robert H. 2002. Diabetes Mellitus. Slim Forever International. Diabetes Care, 1: 27-31.
29. Shillitoe RW. 1988. Psychology and diabetes: Psychosocial factors in management and control;
30. Chapman and Hall. pp 8-109.
31. Shobhana R,. Rao PR, Lavanya A, Williams R, Padman C, Vijay V and Ramachandran A. 2002. Cost incurred by families having Type 1 diabetes in a developing country – a study from Southern India. Diabetes Research and Clinical Practice, 55(1):45-48.
32. Sicree R, Shaw J and Zimmet P. 2006. The Global Burden. Diabetes and Impaired Glucose Tolerance. Prevalence and Projections. In: Gan, D. ed. *Diabetes Atlas*, 3rd edn. Brussels: International Diabetes Federation, pp. 16–103.
33. Sobngwi E, Mauvais-Jarvis F, Vexiau P, Mbanya JC and Gautier JF. 2001. Diabetes in Africans. Epidemiology and clinical specificities. Diabetes Metab., 27(6):628-634.
34. Steiner DF. 1977. Insulin today, Diabetes, 26: 322-340
35. Stiegler RS, Zimmet PZ, Cameron AJ and Shaw JE. 2009. Lifestyle management: preventing Type 2 diabetes and cardiovascular complications. Therapy, Vol. 6, No. 4 , Pages 489-496 (doi:10.2217/thy.09.37)
36. Tappy L. 1995. Regulation of hepatic glucose production in healthy subjects and patients with noninsulin-dependent diabetes mellitus. Diabetes metabolism, 21(4):233-40.
37. Votey SR. and Peters AL. 2004. Diabetes mellitus type 2. A review. http://www.emedicine.com/emerg/topic133.htm Accessed July, 2006.
38. WHO diabetes programme, 2008. [http://www.who.int/diabetes/facts/world_figures/en/index2.html]. Geneva
39. World Health Organization. 1999. Department of Non-communicable Disease Surveillance. Definition, diagnosis and classification of diabetes mellitus and its complications; Geneva.
40. World Health Organization. 1994. Prevention of diabetes mellitus, Technical Report Series no. 844. Geneva: World Health Organization.