(Review Article)

Secondary complications of diabetes

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Abstract

Diabetes Mellitus is caused due to inconsistency in the secretion of insulin or due to defective action of insulin which can be caused by insufficient insulin or a defective pancreas. Diabetes is growing at an alarming rate with an estimation of 8.4% worldwide. Diabetes has 2 types i.e., TIDM1, in which there is excessive beta cell degradation and as result deficiency of insulin occurs in body and TIDM2 where there is insulin resistance that leads to hyperglycemia. Secondary complications of diabetes include cardiovascular damage, due to different types of glycation products, metabolites, inflammation, and endothelial dysfunction. Thyroid malfunction, as glycemic uncontrolled and insulin requirements is typically related to hyperthyroidism thus occurrence of thyroid disorder may also affect diabetes control. Effect on wound healing, as the inflammation and tissue response to wounds are unusual and endogenous growth factors (EGF) show less activity to the wounds site in diabetic patient. Diabetic neuropathy is the most recurrent complication of the diabetes. Another outcome is oxidative stress which increase with growing diabetes. The growth and development of muscles is considerably decreased along with crucial risk aspect for heart failure in type 1 diabetes. Neural and retinal cells are also affected in diabetic patients causing neuropathy and retinopathy.

Keywords: Diabetes; Retinopathy; Neuropathy; Inflammation; Insulin

1 Introduction

Endocrinological disorder Diabetes Mellitus (Lyons et al., 2016), is caused due to inconsistency in the secretion of insulin or due to defective action of insulin or may be both, a combined name of metabolic and heterogeneous illness. Insulin regulates blood sugar level, where in the absence or reduced secretion of which cause tenacious high blood sugar level and person may lead to glucose intolerance (Jahan et al., 2015). This is a primeval disease known to mankind. Due to its death ratio from 14 century, it is regarded as Black Death.

Diabetes mellitus is a disease in which the patient has insufficient insulin or have defective pancreas or may have both conditions. It is portrayed by the hypoglycemia with coalesce of polydipsia, polyuria and glycosuria (Boulton et al., 2005). According to the study of Diabetes Atlas, 366 million peoples were affected by this contagious disease in 2011, and this number is increasing rapidly and may reach to 552 million by the year 2030 in mostly those regions which are economically dominating the world. It is recent report of International Diabetes Federation (IDF) which reveals that 61.4 million people are affected by diabetes in India and this figure is likely to reach to the 101.2 million at the ending of year 2030 (Parikh et al., 2011).

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According to reports of World Health Organization (WHO, 2016) world pervasiveness of diabetes among adults of 18+ years was recoded as nine percent. Predicted deaths rate reached up to 1.5 million in 2012, which is directly contributed by the diabetes (WHO, 2012). Death rate is maximum in low and middle-income regions of the world which is up to 80%. According to WHO estimation that, at the end of 2030 diabetes will take the seven number in the death list of diseases (Mathers and Loncar, 2006). Taking preventive measures like taking healthy diet, taking exercise regularly and maintaining optimum body weight and abstain tobacco use may help to completely avert delay the outbreak of type 2 diabetes. Many heart diseases and strokes are also incorporated with diabetes. Multinational survey has highlighted 50% of people die with cardiovascular diseases strokes (Morrish et al., 2001). Diabetes is not a single disease, but it is combined name of low blood pressure, neuropathy and increases the incidental foot ulcer which cause infection which results in limb amputation. Due to long-term damage accumulation caused to blood vessels it causes an important blindness condition called diabetic retinopathy. World Health Organization reported that up to 1 percent blindness in the world is attributed by diabetes.

The new forecast for Diabetes mellitus (DM) is that, nearly 592 million people will be effect globally by the year 2035 and in present day it costs approximately $250 billion per annum in Health and wellness. A familiar disarray known as Osteoarthritis with a planetary pervasiveness cause suffering in between 20% and 30% of adults .The estimated Joint arthroplasties presume to arrive <4 million per year (Eka and Chen, 2015). As a result, there is an influential overlap between DM and TJA, with leading of 22% of arthroplasty victims diagnosed with DM (Chrastil et al., 2015). DM is not referred as only one illness; it is broad group of diseases vary from disrupt fasting glucose to having all the characteristics of multi organ dysfunction syndrome (MODS) #39; which involves in the secondary to determined non-typical glucose levels. An unusual increase in blood glucose levels as a result of chronic disorder tends to lead to the hemoglobin non-enzymatic glycosylation, forming glycated hemoglobin, known as hemoglobin A1c (HbA1c) (Chrastil et al., 2015).
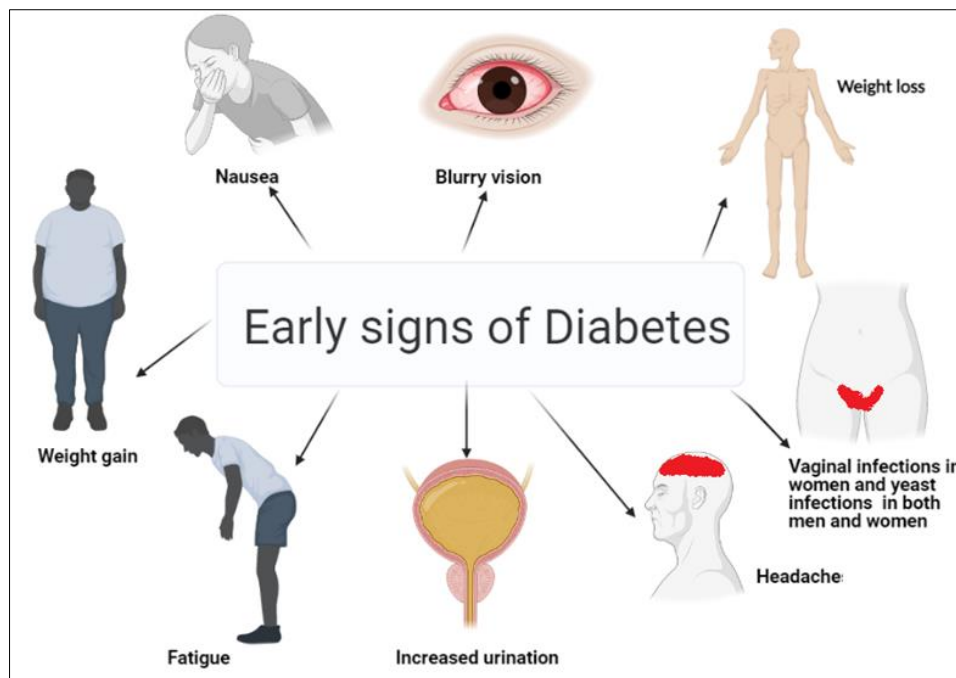

Figure 1 Early sign and symptoms in diabetic patients

Without any specific classification and grouping Hyperglycemia is referred as Elevation in blood glucose level, like pre-diabetes, gestational diabetes, TIDM1 (type 1 diabetes) in which there is not enough insulin in the body to convert glucose and TIDM2 which is characterized by insulin resistance or destruction of beta cells of pancreas, and maturity-onset diabetes of young (MOYD) in an autosomal dominant gene disrupting insulin production, refers to any of several heredity form of diabetes mellitus caused by mutation or diabetes caused by surgeries (Chrastil et al., 2015).

Diabetes is growing at an alarming rate with an estimation of 415 million adults suffering from diabetes and it comes out to 8.4% worldwide. The number is thought to increase up to 642 million by 2040. According to reports one third adult individual in United States will have some form of diabetes (Chrastil et al., 2015).

In old days diabetes was considered as risk factor for periodontitis, but recent research has highlighted that only the diagnosis of diabetes is not important but the level of glucose in the blood seeks to be correctly measured (Borgnakke, 2016). Major sign and Symptoms of diabetes are highlighted in figure 1.

2 Types of Diebeties Mellietus

Characteristic feature of diabetes mellitus is the presence of high blood glucose level. Usually diabetes is present TIDM1, in which there is excessive beta cell degradation and as result deficiency of insulin occurs in body and TIDM2 where there is insulin resistance that leads to hyperglycemia.

2.1 Type 1 Diabeties

Type 1 diabetes is a condition of abnormal metabolism of carbohydrate, proteins and fats as a result of insulin deficiency (Popławska-Kita et al., 2014).Pro-inflammatory problems like higher blood glucose level and high level of cytokines give clue for immunological disturbance (Saxena et al., 2013) and this condition affects quality of life and also this makes impacts on health care system and economy of country (Borges et al., 2011).

T1DM is a caused due to destruction of beta cells of pancreases without the destruction of surrounding cells. The destruction of beta cells leads to a condition known as insulites and this destruction is done by T-cells of immune system. When insulites develops then patient is dependent on secondary insulin throughout life (Ibrahim et al., 2021).

50 genes have so far been discovered which sole cause of heritable T1DM. However genetics is not the only cause diabetes. Beside genetics several environmental factors contribute to diabetes. According to reports that by changing the habitat i.e. the place of residence, the risk rate of diabetes also changes. A study performed on monozygotic twins by changing the place of residence, penetrance rate of both varies which confirms the involvement of environmental factors (Pociot and Lernmark, 2016).

Pathological studies on also indicate that among these environmental factors one is viral infection especially enteroviruses in case of T1DM (Beeck and Eizirik, 2016). The pathological mechanism in T1DM is destruction of beta cells as a result there occurs hyperglycemia (Atkinson, 2012). Among many different factors of immune system contributing to beta cell destruction two are most important which are indicated by the presence of CD8+ T lymphocytes. Studies have proved that pathogenesis is dependent on complex formation of CD8+/MHC class 1. These both forms a complex and causes the damage (DiLorenzo and Serreze, 2005).

2.2 Type 2 Diabetes

T2DM is the crucial health concern universally. Presently the prediction about diabetic victims is that it will reach to 366 million by 2030. The morbidity and mortality rates continue to be high (Mitri et al., 2011). T2DM is the most prevalent form of diabetes which seeks immediate attention. It is estimated that among all-cause mortality 14.5% are due to diabetes which are 9% of total adults worldwide. The individual between 20 and 70 are at more risk of developing diabetes (Zhang and Gregg, 2017).

It is major health load universally, as well as diabetes is also a big economic burden; Globally, about 12% of the health expenditures are used for treatments and coverage, that is why it is become most costly diseases (Zhang and Gregg, 2017) .Three of most populated countries of world China, India and US are in epidemic stage of diabetes and most of the infected individuals are adults (Ibrahim et al., 2021).

In US about 12% of adults are infected with T2DM and this rate has gone up to 60% over the last 25 years. The number accounted for T2DM is about 29 million (Cheng et al., 2013). China has performs controlled and randomized studies among the high risk diabetes individuals in order to diminish or delay the diabetes type 2, Finland (Tuomilehto et al., 2001), the U.S, and India(Ramachandran et al., 2006), and the others, with pre diabetes, can be controlled by modifying their lifestyles, including exercise, consuming fiber in greater amount as compared to total calories, fats, and sugar-sweetened beverages so reduces the risk of type 2 diabetes up to 30–60%. Moreover, the advantages of long term prevention behaviors, leads to the normal levels of sugars, called normoglycemia, maintained lower levels or normal levels of T2DM, and reduces the risk of long term eye disorders and cardiovascular deaths.

Pathophysiology also introduces another term which contributes to type 2 diabetes known

"The ominous octet," means eight core defects (T2DM) (DeFronzo et al., 2013). This causes the lower secretion levels of the insulin, decreased incretion effect, increased lipolysis, higher rates of glucose reabsorption, less glucose uptake,

neurotransmitter malfunction, and hepatic glucose production will be increase, and glucagon secretion will also be increase (Schwartz et al., 2016).

The patients having diabetes almost have no consistent feeding habit and no diet plan (Shaten et al., 1993). In T2DM the individual is detected with insulin resistance and insulin resistance is a condition in which glucose is stored in muscles and liver rather than converting it to energy. During insulin resistance disorder muscle glucose transporters GLUT4 are not translocated from cytoplasm to plasma membrane although both GLUT4 m RNA and there is in normal form (Dela et al., 1994).

Type 2 diabetic obese individuals observed with the lower levels of glucose after moderate or mild exercise (Yki-Järvinen et al., 1994). There is direct relation between glucose level and exercise time and intensity. Glucose level decreases with regular exercise (Ohlson et al., 1985).

Type 2 diabetes is a result of insulin resistance which leads to high blood glucose levels. Which is an abnormality because beta cells in the pancreas subsequently increases their production of insulin (Association, 1998). The process of insulin moderate glucose uptake is directly proportional to the amount of muscle mass, and is inversely related to the fat mass and occur primarily in the skeletal muscles (Yki-Järvinen and Koivisto, 1983) .Food to be eaten and food to be avoided by the diabetic patients are highlighted in figure 2.
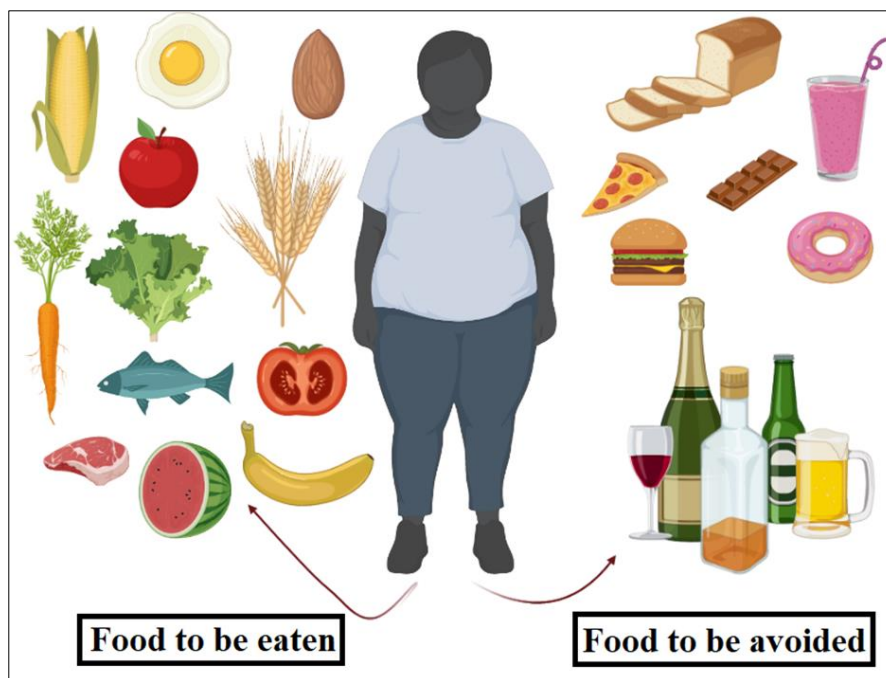

Figure 2 Precautions of food eaten and food avoided for diabetic patient

3   Secondary Complications of Diabetes

3.1   Cardiovascular Damage

Risk factors for type 2 diabetes mellitus includes cardiovascular damage, responsible for affecting millions of individuals globally. Different types of glycation products, metabolites, inflammation and endothelial dysfunction leads to T2DM induced cardiovascular problems (Eckel et al., 1985). All these variations and modifications involves the changes in atrial systems which are the high risk for cardiovascular diseases. Since 10 years, by measuring the varying degree changes in blood flow in diabetic patients, shows high central blood pressure (BP) levels and stiffening of arteries compared with control populations (Lacy and Williams, 2005).

Patients with diabetes shows greater complications as the disease progresses.so, it is concluded that the time and duration of disease has an automatic effect on diabetic patients as the aging occur so the cardiovascular complication get worse and death may occur due to cardiovascular disease if the duration of diabetes lengthen (Wannamethee et al., 2011) of death from natural causes (Brun et al., 2000) and of alterations in myocardial function. In literature, most

studies indicates the direct relation between the diabetes type 2 and the stiffening of arteries with the duration, but no significant alterations has been observed in diabetes type 2 lasts for shorter time period (Wadwa et al., 2010), but the significant changes has been observed in diabetes type 2 patients, in which disease lasts for longer period of time (Charvat et al., 2010).

Besides, individuals having a great risk of cardiovascular morbidity and mortality they also suffer from renal diseases. Diabetic patients are 2 to 4 time more likely to develop cardiovascular disease than non-diabetic patients. The most common biochemical abnormalities include, T2DM are TC, TG, LDL, VLDL, HDL and S CRET (Verma et al., 2013).

Diabetic patients are more susceptible to cardio attacks and strokes, and it is stated from a multinational company that about 50% of deaths have been occur due to diabetes (primarily heart disease and stroke).

3.2   Thyroid Malfunction

Diabetes Mellitus (DM) and thyroid dysfunction (TD) both commonly considered as endocrine disorders. For this purpose in 1979, the report was published about association between Diabetes Mellitus and thyroid dysfunction then after this many researcher had worked over it (Feely and Isles, 1979).

Thyroid disorder depend on environmental and host factors, occur in different population ranging from 6.6% to 13.4. The prevalence of Thyroid disorder further rises in precise population like diabetics, where prevalence varies from 10 to 24% (Papazafiropoulou et al., 2010). The occurrence of thyroid disorder may also affect diabetes control. Glycemic uncontrolled and insulin requirements is typically related to hyperthyroidism. Repaid gastrointestinal glucose absorption, increased hepatic gluconeogenesis and probably increased insulin resistance, hence thyrotoxicosis may unmask the hidden diabetes.

Recent reviewing and expected (Ishay et al., 2009) analyses have revealed that patients with T2D have a remarkably high prevalence of unidentified thyroid disease, for hypothyroidism is 3-10% and 5-13% for overall thyroid dysfunction. Female gender, advance age and thyroid autoantibodies are risk factor for thyroid disorders as well as in patients with diabetes.

3.3   Effect on Wound Healing In Diabetes

Wound healing is one of the evolutionarily conserved process that basically aimed to repair cutaneous barrier at the injury site. It comprises of basic phases of hemostasis, inflammation, proliferation, and tissue remodeling (Eming et al., 2014).

Normal wound healing consists of three overlying phases: (a) acute inflammation, (b) proliferation/angiogenesis and (c) tissue remodeling. Monocytes and macrophages first line of defense cell derived from hematopoietic stem cells work as a supreme inflammatory cell types in all stages of wound healing.

Epigenetic changes, that consist of DNA methylation, histone modification and small non-coding RNAs, are necessary in sustaining proper lineage commitment and self-renewal of (HSCs) (Haetscher et al., 2015). Recent study suggest that Type 2 Diabetes Mellitus reduce the repressive histone methylation marker H3K27me3 in the promoter of the IL-12 in bone marrow progenitors. This epigenetic mark goes to terminally differentiated wound-resident macrophages in Type 2 Diabetes Mellitus mice (Gallagher et al., 2015).

Diabetic foot ulcer is the most common complications of diabetes which leads to delayed wound healing. Wound healing hemostasis, inflammation, proliferation remodeling these all phases are occur in efficient manner (Wang et al., 2016). But, in diabetic patient the inflammation and tissue response to wounds are unusual and endogenous growth factors (EGF) show less activity to the wounds site (Losi et al., 2013). The clear reduction in wound fluid growth factors throughout diabetic compared with acute wound repair (Cooper et al., 1994) arises from their deprivation or inhibition owing to the existing of proinflammatory cytokines and metalloproteinase in the diabetic wound site. Previous studies determined that the growth factors like epidermal growth and basic fibroblast growth factor are deregulated during diabetic patient wound healing (Barrientos et al., 2014). Several types of wound-dressing ingredients having growth factors (Knott et al., 1996), cells, or chemokines (Yoon et al., 2016) have been used to speed up wound healing, because EGF and bFGF both have important role in promoting tissues repair.

Epidermal growth factor helps by stimulating the proliferation and migration of keratinocytes and thus speed up dermal regeneration (Hardwicke et al., 2008). On the other hand, basic fibroblast growth factor promote wound healing and angiogenesis. Beside these therapeutic effects, commercially available (EGF) and (bFGF) also have some limitations such

as lack of stability at room temperature, short half-life and loss of activity while loading onto a matrix (Dogan et al., 2009). In addition to that, the wound environment can potentially deactivated and induce the degradation of exogenous growth factors as a result, matrix metalloproteinase activity increase (Trengove et al., 1999).

The so-called "diabetic foot" remains major problem for people suffering from diabetes and cause significant burden on national healthcare systems due to high morbidity and the high risk of amputation (Falanga, 2005). A damage skin repair process underlies this kind of medical situation in type 2 diabetic patients (Blakytny and Jude, 2006). Definitely, physiological wound healing consists of a complex sequence of cellular events characterized by inflammatory cascade, migration of calls, creation of new vessels from vascular remodeling and through the activity of endothelial progenitors cells, synthesis of well-establish provisional matrix, collagen apposition and re-formation of an primary epithelium (Reiber and Raugi, 2005).

Among all these cellular procedures, angiogenesis is one of the difficult process during wound healing in diabetes. The agiogenic cytokine vascular endothelial growth factor (VEGF) promotes capillary sprouting and endothelial cell migration and proliferation to form new capillaries. Remarkably, VEGF regulation of angiogenesis is severely decreased in diabetes: the expression of this hematopoietic factor is reduced because of increased oxidative stress (Altavilla et al., 2001). One possible approach to repair diabetic wounds has focused on VEGF-based gene therapy targeted to replace the depressed hematopoietic factors that improve wound healing in diabetic mice model.

3.4 Diabetic Neuropathy

In western world diabetic neuropathy is the most predominant type. It's the most recurrent complication of the diabetes whose impermanence and morbidity rate is extremely high posing a burden on economy (Vinik and Ziegler, 2007). The pervasiveness of the diabetic autonomic neuropathy and (DAN) as well as diabetic peripheral neuropathy (DPN) differs from one population to another, and it also depends on the mechanism causing the disease. Various factors play a part in the pathogenesis of the diabetic neuropathy out of which a few are non-metabolic elements, and some are metabolic elements. Non-metabolic elements consist of age and height (Partanen et al., 1995), whilst metabolic elements comprise of the hypertension, hyperglycemia, syslipidimia, and obesity (Elliott et al., 2009).

3.5 Oxidative Stress

Reactive oxygen species (ROS) along with free radicals have been implicated in several types of neurodegenerative disorders like cancer, diabetes, and cardiac diseases. The reports indicate that oxidative pressure in diabetes rises in response to the rise of the heightened production of the ROS and in comparison, the reduced antioxidant defense system. This decline in the antioxidant defense system is low in the beginning but it gets worse with the passage of time. Once diabetes grows, the oxidation of proteins, lipids and DNA rises with the progression of the illness (Johansen et al., 2005). In diabetes the oxidative pressure is believed to be the reason of the auto-oxidation of the glucose, non-enzymatic protein glycosylation, alterations in the antioxidant enzymes, impaired glutathione metabolism, reduced ascorbic acid concentrations and the development of lipid peroxides. Superoxide, hydroxyl radicals and hydrogen peroxides are removed by the antioxidant enzymes i.e., superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPxs) (Soto et al., 2003).

3.6 Prostate Cancer

Type 2 diabetes and prostate tumor have inverse relation to each other. Recent study confirms that there is less likelihood of prostate cancer in Diabetes affected is because of the usage of anti-diabetic medications (Murtola et al., 2008). Metformin is the one of the most used anti-diabetic drugs now a days. In the latest study the involvement of metformin with prostate tumor was examined but the results it gave were not consistent. In some metformin consumers, the investigators reported a reduced risk of prostate cancer whereas in some other consumers it exhibited not any relationship. Despite the findings of this research, it must be observed that this research has not considered the kind of the diabetes, its seriousness and time of the beginning which are all very essential for such sort of the research. To prevent the unfairness in the findings, aspect of the onset of type 2 diabetes and prostate cancer, (Harding et al., 2015) usage of the anti-diabetic medication and more factors which may affect the outcomes of the method of correlation.

Various types of the tumors have the amplified risk in affected persons with diabetes mellitus i.e. liver, pancreas, biliary track, kidney, endometrium, esophagus, and colon (Strickler et al., 2001). The trials on the involvement of diabetes and prostate tumor have indicated that this cancer have reduced risk in diabetic patients. An evaluation of the 14 reports that was completed by Bonovas et al. and this research was published in 2004, has statistically demonstrated a reduced risk (9%) of the prostate tumor in diabetic patients (Bonovas et al., 2004). The study indicated that there was not any

substantial variation between the control and the patient nor the exclusion of one research amongst the 14 significantly altered the findings of the research.

Experiments conducted in the European lineages, where prostate tumor is epidemic there is inverse relation amongst these disorders. These findings revealed that diabetic patients have about 20% low risk of acquiring prostate tumor than non-diabetic patients (Calton et al., 2007). The relation of type 2 diabetes and prostate cancer differs between the various populations, however the association in various ethnics is not shared (Jemal et al., 2008).

3.7   Dyslipidimia

The two main causes of the metabolic dysregulation in type 2 diabetes are hyperglycemia and dyslipidemia. Both components are the main risk aspects for cardiovascular disease.

Articles have indicated a definite relation amongst diabetes mellitus and the probability of cardiovascular diseases. Globally there is reported a 52% to 65% of the casualties from diabetes mellitus that are due to cardiovascular causes. Including these cardiovascular diseases, the essential contributors are cerebrovascular and ischemic heart diseases US Department of Health and Human Services. A diabetic patient has double to quadruple heightened risk of the coronary artery disease. Similar heightened risk is likewise for the peripheral artery diseases and of the stroke (Beckman et al., 2002).

Dyslipidemia is a prominent risk element of the cardiovascular disorders in type 2 diabetes. In diabetic dyslipidemia the serum VLDL-triglycerides rises above average and the amount of HDL-cholesterol gets reduced. However, the amount of LDL-cholesterol stays the same or changes marginally.

3.8   Diabetic Myopathy

Diabetic myopathy is the decrease in the muscle mass, strength, as well as decreased physical capability (Andersen et al., 1997). Diabetic myopathy is provided less consideration by the investigators, but it is believed to be clearly involved to rise the disease rate. The report is backed by the statistic and the fact that skeletal muscles have the greatest level of the glucose uptake in the body. If any defect appears in muscles of the body, then the entire-body glucose homeostasis will be altered.

Skeletal muscles have the amazing ability of development, regeneration, and adaptation. The muscles cells have better ability of growing and regeneration in the childhood and teenage years. This capability in the infantile age and teenage years is greater because the amplified protein production and combination of the myoblast cells (Hawke, 2005). Reduction in the above stated elements are not the only factor but also some other factors i.e. lightness, casting and some other disease form are also accountable for the decrease in the muscle mass, myoblast cell quantity and muscle power (Wanek and Snow, 2000). In old muscle the atrophic aspects have additional quick and permanent remodeling procedure i.e., reduced proliferative ability, myonuclear accretion as well as reduced myoblast cells (Mozdziak et al., 2000).

The growth and development of muscles is considerably decreased in type 1 diabetes. This deficiency results in decreased myofiber size, decrease in the muscle mass and shift to glycolytic phenotype (Krause et al., 2009). It has been described in the trials of human type 1 diabetes that thickness of the capillaries is not influenced but mice trials indicate that the disease is accountable for the reduction in the capillarization of skeletal muscles as well as angiogenesis (Kivelä et al., 2006).

In corresponding accounts of the type 1 diabetes, type 2 diabetes studies have additionally indicated muscle atrophy, amplified glycolytic fiber in addition to reduction in the concentration of the capillary. Disturbance in muscle metabolism is very common in type 2 diabetes that results cause lowered intermyofibrillar mitochondrial content. Deposition of fats becomes irregular when muscle metabolism is disturbed (Chomentowski et al., 2011). As an outcome of such variations in the muscle natural environment the muscle grows to be metabolically rigid and thus cannot interchange the lipid and carbohydrate metabolism caused in reaction to the insulin.

3.9   Cardiomyopathy

Kannel et al, 1974 described the effect of diabetes in causing heart problems. A Framingham research of Kannel et al. comprised of 292 diabetic subjects and 4900 non-diabetic test subjects showed that in 18-year period of diabetes in a person has 2.4-fold extra risk of growing of congestive heart disease. The females in parallel have a high quantity than male i.e., 5:1 (Kannel et al., 1974).

The affected people who were utilizing insulin have the heightened risk of growing congestive heart failure. Even Though that, the affected people that were consuming the hypoglycemic agents displayed no heightened probability of the congestive heart failure. The studies indicate that type 1 diabetes is the crucial risk aspect for heart failure (Margolis et al., 1973).

3.10 Neuropathy

Diabetic neuropathy is believed to be problematic for almost 50% of the overall diabetic affected people either type 1 or type 2. Diabetic neuropathy has FDA passed treatment and that is why it is serious form in diabetic people. The single technique to avoid or decelerate the diabetic neuropathy is to sustain the glycemic concentration (Pop-Busui and Martin, 2016).

One of the very recurrent problem of the diabetes is the distal symmetric neuropathy (DPN). It is not understood completely till date as a problem of the diabetes. Nearly 30-50% of the diabetic affected role are disturbed by the high health care expenses and high disease rate. Low glycemic regulation is assumed to be the key aspect of the DPN (Ismail-Beigi et al.,2010). Elevated levels of blood-glucose ratio are related to the endothelial disfunction, inflammatory progressions, and the accumulation of the advanced glycation end products (AGEs) in the external matrix of Schwan cells. This destroys the myelin and interrupts the regeneration procedure after the injury (Albers and Pop-Busui, 2014). Elevated levels of triglycerides and lower levels of the serum HDL is the reason of the DPN. It initiates the microvascular angiopathy in addition to increased signs of neuropathy. It isn't completely established whether the dyslipidemia cause polyneuropathy or is it just effecting due to hyperglycemia in DPN (Nienov et al., 2017).

Methylene-tetrahydrofolate reductase enzyme is encoded by MTHFR gene. MTHFR is participate in homocysteine and folate metabolism. Abnormality in the MTHFR gene cause decreased action of this enzyme that leads to hyper-homocystenemia. Studies have demonstrated that high homocystenemia has cytotoxic impacts which harms the nervous function by performing the oxidative wounds to the endothelial cells. In diabetes, because of hyper-homocystenemia macro as well as microvascular problems occur that results in the nervous damages (Yigit et al., 2013).

There are numerous accounts of the weakening of the axons in diabetes that suggests diabetes as a cause to the problems of neurons which may cause diabetic neuropathy (Rahmati et al., 2015).

PDN pervasiveness depends on the gender of the population that may vary among men and women. Studies indicates that men can grow diabetic neuropathy prior as compared to women. Nerve signaling also gets disturbed frequently more in men than women (Kiziltan and Benbir, 2008). The paw removal threshold is lowered more in women in contrast than men. On the contrary men have more damage of intra epidermal nerve fiber thickness (O'Brien et al., 2016).

3.11 Retinopathy

In US single leading reason of the loss of sight is the retinal vascular disorder which occurs due to diabetes mellitus. This complication is frequently noted in the working phase of people of the US (Emptage et al., 2014). Disease symptoms comprises of the rise in permeability of vascular retina. Retinal ischemia is too frequently seen in retinal vascular condition. Blindness is of many types of processes i.e., vitreous hemorrhage caused by neovascularization, retinal capillary non perfusion along with macular edema. Retinopathy is frequently seen in those people who have long-lasting disease of diabetes. The pervasiveness of retinopathy can be regulated by regulating hypertension and hyperglycemia (Stratton et al., 2001). Retinopathy is believed to be common problem up till now and this figure is estimated to grow in the forthcoming time. The disorder is likely to rise by the view of epidemic of type 2 diabetes globally along with the absence of specific medication except to regulate the glucose concentration. Other therapies such as intravitreal injection and laser photocoagulation are also used to cure diabetes in rather late phases, but these medicines have serious side effects. Diabetic neuropathy disturbs almost all types of cells in both rodents and humans that lead to reduced structure as well as function in body.

Vasoregression is single vascular phenotype seen in this problem. In this endothelial and pericytes cells are lost. The constant drops out of capillary lead to neurodegeneration which in turn cause neurofeneration leading to retinal thickness. This process could also lead to apoptosis that eventually cause cell death.

Accumulation of reactive elements like ROS, RCS and RNS can also lead to diabetes. It is believed that the accumulation of these substances cause TRPC to change function but up to now no clear evidence is found (Kolibabka et al., 2016).

4 Conclusion

Diabetes is a persistent disorder caused due to malfunction in the insulin production or its working or both at the same time. The most severe complication produced in the situation of DM is its side effect as well as secondary difficulties which arise from the accumulation of glucose. This collected glucose is held into various metabolic paths which can cause the production of several complexes and metabolites along with free radicals that can harm the systemic tissues as well as organelles. Glycemic management has a constructive effect for managing and avoiding the onset of the secondary problems and slowing the development of these problems.

Compliance with ethical standards

Disclosure of conflict of interest

All authors confirm that there is no conflict of interest.

Authors Contribution

All authors contributed equally in collecting data and drafting manuscript.

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