



A SCIENTIFIC CRITIQUE ON DIABETEOLOGY

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Abstract: Diabetes mellitus is a chronic disease characterized by chronic hyperglycemia due to malfunction of insulin. It is characterized by severe lack of insulin due to the destruction of most or all of the beta cells in the islets of Langerhans by an autoimmune process, usually leading to absolute insulin deficiency. In hyperglycemia, there is an imbalance of glucose production and glucose intake as opposed to insulin-stimulated glucose uptake in target tissues, mainly skeletal muscle. Although resistance to peripheral insulin action contributes to altered glucose homeostasis, current evidence has found that the direct effect of aging on diabetes pathophysiology is through impairment of β -cell function, resulting in a decline in insulin secretion. Coexisting illnesses and any acute illness can precipitate hyperglycemia because of effects of stress hormones to cause insulin resistance combined with the α -adrenergic effects of catecholamine released during stressful illness to inhibit insulin secretion. Medications used in treating chronic ailments may affect in insulin resistance or worsening hyperglycemia. The diagnosis is using either the estimation of plasma glucose or HbA1c. Many of oral antidiabetic agents have a number of serious adverse effects, thus, the management of diabetes without any side effects is still a challenge. There are about 200 pure compounds from plant sources reported to show anti-diabetic effect. The International Diabetes Federation mentions management of diabetes includes monitoring and controlling the level of plasma glucose. Similarly, optimal management of diabetes requires investigation of potential DM complications with modify the risk factors for different diabetes related conditions.

Index Terms – diabetes, insulin, oral medications, herbs, complications

I. INTRODUCTION

Diabetes, which is a serious, chronic disease characterized by chronic hyperglycemia due to insufficient insulin action that occurs either when the pancreas does not produce enough insulin (insulin deficiency) or when the body cannot effectively use the insulin (insulin resistance) leading to abnormalities in almost the entire metabolic system, including carbohydrate, lipid and protein metabolism. (WHO, 1999). Type 2 Diabetes mellitus develops in association with multiple genetic factors that lead to decreased insulin secretion or insulin resistance augmented by lifestyle habits, such as overeating (especially high fat diet), lack of exercise and resultant obesity, as environmental factors and results in insufficient insulin action. (Seino, et al., 2010). The number of people with diabetes is increasing due to population growth, aging, urbanization, and increasing prevalence of obesity and physical inactivity. (Sarah, et al., 2004).

II. CLASSIFICATION OF DIABETES MELLITUS

With a better understanding of the pathophysiology and regulation of glucose metabolism, new classifications of diabetes based on etiologies and clinical staging have been recommended by the World Health Organization and American Diabetes Association. They define four main subtypes of diabetes. (Dr. Mohammad, et al., 2003).

Type 1 diabetes - Insulin dependent diabetes mellitus - (IDDM)

It is characterized by severe lack of insulin due to the destruction of most or all of the beta cells in the islets of Langerhans by an autoimmune process, usually leading to absolute insulin deficiency. The onset is usually acute, developing over a period of a few days to weeks. (Langeh, et al., 2018). The subclass of diabetes, type I diabetes, is generally characterized by the abrupt onset of severe symptoms, dependence on exogenous insulin to sustain life and proneness to ketosis even in the basal state, all of which is caused by absolute insulin deficiency. IDDM is the most prevalent type of diabetes among children and young adults in developing countries, and was formally termed juvenile diabetes. (Harris, et al., 1997). Over 95% of persons with type 1 diabetes mellitus develop the disease before the age of 25 and most often between the ages of 10 and 16, with an equal incidence in both sexes. (Langeh, et al., 2018).

Type 2 diabetes - Non-insulin dependent diabetes mellitus (NIDDM)

Which may originate from insulin resistance and relative insulin deficiency or from a secretory defect. Type 2 diabetes is the most common form of diabetes in the world especially in minority communities and the elderly. Approximately 95 % of all persons with diagnosed diabetes and 100 % of undiagnosed diabetes have type 2 diabetes. (Dr. Mohammad, et al., 2003). Insulin resistance in peripheral tissue and insulin secretory defect of the beta cell of pancreas, so that less glucose is produced, and impairment of insulin's ability to stimulate the uptake of glucose in muscles and other tissues. The cause of this insulin resistance has not yet been fully established, but may involve defects in the action of insulin after it has bound to the insulin receptors on the surface of cells. This is the most common form of diabetes mellitus and is highly associated with a family history of diabetes older age, obesity and lack of exercise. (Rang, et al., 2003).

Type II diabetes greatly out numbers all other forms of diabetes. Patients with NIDDM are not dependent on exogenous insulin for prevention of ketonuria and are not prone to ketosis. However, they may require insulin for the correction of fasting hyperglycemia if this cannot be achieved with the use of diet or oral agents, and they may develop ketosis under special circumstances such as severe stress precipitated by infection or trauma. (Harris, et al., 1997). The pathogenesis in type II diabetes is that the pancreas produces insulin but the body does not utilize the insulin correctly. This is primarily due to peripheral tissue insulin resistance where insulin-receptors or other intermediates in the insulin signaling pathways within body cells are insensitive to insulin and consequently glucose does not readily enter the tissue leading to hyperglycemia or elevated blood glucose concentrations. (Albright A.L., et al., 1997). Obesity, which generally results in impaired insulin action, is a common risk factor for this type of diabetes, and most patients with type II diabetes are obese (Nolte, et al., 2001) and will ultimately require multiple anti-diabetic agents to maintain adequate glycemic control (Gerich, et al., 2001).

Other specific types

Specific genetic / molecular defects have been identified in a minority of what were considered type II diabetes: (Langeh, et al., 2018).

- Genetic defects of function of beta cell - Ex -: Hepatic nuclear factor 4 alpha-autosomal dominant condition of impaired insulin secretion; early onset and slowly progressive; type 1 (mature onset diabetes of the young)
 - Ex -: Mutation of mitochondrial DNA.
- Genetic defects in the action of insulin. - Ex -: insulin receptor (sever insulin resistance), lipotropic diabetes.
- Drug/chemical induced - Ex -: vacor, pentamidine, glucocorticoids, thiazides, Dilantin
- Immune mediated (uncommon) - Ex -: stiff man syndrome, anti- insulin receptor antibodies
- Infection - Ex -: congenital rubella, cytomegalic virus
- Endocrine disorders
 - diseases of the pancreas - Ex -: pancreatitis, neoplasia, cystic fibrosis, haemochromatosis
 - endocrinopathies - Ex -: acromegaly, cushing's syndrome, hyperthyroidism, pheochromocytoma

Gestational Diabetes Mellitus (GDM)

Occur during pregnancy, sensitivity to insulin decreases (placental hormones affect glucose tolerance). Beta cells may not be able to meet this increased need for insulin gestational diabetes. They are occurring in up to 14% of pregnancy. This increases subsequent risk of developing type II diabetes. Increased risk for perinatal mortality and neonatal morbidity. (Langeh, et al., 2018).

III. HYPERGLYCEMIA

Hyperglycemia is a condition of high blood sugar. An elevated level specifically of the sugar glucose in the blood. Hyperglycemia is often found in diabetes mellitus. It occurs when the body does not have enough insulin or cannot use the insulin it has to turn glucose into energy. The term "hyperglycemia" comes from the Greek "hyper" = high, over, beyond, above + "glykys" = sweet + "haima" = blood. High sweetness (sugar) in the blood. (William, et al.,).

Patients with type 2 diabetes are at increased risk for cardiovascular disease. These complications are directly and strongly related to hyperglycemia. Hyperglycemia affects biochemical parameters and influences the progression of coronary heart disease and mortality rates in diabetic patients. Aggressive treatment to control hyperglycemia is much more effective in reducing the number of complications than standard treatment. In the Paris Prospective study, in the upper levels of glucose distributions, the risk of death progressively increased with increasing fasting and 2-h glucose concentrations. There were no clear thresholds for fasting or 2-h glucose concentrations above which mortality sharply increased. (Dr. Eid, et al., 2003).

IV. ETIOLOGY

Heredity	-	family history of late onset diabetes
Obesity	-	ex-: over weight
Lack of physical activity	-	ex-: sedentary life style
Women with prior gestational diabetes		
Stress and Strain		(Langeh, et al., 2018).

V. SYMPTOMATOLOGY

- Increased thirst and Increased urination - When excess glucose builds up in the bloodstream, the body will extract fluid from tissues. This can lead to excessive thirst and the need to drink and urinate more
- Constant hunger - In type 2 diabetes, the cells are not able to access glucose for energy. The muscles and organs will be low on energy, and the person may feel more hunger than usual.
- Weight loss - When there is too little insulin, the body may start burning fat and muscle for energy. This causes weight loss.
- Blurred vision - High blood glucose can cause fluid to be pulled from the lenses of the eyes, resulting in swelling, leading to temporarily blurred vision.
- Fatigue, or a feeling of being tired When cells lack glucose, the body becomes tired. Fatigue can interfere with daily life when a person has type 2 diabetes.
- Infections and sores: It take longer to recover from infections and sores because blood circulation is poor and there may be other nutritional deficits. (Lana, et al., 2019). (William, et al., 2005).

Symptoms of type I diabetes

- Increased thirst and urination
- Blurred vision
- Feeling very hungry
- Weight loss in spite of increased eating (Aryan, et al., 2018).

Symptoms of type II diabetes

- Feeling tired or ill
- Frequent urination (especially at night)
- Unusual thirst
- Blurred vision
- Frequent infections
- Slow healing of sores
- Having dry itchy skin
- Having tingling in the feet (Aryan, et al., 2018).

VI. PATHOPHYSIOLOGY OF DIABETES MELLITUS

The human pancreas is basically composed of two types of secretory cells that are both involved in nutrient handling: 98% of the cells- the exocrine type – secrete a food processing enzyme bicarbonate mixture into the duodenum, while the remaining 2% - the endocrine type- have a metabolic function and secrete a mixture of nutrient – generated hormones into the portal vein. This small endocrine part is of vital importance in maintaining glucose homeostasis through the action of the 51-amino acid peptide insulin. Four endocrine cell types can be distinguished: A cells (alpha), B cells (beta), D cells (delta) and PP cells (pancreatic polypeptide). (Klöppel, et al., 1997). These endocrine cells are distributed throughout the pancreas in areas known as islets.

Pathophysiology of type 2 diabetes

Type 2 diabetes is by far the most prevalent form of diabetes in older adults and is an age-related disorder. The criteria for diagnosing diabetes are the same for all age groups because the risks of diabetes-related complications are associated with hyperglycemia over time across all age groups. (American Diabetes Association, et al., 2006). Older adults are at high risk for the development of type 2 diabetes due to the combined effects of genetic, lifestyle, and aging influences. These factors contribute to hyperglycemia through effects on both β -cell insulin secretory capacity and on tissue sensitivity to insulin. The occurrence of type 2 diabetes in an older person is complicated by the comorbidities and functional impairments associated with aging. (Pearl, et al., 2017).

Hyperglycemia develops in type 2 diabetes when there is an imbalance of glucose production (ex. hepatic glucose production during fasting) and glucose intake (ex. food ingestion) as opposed to insulin-stimulated glucose uptake in target tissues, mainly skeletal muscle. Multiple factors in an older person contribute to such an imbalance of glucose regulation (Pearl, et al., 2017). Although resistance to peripheral insulin action contributes to altered glucose homeostasis, current evidence has found that the direct effect of aging on diabetes pathophysiology is through impairment of β -cell function, resulting in a decline in insulin secretion.

Pathophysiology of Genetic induced type 2 diabetes

There is a strong genetic predisposition to type 2 diabetes. (Medici, et al., 1999). The genetic susceptibility to type 2 diabetes is polygenic, involving a number of variants, where each allele has a modest effect on the risk of disease in an individual person. Genome-wide association studies, linkage analysis, candidate gene approach, and large-scale association studies have identified ~70 loci conferring susceptibility to type 2 diabetes. (Billings, et al., 2010). These genetic alleles appear to affect the risk of type 2 diabetes primarily through impaired pancreatic β -cell function, reduced insulin action, or obesity risk. Genome-wide association studies have consistently found that p16INK4a, a cyclin-dependent kinase inhibitor (CDKI), encoded by the Cdkn2a locus, is associated with type 2 diabetes risks (Zeggini, et al., 2007). Expression of p16INK4a was increased in aging mice (Krishnamurthy,

et al., 2004). and an additional copy of p16INK4a was associated with markedly reduced pancreatic islet cell proliferation. (Krishnamurthy, et al., 2006). β -Cell proliferation was increased in p16INK4a knockout mice. Therefore, p16INK4a increases with age and appears to mediate an age-associated decline in the replicative capacity of mouse islets; p16INK4a could be a potential link between aging, metabolic derangements, and β -cell failure in type 2 diabetes. (Pearl, et al., 2017).

Pathophysiology of Effect of aging induced type 2 diabetes

Pathophysiology is related with impaired Insulin Secretion, Insulin Resistance, and Their Interaction (Pearl, et al., 2017). In the setting of genetic and lifestyle-related risk factors, aging contributes to the development of type 2 diabetes through impaired β -cell function and impaired β -cell adaptation to insulin resistance (Chang, et al., 2006). leading to impaired insulin secretion (Basu, et al., 2003), (Chang, et al., 2003). as illustrated in Fig. 1. Studies in rodents and humans have found that aging may exert a distinct influence on β -cell turnover as well as function. In older patients who have developed diabetes, autoimmune destruction of β -cells is rarely observed. Limited pathologic investigation suggests that total β -cell mass may be moderately reduced, but severe loss of β -cell mass is uncommon. Pancreatic β -cell mass in adult humans exists in a dynamic state such that the cells can undergo compensatory changes to maintain euglycemia. Aging is thought to be associated with reduced capacity to regenerate β -cells, as suggested by studies involving rodents (Teta, et al., 2005), (Tschen, et al., 2009) and humans (Saisho, et al., 2013), (Menge, et al., 2008). On the one hand, for example, the β -cell toxin streptozotocin, partial pancreatectomy, or exendin-4 were more effective in stimulating β -cell proliferation in younger mice (younger than 12 months old) than in older mice (Teta, et al., 2005), (Tschen, et al., 2009), (Saisho, et al., 2011). On the other hand, the age-associated decline in β -cell function in older rats has been shown to be reversible with glucagon-like peptide 1 (GLP-1; exendin) treatment (Wang, et al., 1997). suggesting stimulation of β -cell regeneration (Xu, et al., 1999). In humans, the baseline β -cell population and appropriate association with other islet cell types is established before 5 years of age (Gregg., et al., 2012). Other studies using C14 or Ki67 have found that human adult β -cell turnover is very low (Saisho, et al., 2013), (Perl, et al., 2010), (Gregg, et al., 2012), (Meier, et al., 2008). Similarly, among middle-aged and older adults, minimal β -cell regeneration was observed after a mean follow-up period of 1.8 ± 1.2 years after a 50% partial pancreatectomy: β -cell mass and new β -cell formation were not increased, and β -cell turnover was unchanged (Menge, et al., 2008). The follow-up time of this study may have been too short for human β -cells to replicate, but other studies have also found evidence of slow β -cell proliferation in humans with advancing age (Butler, et al., 2003), (Reers, et al., 2009).

The decline in β -cell replication was directly associated with a decrease in the expression of a transcription factor known as the pancreatic and duodenal home box 1 (pdx1) (Gunasekaran, et al., 2011). Thus, the overall evidence suggests that human β -cells survive for a long time and are unlikely to be replenished by replications once adulthood is reached (Kushner, et al., 2013). Several age-related potential molecular pathways have been found to restrict β -cell regeneration. For example, the replication refractory period, the time between cell divisions (G0 stage of cell cycle), appears to lengthen with age (Salpeter, et al., 2010). the replicative capacity of β -cells might be reduced due to accumulation of DNA mutations with aging.

Therefore, β -cell function in human adults might be enhanced in the setting of hyperglycemia or insulin resistance to maintain euglycemia. Pancreatic β -cells appear to primarily compensate for limited replication capacity through hyperplasia and hypertrophy. However, a number of studies have demonstrated a decline in β -cell function and insulin secretion with age in rodents (Gunasekaran, et al., 2011). In humans, the insulin secretion rate in response to glucose was significantly and progressively decreased in older individuals, with the greatest impairment in older individuals with impaired glucose tolerance compared with older individuals with normal glucose tolerance or with younger individuals matched for degree of insulin resistance (Chang A.M., et al., 2006). In fact, a 50% reduction in β -cell secretory capacity has been observed in older men compared with younger men in response to arginine stimulation. (Chen M., et al., 2017).

VII. COMORBIDITIES AND THEIR EFFECT ON INSULIN SENSITIVITY AND SECRETION

Coexisting illness is another factor that can affect insulin sensitivity and insulin secretion in an older person. Hypertension, for example, is common in older people and has been associated with diminished insulin sensitivity. Furthermore, any acute illness can precipitate hyperglycemia because of effects of stress hormones to cause insulin resistance combined with the α -adrenergic effects of catecholamine released during stressful illness to inhibit insulin secretion. (Ferrannini, et al., 1987). Medications used in treating chronic medical conditions may induce or increase insulin resistance or worsening hyperglycemia among patients with diabetes. Glucocorticoids, for example, promote hepatic gluconeogenesis, thus increasing hyperglycemia, and contribute to insulin resistance by increasing visceral fat and promoting proteolysis, lipolysis, free fatty acid production, and fat accumulation in the liver. (Mazziotti, et al., 2011).

Impaired glucose regulation over time leads to overt diabetes, which in turn leads to microvascular or microvascular complications. Diabetes-associated complications, along with other comorbidities prevalent among older adults, such as arthritis, cognitive impairment, and depression, may contribute to decreased physical activity and disability (Fried, et al., 1999). All of these changes can further impair glucose regulation and adversely affect glycemic management.

Diabetes-related islet changes

The islet changes, from a morphological point of view, associated with various types of diabetes can be divided into those with and without severe beta-cell loss. Severe beta-cell loss is found in type I diabetes and some uncommon forms of diabetes such as virus-related diabetes and congenital diabetes. Islets without severe loss of beta-cell are encountered in type 11 diabetes and in the secondary forms of diabetes. (Klöppel, et al., 1997).

Insulin secretion

Insulin is released from pancreatic β -cells at a low basal rate and at a much higher rate in response to a variety of stimuli, especially glucose. Hyperglycemia results in increased intracellular ATP (adenosine triphosphate) levels, which close the ATP-dependent potassium channels. Decreased outward potassium current through this channel results in depolarization of the B-cell and the opening of voltage-gated calcium channels. The resulting increased intracellular calcium triggers the secretion of the hormone. (Nolte, et al., 1997).

Insulin degradation

The liver and kidney are the two main organs that remove insulin from circulation, presumably by hydrolysis of the disulfide connection between the A and B chains through the action of glutathione insulin transhydrogenase (insulinase). After this reductive cleavage further degradation by proteolysis occurs. The liver normally clears the blood of approximately 60% of the insulin released from the pancreas by virtue of its location as the terminal site of the portal vein blood flow, with the kidneys removing 35-40% of the endogenous hormone. However, in insulin-treated diabetics receiving subcutaneous insulin injections, this ratio is reversed, with 60% of exogenous insulin being cleared by the kidney and the liver removing no more than 30-40%. The half-life of circulating insulin is 3-5 minutes. (Nolte, et al., 1997).

Action of insulin on glucose transporters

Insulin has an important effect on several transport molecules that facilitate glucose movement across cell membranes. These transporters may play a role in the etiology as well as the manifestation of diabetes. GLUT 4, quantitatively the most important in terms of lowering blood glucose, is inserted into the membranes of muscle and adipose cells from intracellular storage vesicles by insulin. Defects in GLUT 2 mediated transport of glucose into pancreatic beta-cell may contribute to the reduced insulin secretion that characterizes type 11 diabetes. (GLUT) (Nolte, et al., 1997).

Action of insulin on the liver

The first major organ reached by endogenous insulin via the portal circulation is the liver, where its function is to increase storage of glucose as glycogen and to reset the liver to the fed state by reversing a number of catabolic mechanisms, such as glycogenolysis, ketogenesis, and gluconeogenesis, which are associated with the post-absorptive state. These effects are brought about directly through insulin-induced phosphorylation, which activate pyruvate kinase, phosphofructokinase and glucokinase, while relieving gluconeogenic enzymes, including pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose biphosphatase, and glucose 6-phosphatase. Insulin also exerts indirect effects to decrease hepatic gluconeogenesis and ketogenesis by reducing the fatty acid flux to the liver through its antilipolytic action on adipocytes. In addition, insulin decreases urea production, protein catabolism, cAMP (cyclic adenosine monophosphate) in the liver, promotes triglyceride synthesis and, increases potassium and phosphate uptake by the liver. (Nolte, et al., 1997).

Effect of insulin on muscle

Insulin promotes protein synthesis by increasing the amino acid transport and by stimulating ribosomal activity. It also promotes glycogen synthesis to replace the glycogen stores expended by muscle activity. This is accomplished by increasing the glucose transport into the muscle cells, inducing glycogen synthase, and inhibiting glycogen phosphorylase. (Nolte, et al., 1997).

Effect of insulin on adipose tissue

Insulin acts on reducing circulating free fatty acids and promoting triglyceride storage in adipocytes by three mechanisms:

- Induction of lipoprotein lipase, which actively hydrolyzes triglycerides from circulating lipoproteins;
- Glucose transport into cells to generate glycerophosphate as a metabolic product, which permits esterification of fatty acids supplied by lipoprotein hydrolysis;
- Reduction of intracellular lipolysis of stored triglyceride by a direct inhibition of intracellular lipase (Nolte, et al., 1997).

VIII. DIABETES AND GLOBAL HEALTH

The worldwide picture of diabetes is not much better either, with 387 million people with confirmed diabetes according to the latest census. According to the 2014 estimate, the prevalence of diabetes in the world was 9%, among adults aged 18 years or older. It is projected that by the year 2035, those affected by diabetes will be around 592 million. The population with type 2 diabetes continues to increase worldwide. Among the total diabetes patients, 77% live in low- and middle-income countries and 40–49-year-old have the largest number of people of any group. It is estimated that as many as 179 million people remain undiagnosed, for various reasons, but may be affected by diabetes. Every seven seconds, diabetes causes the death of an individual worldwide, and in 2014 alone, 4.9 million deaths were attributed to diabetes with 80% of deaths related to diabetes reported from low- and middle-income countries. In 2014, the overall health expenditure, as a result of diabetes, was estimated as \$612 billion, which is approximately 11% of the total spending on adults. In 2013, type 1 diabetes was reported in more than 79,000 children. According to WHO projection, the diabetes population is likely to increase to 300 million or more by the year 2025. (Meenakshi, et al., 2010). The current studies in India indicate that there is an alarming rise in prevalence of diabetes which has gone beyond epidemic form to a pandemic one. (Pareek, et al., 2009).

Globally, diabetes mellitus presents enormous and increasingly important public health issues. The occurrence and consequences associated with diabetes are found to be high in countries like India (31.7%), China (20.8%) and United State of America (17.7%) (Balaraman, et al., 2010). It is predicted that by 2030, India, China and the United States will have the largest number of people with diabetes. (Fröde, et al., 2008). In most western countries, type 1 diabetes accounts for over 90% of childhood and adolescent diabetes although less than half of individuals with type 1 diabetes are diagnosed before the age of 15 years. Type 2 diabetes is becoming more common in youth onset diabetes in certain at-risk populations. (Patel, et al., 2012).

Diabetes mellitus is a global public health problem with a majority in developing countries. The projected increase over the period from 1995–2025 for developed and developing countries was 42 % and 170 % respectively. In 2025 it is expected that 75 % of diabetics will reside in developing countries. (De Silva, et al., 2016). Diabetes mellitus has become an important health concern in the South Asian region with an estimated increase in the prevalence of diabetes of over 151% between year 2000 and 2030. In the same period, diabetes is projected to increase by 40%. (Wild, et al., 2004). Sri Lanka is a low-middle income country with undergoing rapid epidemiological and nutritional transition. Despite nutritional deficiencies such as iron deficiency anemia, vitamin A deficiency and protein energy malnutrition are reported in some segment of the Sri Lankan population. (Shekar, et al., 2007). Non-Communicable Diseases (NCDs) are also emerging as the major diet associated health problem in Sri Lanka. The prevalence of overweight, obesity and central obesity among Sri Lankan adults were 25.2%, 9.2% and 26.2%, respectively in 2005–2006, as defined by Asian Body Mass Index (BMI) cutoffs (Katulanda, et al., 2010). and there is a clear upward trend. (Jayawardena, et al., 2012). The age-adjusted prevalence of metabolic syndrome among Sri Lankan adults was 24.3% (95% CI: 23.0–25.6). (Katulanda, et al., 2012). The prevalence of obesity related metabolic problems such as diabetes and hypertension among Sri Lankan adults were 13–14% and 18–19% respectively. (Wijewardene, et al., 2005). Moreover, in Sri Lanka, diet-related chronic diseases currently account for 18.3% of all deaths and 16.7% of hospital expenditure. (Popkin, et al., 2001).

IX. DIABETES AND GENERAL HEALTH

Diabetes mellitus is associated with a broad range of clinical presentations, from being asymptomatic to keto acidosis or coma, depending on the degree of metabolic disorder. (Seino, et al., 2010). The long - term persistence of metabolic disorders can cause susceptibility to specific complications and also foster arteriosclerosis leading to substantial morbidity and mortality globally. (Demmer, et al., 2013). The chronic complications of diabetes mellitus include accelerated development of cardiovascular diseases, end-stage renal disease, loss of visual acuity, and limb amputations. All of these complications contribute to the excess morbidity and mortality in individuals with diabetes mellitus. (Reinehr, et al., 2013).

Diabetes mellitus is a progressive disease requiring effective lifelong medical care for the prevention of secondary and tertiary complications. The optimal control of blood glucose has clearly demonstrated a significant decrease in the development of complications. Control of diabetes mellitus requires the combination of treatment and preventive action, taking into account biological and health behavioral factors, health service responsiveness, and socioeconomic conditions. (De Silva, et al., 2016).

The available data on complications and management of diabetes mellitus in Sri Lanka are limited to state hospital attendees, excluding many patients who obtain services from the private healthcare sector. In Sri Lanka the out-patient care for more than 50 % of the population is provided by the private healthcare sector while in-patient care for more than 90 % is provided by the state healthcare sector.

State healthcare in Sri Lanka is free at the point of delivery to all citizens of Sri Lanka. This includes all visits / consultations (out-patient as well as in-patient care including intensive care services and surgical care), medications, investigations and procedures including ambulance transportation / transfers and hospital meals. (De Silva, et al., 2016).

In WHO STEP Survey reported that 3% of Sri Lankan consume more than five fruits and vegetable per day. (Somatunga, et al., 2004). Sri Lankans consume excess number of starchy foods but per below number of fruits, vegetables and dairy products. (Jayawardena, et al., 2012). Predominantly carbohydrate diets raise plasma glucose, insulin, triglycerides and non-esterified fatty acids leading to insulin resistance. (Wolever, et al., 2003). High prevalence of diabetes and its complications among Sri Lankan adults may be associated with starch based but poor variety meals. (Katulanda, et al., 2008).

A diabetic person should take more care about his body weight and food habit, regular exercise can also improve the utilization of the blood glucose through different tissue in the body which can reduce the symptoms of diabetes. (Patel, et al., 2012). Amongst the food groups of dietary pyramid, meat, green leafy vegetables, milk and fruits were least frequent. Increased intake of fruits and vegetables could play a protective role against obesity associated metabolic risk factors in South Indians who is prone to get premature coronary artery disease. (Radhika, et al., 2012). Reasons for monotonous diet among Sri Lankan adults needed to be explored

although it is associated with low obesity level. Public Health initiatives to improve appropriate diversity of diet are important. When a diet is composed of foods that differ on sensory characteristics such as color flavor and shape may cause hyperphagia (Raynor, et al., 2001).

Animal and human studies showed that food intake increases when there is more variety in a meal or diet and that greater dietary variety is associated with increased body weight and subsequently obesity. (McCrary, et al., 1999). Dietary variety within food groups was positively associated with body fatness among healthy adults. (Mirmiran, et al., 2006). Several studies showed a positive correlation between calorie intake and dietary diversity. (Torheim, et al., 2004). Additionally, to achieve good metabolic control in diabetes and keep long term, a combination of changes in lifestyle and pharmacological treatment is necessary.

X. IMPACT OF ANTI- DIABETES MEDICATION

Four categories of oral antidiabetic agents are available namely; insulin secretagogues, biguanides, thiazolidinediones, alpha-glucosidase inhibitors. (Nolte, et al., 1997). The treatment of diabetes mellitus is considered as the main global problem and successful treatment has yet to be discovered. Even though insulin therapy and oral hypoglycemic agents are the first line of treatment for the diabetes mellitus they have some side effects and fail to significantly alter the course of diabetic complications. (Venkatesh, et al., 2010).

Many of these oral antidiabetic agents have a number of serious adverse effects, thus, the management of diabetes without any side effects is still a challenge. (Pareek, et al., 2009), (Meenakshj, et al., 2010), (Patel, et al., 2012). Sulphonylureas are useful in the treatment of diabetes which cannot be controlled by diet or other available therapy. Sulphonylureas are absorbed rapidly from the intestine, some important drugs of this group are tolbutamide, chlorpropamide, glibenclamide, tolazamide etc. Biguanides is the other class of oral anti-diabetic agents which control all types of diabetes mellitus. It reduces glucose absorption from the intestine and can also be used to treat mild diabetes during pregnancy. (Patel, et al., 2012).

Metformin can rarely cause a serious (sometimes fatal) condition called lactic acidosis. Stop taking metformin and get medical help right away if develop any of the following symptoms of lactic acidosis: unusual tiredness, dizziness, severe drowsiness, chills, blue/cold skin, muscle pain, fast/difficult breathing, slow irregular heartbeat, stomach pain with nausea, vomiting, or diarrhea. Lactic acidosis is more likely to occur in patients who have certain medical conditions, including kidney or liver disease, recent surgery, a serious infection, conditions that may cause a low level of oxygen in the blood or poor circulation (such as congestive heart failure, recent heart attack, recent stroke), heavy alcohol use, a severe loss of body fluids (dehydration), or X-ray or scanning procedures that require an injectable iodinated contrast drug. Tell your doctor immediately if any of these conditions occur or if you notice a big change in your overall health. You may need to stop taking this medication temporarily. Natural anti-diabetic drugs from medicinal plants, is the other available therapy for the treatment of diabetes mellitus due to their well-known biological activity. Substances extracted from fruiting bodies, cultured mycelia, and culture media have exhibited promising in vitro and in vivo biological activity including anti-diabetic. (Ding, et al., 2010).

Insulin secretagogues: sulphonylureas

The major action of sulphonylureas is to increase insulin release from the pancreas. Sulphonylureas binds to a 140kDa high-affinity sulphonylurea receptor that is associated with a beta cell inward rectifier-type ATP-sensitive potassium channel. The binding of a sulphonylurea inhibits the efflux of potassium ions through the channel and results in depolarization. Depolarization, in turn, opens a voltage-gated calcium channel that results in a calcium influx and the release of insulin. Insulin synthesis is not stimulated and may even be reduced by sulphonylureas. Some evidence indicates that after prolonged sulphonylurea therapy, serum insulin levels no longer increase but may even decrease. It was also established that chronic administration of sulphonylureas to type 2 diabetic patients reduced serum glucagon levels but increased the binding of insulin to the tissue receptors. Seven sulphonylurea drugs are available in the USA and are conventionally divided into first- and second-generation agents, which differ primarily in their potency. The first-generation includes tolbutamide, tolazamide, acetohexamide and chlorpropamide and the second generation includes glyburide, glipizide and glimepiride. (Nolte, et al., 2001).

Insulin secretagogues: meglitinides

Meglitinides are a new class of insulin secretagogues. Repaglinide, the first member of the group, was approved for clinical use by the FDA in 1998. These drugs modulate Beta cell insulin release by regulating potassium efflux through the potassium channels. Meglitinides and sulphonylureas overlap in their molecular binding sites since meglitinides have two binding sites in common with sulphonylureas and one unique binding site. They have however, no direct effect on insulin exocytosis as does sulphonylureas. (Nolte, et al., 1997).

Biguanides

Three types of biguanides are being used in the treatment of diabetes namely phenformin, buformin and metformin. The use of the first two mentioned was discontinued in the United States of America due to its association with lactic acidosis. Metformin originates from the French lilac, Galega officinalis L., a perennial herb known for centuries to reduce the symptoms of diabetes. The active compound is galegine, a guanidine derivative. Metformin's clinical trials were successfully completed in 1995 and its use approved in the United States of America. The full extent of the mechanism of the action of biguanides is unknown, but its blood glucose-lowering action does not depend on the presence of functioning pancreatic beta cells. Proposed mechanisms of action include direct stimulation of glycolysis in the tissue, and the increase of glucose removal from the blood; reduced hepatic gluconeogenesis;

slowing of glucose absorption from the gastrointestinal tract; with increase glucose to lactate conversion by enterocytes and the reduction of plasma glucagon level.

Biguanides have been most often prescribed for patients with refractory obesity whose hyperglycemia is due to insulin resistance. As metformin is an insulin-sparing agent and does not increase weight or provoke hypoglycemia it has the advantage over insulin and sulfonylureas in treating hyperglycemia. The most frequent toxic effects of metformin are gastrointestinal and there is a risk of lactic acidosis. (Nolte, et al., 1997).

Thiazolidinediones

Thiazolidinediones is a recently introduced class of oral antidiabetic drug that enhances target tissue insulin sensitivity. Two types are commercially available namely rosiglitazone and pioglitazone. The exact mechanism of their action is not known, but their major action is to diminish insulin resistance in muscle and adipose tissue.

Troglitazone was the first thiazolidinedione to be approved but was withdrawn due to its association with a low but significant rate of idiosyncratic liver damage. Two other thiazolidinediones namely rosiglitazone and pioglitazone demonstrated efficacy similar to that of troglitazone but with no evidence of hepatotoxicity. (Nolte, et al., 1997).

Alpha- glucosidase inhibitors

Acarbose and miglitol are the two agents available in this class. Alpha-glucosidase inhibitors act by inhibiting the enzymes, pancreatic alpha-amylase and alpha-glucosidase, found in the brush border cells that line the small intestine. They cleave the more complex carbohydrates such as starches, oligosaccharides and disaccharides into monosaccharide molecules before being absorbed in the duodenum and upper jejunum. Acarbose and miglitol are competitive inhibitors of alpha glucosidase and modulate the postprandial digestion and absorption of starch and disaccharides. Miglitol differs structurally from acarbose and is six time more potent in inhibiting sucrose.

The binding affinity of the two compounds differ, acarbose and miglitol both target alpha-glucosidases: sucrase, maltase, glycoamylase, dextranase. Isomaltase and Beta-glucosidase are targeted only by miglitol and alpha-amylase only by acarbose. The clinical consequence of enzyme inhibition is to minimize upper intestinal digestion and absorption of ingested starch and disaccharides in the distal small intestine, lowering post meal glycemic excursions and creating an insulin-sparing effect. Prominent adverse effects include flatulence, diarrhea, and abdominal pain which results from the appearance of undigested carbohydrate in the colon that is then fermented into short-chain fatty acids, releasing gas. (Nolte, et al., 1997).

XI. HERBAL MEDICINE FOR DIABETES MELLITUS

There are many herbal formulations available in the market which are used to treat diabetic mellitus such as Diabecon, Diasulin, Pancreatic tonic 180 cp, Chakrapani, Bitter gourd Powder, Dia-care, Diabetes-Daily Care, Gurmar powder, Epinsulin, Diabecure, Diabeta and Syndrex. (Modak, et al., 2007). If the diet of the diabetic patients is not properly controlled, insulin or oral hypoglycemic drugs will not act properly. Herbal medications have been used for the treatment of variety of ailments, a huge number of populations in the world is entirely dependent on traditional medicines. (Meenakshi, et al., 2010), (Feshani, et al., 2011).

A number of medicinal plants and their formulations are used for treating diabetes in Ayurveda medicine system as well as in ethno-medicinal practices. (Pareek, et al., 2009). In India, indigenous remedies have been used in the treatment of diabetes mellitus since the time of Charaka and Shusrutha. From the ethnobotanical information, about 800 plants which may possess anti-diabetic potential have been found. (Wariet, et al., 2011), (Venkatesh, et al., 2011), (Patel, et al., 2011). Several plants have been used as dietary adjuvant and in treating the number of diseases even without any knowledge on their proper functions and constituents. This practice may be due to its fewer side effects compare to the synthetic hypoglycemic agents and because of their safety, effectiveness, and availability. (Balaraman, et al., 2010), (Deewanjee, et al., 2009).

Although various synthetic drugs were developed to treat diabetes but still very a smaller number of drugs is available for the treatment of diabetes. (Deewanjee, et al., 2009). There are about 200 pure compounds from plant sources reported to show blood glucose lowering effect. The compounds may be alkaloids, carbohydrates, glycosides, flavonoids, steroids, terpenoids, peptides and amino acids, lipids, phenolics, glycopeptides and iridoids. Many anti-diabetic products of herbal origin are now available in the market. More than 1 200 species of plants have been screened for activity on the basis of ethno medicinal uses. (Patel, et al., 2012).

XII. DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS

Diabetes mellitus is diagnosed using either the estimation of plasma glucose (FPG or OGTT) or HbA1c. Estimation of the cut off values for glucose and HbA1c is based on the association of FPG or HbA1c with retinopathy. Fasting plasma glucose of ≥ 126 mg/dL (7.0 mmol/L), plasma glucose after 2-h OGTT ≥ 200 mg/dL (11.1 mmol/L), HbA1c $\geq 6.5\%$ (48 mmol/mol) or a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) along with symptoms of hyperglycemia is diagnostic of diabetes mellitus.

The advantages of using HbA1c over FPG to diagnose diabetes include greater convenience and pre analytical stability, lower CV (3.6%) compared to FPG (5.7%) and 2h OGTT (16.6%), stronger correlation with microvascular complications especially retinopathy, and a marker for glycemic control and glycation of proteins which is the direct link between diagnosis of diabetes and its complications. (Akram, et al., 2015).

XIII. INVESTIGATION OF HbA1c IN DIABETES MELLITUS

HbA1c is an important indicator of long-term glycemic control with the ability to reflect the cumulative glycemic history of the preceding two to three months. HbA1c not only provides a reliable measure of chronic hyperglycemia but also correlates well with the risk of long-term diabetes complications. Elevated HbA1c has also been regarded as an independent risk factor for coronary heart disease and stroke in subjects with or without diabetes.

The valuable information provided by a single HbA1c test has rendered it as a reliable biomarker for the diagnosis and prognosis of diabetes. The formation of the glycated hemoglobin is a normal part of the physiologic function cycle. However, as the average plasma glucose increases, so does the amount of glycated hemoglobin in the plasma. This specific characteristic of the hemoglobin biomarker is utilized for estimating the average blood glucose levels over the previous two to three months. (Shariq, et al., 2016).

HbA1c can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardized to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement. An HbA1c of 6.5% is recommended as the cut point for diagnosing diabetes. A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests. (WHO, et al., 2011). Achieving near-normal glycated hemoglobin (HbA1c) significantly decreases risk of macro vascular and microvascular complications. (Sinclair, et al., 2000). However, only about 50% of diabetic patients reach their HbA1c target. (Bruce, et al., 2009).

XIV. DIAGNOSTIC CRITERIA FOR DIABETES MELLITUS

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XV. COMPLICATIONS OF DIABETES MELLITUS

Diabetes complications are common among patients with type 1 or type 2 diabetes but, at the same time, are responsible for significant morbidity and mortality. The chronic complications of diabetes are broadly divided into microvascular and macro vascular, with the former having much higher prevalence than the latter. Microvascular complications include neuropathy, nephropathy, and retinopathy, while macro vascular complications consist of cardiovascular disease, stroke, and peripheral artery disease (PAD). Diabetic foot syndrome has been defined as the presence of foot ulcer associated with neuropathy, PAD, and infection, and it is a major cause of lower limb amputation. There are other complications of diabetes that cannot be included in the two aforementioned categories such as dental disease, reduced resistance to infections, and birth complications among women with gestational diabetes

The present special issue has been devoted to showcase a broad spectrum of research and review papers addressing recent fundamental advances in our understanding of diabetic complications. It includes 12 articles in total, which cover 5 thematic areas: (a) epidemiology and pathogenesis of diabetic complications, (b) microvascular complications, (c) macro vascular complications, (d) miscellaneous complications, and (e) treatment options. (Konstantinos, et al., 2017).

XVI. MANAGEMENT OF DIABETES MELLITUS

Through lifestyle and diet modification. Studies have shown that there was significant reduction in the incidence of type 2 DM with a combination of maintenance of body mass index of 25 kg/m², eating high fiber and unsaturated fat and diet low in saturated and trans-fats and glycemic index, regular exercise, abstinence from smoking and moderate consumption of alcohol. Suggesting that majority of type 2 DM can be prevented by lifestyle modification. Patients with type 2 DM should receive a medical nutrition evaluation; lifestyle recommendations should be tailored according to physical and functional ability. (American Diabetes Association., et al., 2013).

Diabetes is a chronic condition the control of which demands the combining efforts of the patients and a group of specialized care providers. The patient participation, motivation and enthusiasm are critical for achieving optimal control of the disease. The successful management of diabetes requires more than just controlling the plasma glucose levels. It requires a multidisciplinary approach. Giving the fact that most patients will have developed one or more complications of diabetes at the time they show up at the health care provider and the diagnosis is set, then the case management will focus on two directions:

1. history and physical examination, in order to check for any signs and symptoms of acute hyperglycemia
2. screening for long-term or chronic complications related to DM.

According to the International Diabetes Federation (IDF) the idea behind diabetes management is that, although monitoring and controlling the level of plasma glucose is essential, the optimal management of diabetes requires also the investigation of potential DM complications and their management, accompanied by efforts to modify the risk factors for different diabetes related conditions. Diabetes care and management might also be dependent on a certain number of other factors such as social and economic factors.

Cultural factors and employment factors are also very important as they relate to life-style, including smoking, drinking, physical activity, the patterns of feeding, stress and a whole range of other activities which could serve as risk factors for triggering diabetes. (Arjan, et al., 2012).

CONCLUSION

Diabetes mellitus is a progressive disease requiring effective lifelong medical care for the prevention of secondary and tertiary complications. The optimal control of blood glucose has clearly demonstrated a significant decrease in the development of complications. Control of diabetes mellitus requires the combination of treatment and preventive action, taking into account biological and health behavioral factors, health service responsiveness, and socioeconomic conditions. The chronic complications of diabetes are broadly divided into microvascular and macro vascular, with the former having much higher prevalence than the latter. Microvascular complications include neuropathy, nephropathy, and retinopathy, while macro vascular complications consist of cardiovascular disease, stroke, and peripheral artery disease. A number of medicinal plants and their formulations are used for treating diabetes in Ayurveda medicine system as well as in ethno-medicinal practices. In India, indigenous remedies have been used in the treatment of diabetes mellitus, from the ethnobotanical information, about 800 plants which may possess anti-diabetic potential have been found.

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