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Endothelium Disfunction Distracts Wound Healing Of Diabetics

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Abstract.Diabetes Mellitus (DM) is non-communicable prevalent disease and has been in increase from year to year. According to the WHO estimation, patients with DM in Indonesia in 2000 accounted for 5.6 million, this increased to 14 million in 2006. This number is expected to be 6.3% of the total world population in 2025. In diabetics insulin resistance occurs, the failure of the pancreatic beta cells to lower the amount of insulin circulation. Decrease in insulin function is as a result of the glucose transporter derived from daily consumption that cannot be converted to energy, this leads to hyperglycemia. This causes the activation pathways polyols, AGEs, PKC and hexosamine (Glena). This result in increase of ROS derived from mitochondria, resulting in endothelial dysfunction. Endothelial dysfunction induces failure of formation of acute phase proteins, antioxidants immunonutrition, deficiency of oxygen and nutrients to the injured blood vessels. This impairs wound healing in diabetes. The process of wound healing requires a high energy intake with a low glycemic index. The management is aimed to plan a healthy diet and lifestyle so that blood glucose levels, blood pressure, blood lipid are in control.

Keywords: *hyperglicemia, ROS, endothelium disfunction, wound healing*

1. Introduction

Changes from agricultural to industrial practice, and in life style and socio-economic are likely to cause the increase in non-communicable diseases (NCDs). World Health Organisation estimated that NCDs contribute to about 60% death and 43% diseases globally. One of the communicable diseases that steadily increase is diabetes mellitus (DM)[1]. According to WHO, the number of diabetic in Indonesia in 2000 was 5.6 million, and increased to 14 in 2006. This would increase to 333 million or 6.3% of world population in 2025. The high prevalence of diabetic in Indonesia positions the country to the 4th of world highest DM prevalence following United States, India, and Chine[2].

Unhealthy food choice, including consuming food more than required, are triggering factors for DM. Indonesian meal in urban area tipically composes of 67% carbohydrates while in the rural is 69.6% of total energy daily [3].

Dramatic increase of blood glucose requires much effort to normalize it. This causes beta pancreatic cell to release a large amount of insulin quickly. Pancreatic beta cell fatigue results in decrease of insulin secretion[4]. This furthermore causes high level of blood glucose or more commonly known as diabetes mellitus type 2 (*hyperglycemic chronic*) which is frequently accompanied by various metabolic and hormonal disorders [5].

Hyperglycemic may trigger protein glication through Maillard reaction producing *Advanced Glication end Products* (AGEs). This proces also produces *Reactive Oxygen Species* (ROS) which further causes tissue damage [6]. Prolonged hyperglycemic may also activates paths which increase *flux free fatty acid* (FFA) and oxydises in mitochondria resulting in increase of ROS. This elevates apoptosis of beta pancreatic cells and supress insulin biosyntesis. Unbalance between increased exposure to free radicals and antioxidant defenses resulting in a state of stress. Free radicals are generally unstable and highly reactive. ROS are highly reactive oxidant activity and can have a negative impact. Each formed ROS can initiate a chain reaction that continues until the ROS are neutralized by other ROS or antioxidant systems [7]. There are three main types of ROS, namely superoxide (O_2• -), hydrogen peroxide (H_2O_2), and hydroxyl (HO•). ROS are formed naturally in a variety of metabolic processes. The main source of ROS production in cells is the mitochondrial respiratory chain that utilizes 80-90% oxygen. Other sources of ROS, namely cytochrome P450 oxidase enzymes located in liver. Enzymes involved in the metabolism of fatty acids, cholesterol, steroids, and bile acids using molecular oxygen and the reaction produces ROS [8]. Excessive ROS formation has been seen in various pathological conditions such as diabetes, atherosclerosis, ischemia-reperfusion injury, cardiovascular diseases and neurodegenerative diseases[9]. Free radicals can be formed endogenously from a variety of sources, such as the process of phagocytosis, or derived from exogenous sources such as the environment and toxins from cigarette smoke[10,[11] as well as having a tendency to cause damage to important macromolecules, DNA, lipids, and proteins. This damage can cause interference with normal physiological function[12].

Oxidative stress in diabetes is caused by imbalance of the redox reactions due to changes in carbohydrate and lipid metabolism and lower the antioxidant defense system, including glutathione (GSH)[13]

In people with diabetes can occur acute hyperglycemic conditions. This causes an increase in ROS production and oxidative damage can trigger acute vascular endothelium, the cell membrane and lipoprotein components and lead to the existence of a more stable plaque in patients with DM [14],[15],[16].

Common problems that diabetics encounter include hard-cured wound. Foot ulcer occurs to 15% of diabetics and approximately 84% of which require amputations[17,[18]. This medical treatment unfortunately very often results in increase of wound complication. This paper examines the occurrence of endothelial dysfunction and failure of wound healing in Diabetes Mellitus.

2. Literature Review

A. Diabetes Mellitus Concept

Definition

Diabetes mellitus is symptoms that occur in individu who blood glucose level increases as a result of insulin deficient both absolutely or relatively [19].

Epidemiology

As shown by epidemiological studies incidence and prevalence of DM type 2 tend to increase worldwide. WHO estimated that number of diabetic in Indonesia increased from 5.6 million in 2000 to approximately 14 million in 2025. Research conducted in urban areas Jakarta showed that prevalence of DM in 1982 was 1,7%, increasing significantly to 5.7% and 12.8% in 1993 and 2001 respectively. Data from Statistics Beureu of Indonesia indicated that in 2003 the number of people who were more than 20 years old was 133 million, and it is predicted that the figure will increase to 194 million. Assuming that urban and rural prevalences of DM are 14.7% and 7.2% respectively, then there will be 12 million diabetics in urban areas and 8.1 million in rural areas.[2] Health Baseline Research of 2007 shows that national prevalence of DM is 1.1%. East Java is a province that has a higher prevalence of diabetes than the national prevalence [20].

DM is closely related to increase of mortality and morbidity as a result of macro and micro-vascular. Oxidative stress will stimulate endothelial cell apoptosis by a mechanism involving the formation of hyper-production of ROS and superoxide anion (O_2-). The interaction of two types of free radical superoxide ($\bullet O_2$) and nitric oxide (NO•) will form peroxinitrate (ONOO•) [21] and further facilitates susceptibility to a number of serum proteins undergoing oxidation, which contributes to the inhibition of endothelial proliferation and impact on endothelial dysfunction. Endothelial dysfunction resulting in the production of Nitric Oxide (NO) in the endothelium is not formed, thus adding its contribution to vascular disease and in general can stimulate the occurrence atherosclerosis, nephropathy, neuropathy and retinopathy and increase the risk of amputation[22],[23],[24],[25],[26],[27].

Incidence of cardiovascular diseases is 3 time higher among diabetic patient, and life expectancy decreases regardless of age with the increase of disease severity [28]. Major death-caused diseases in Indonesia are shown on Table 1[1] As depicted on Table 1 DM is regarded an important cause of death.

Table 1. Major Diseases Causing Death in Hospital [1]

No.	Jenis Penyakit	%
1	Stroke, with no bleeding	5,9
2	Pneumonia	3,5
3	Thyphoid fever	3,5
4	Lung tuberculosis	3,3
5	Intracranial bleeding	3,1
6	Diabetes Mellitus	3,0
7	Slow growth of fetus, malnutrion, and preterm-related complication	3,0
8	Trauma	3,0
9	Heart disease	2,9
10	Renal failre	2,9

Table 2. DM and Other Metabolic-related Dieseases of In-hospital Patien 2005 [1].

No.	Disease	Number of Case	Number of Death	CFR (%)
1	Diabetes Mellitus	42.000	3.316	7,9
2	Thyrotoxicosis	913	67	7,3
3	Other thyroid disorders	4.065	148	3,6
4	Other endocrine and metabolic diseases	9.912	823	8,3

Table 2 shows that DM is the main cause of death of in-hospital patient, despite being the 6th cause of death in hospital in Indonesia [1].

Etiology

Carbohydrate consumption in developing countries reach 85% of daily total energy. Composition of typical Indonesian diet comprises of 67% carbohydrate in rural areas and 69.6% in urban [3]. Several diseases relates to high fructose consumption. These include hypertention, insulin retention, hypertriacilglycerolemia, obesity, type 2 DM, pre-eclampsia, chronic renal failure, stroke, cardiovascular and death [29].

Etiology of DM varies, however they lead to insulin deficiency. Genetic plays important role in diabetes mellitus, mostly in type 2 DM. The probability of DM occurence of monozygote twin is almost 100%, whereas on brother or sister almost 40%, and on offspring 33% [30].

Type 1 DM is known as *Insulin-Dependent Diabetes Mellitus* (IDDM), or *absolute insulin deficiency*. This autoimmune disorder is genetically trait and is caracterized by damage of pancreatic cells. The occurence is usually acute and can be found on all group of age, but more commonly of children and women on her 40s. Sensitive individu may respond to trigger factors that may in form of virus infection as a result of poor environment. Insulin administration should in line with proper dieting which focuss on carbohydrate control. In order to avoid hypoglycemic food intake should be well maintained both as meal and snack. The main concern of this type of DM is to prevent microvascular diseases and supress the incident of cardiovascular disease and nephropathy [31].

Type 2 DM is caused by failure of insulin production and resistance to insulin or decrease of sensitifity to insulin. From insulin resistance view the disease is known as *disease of nutrient storage.* The abnormality is initially shown by decrease sensitifity to insulin with the sign of high level of insulin in the blood. There are hyphothesis explaining this, however obesity and lack of physical activities as well as genetic involvement are supposed to be disposition factors to occurence of insulin resistance [31],[32].

Diagnosis and Management of type 2 DM

Type 2 DM is diagnosed using level of blood glucose as presented in Table 3 [5].

Table 3. Blood Glucose Level for NIDDM Diagnosis [5].

	DM (mg/100 mL)
Random blood glucose	
Venous plasma	>200
Capillary blood	>200
Fasting blood glucose	
Venous plasma	>126
Capillary blood	>110

Management of DM [33].

Management of diabetic focuses on education, nutrition therapy, physical exercise, and medical intervention.

As type 2 DM is usually found on individual whose behaviour and life style has been settled down, therefore active involvement of the patient, family, and people in patient environment are indispensably required. Education should be prioritised on motivating the patient and be carried out comprehensively.

Nutrition therapy is an essential component of DM management. Key success for the therapy is solid team work comprising of physician, nutritionist, and other health professional and the patient. The basic recommendation of DM diet consisting of the right amount, right type, and right schedule of meal should be emphasized especially to patients who use insulin or medication to decrease blood glucose.

The recommended nutrient composition on the DM diet follows. Carbohydrate intake is recommended between 45– 65% of total energy and fat is 20–25%. Fat intake more than 30% of energy is not allowed whereas cholesterol should be limited to less than 300mg/day. Recommended intake of protein is 10–20% total energy and natrium is 3000mg or equal to 6–7g table salt (1 teaspon). Natrium intake for people with hipertension should not exceed 2400 mg.

Intake of fibre should be±25g/1000 kcal energy/day. Fruits, vegetables and beans are excellent fibre sources and contain vitamin, minerals as well as other active ingredient which benefit health. Energy form sweetener should be considered in calculating daily total energy. Non-nutritive sweeteners such as aspartam, sacharine, acesulfame-K, sucralose, and neotame may be consumed within the ADI (Acceptable Daily Intake).

Physical activities is also essential for DM management. Walking to market, choosing stair instead of elevator, gardening should be part of daily activities. Furthermore, exercise in regular basis (3–4 times per week for approximately 30 menit each), is a fundamental for managing type 2 DM. The exercise is preferably aerobic, for example walking, cycling, jogging, and swimming. The choice of this type of exercise should consider age and physical fitness. Those who has DM with complication should be more careful. Exercise helps achieve physical fitness and maintain normal body weight and improve insulin sensitivity and better control blood glucose accordingly.

Medical intervention is another resource in managing DM. When normal blood glucose could not be achieved by diet and exercise then insulin, hypoglycemic medication or their combination may be administered.

B. Effect of Hyperglycemia on Endothelium Function

Endothelial cells play important roles in controlling blood vessels. The cells coat internal lumen of blood vessels and act as media between blood circulation and unstriated muscles of blood vessels. The endothelium also fasilitates complex function of unstriated muscle of blood vessel and cells within blood compartment. Endothelial cells further has significant conntribution in controlling blood vessel [34].

DCCT (Diabetes Control and Complication Trial) and *UKPDS (United Kingdom Prospective Diabetes Study)* indicates that hyperglycemia causes initial tissue damage. Other contributing factors include genetic, hypertension and dyslipidemia. The most sensitive cell to the damage are endothelial and meningeal cells, for instance endothelial capillary cell in the retina (*retinopathy diabetic*), meningeal cell in the glomerulus (*nephropathy diabetic*), neuron (*neuropathy diabetic*), and damage of blood vessels of the leg (*macro-angiopathy diabetic*) [16].

Tissue damage due to hyperglycemia may occur through various pathways, as shown on Table 4 [35].

Table 4. Pathway of Tissue Damage [35].

No	Year of Invention	Pathway Name
1	1966	Polyol
2	End of 1970	Advanced Glycation end Products (AGEs)
3	Beginning of 1990	Hyperglycemia-induced activation of Protein Kinase C (PKC)
4	End of 1990	Hexosamine pathway flux

Polyol Pathway

As shown on Figure 1, in normal condition aldose reductase decreases toxic aldehyde in the cells and converts to inactive alcohol. Most of cellular glucose phosphorylates to glucose-6 phosphate catalysed by hexokinase. This process requires essential co-factor NADPH during the intracellular antioxidant formation. In hyperglycaemia condition aldose reductase converts cellular glucose to sorbitol which resulted in increased concentrations of sorbitol and enzyme NADPH concentration decreased. Sorbitol then oxidizes to fructose with the aid of sorbitol dehidrogenase (SDH). This sorbitol conversion occurs slowly because sorbitol dehydrogenase enzyme activity is very low on the condition of hyperglycemia causing accumulation in the cell and increases

osmotic pressure and may cause cell damage [36]. With the glutathione decrease, the polyol pathway increases intracellular oxidative cell and results the condition of neuropathy and vasculopathy in patients with diabetes mellitus [16].

AGE Pathway

Hyperglycaemia elevates *AGE precursor's* production which in turn damages cells through 3 mechanisms. First, it modifies intracellular protein including protein that involves in gene transcription. Second, AGE precursor may diffuse out the cells, leading to modification of ECM (extra cellular matrix) molecule close to the cells and disorganization of signalling between matrix and cells, and the cell dysfunction. The presence of AGEs will produce ROS which increases damage of blood vessels. Third, the diffusing AGE precursors also modifyy plasma protein which then reacts and activates AGE receptor. This results in formation of inflammatory cytokines and growth factors that causes vascular damage as shown on Figure 2 [35][37],[16].

Activation Pathway of Protein Kinase C (PKC)

PKC group consists of 12 serine/threonine-kinases which involve in intracellular signal related to function of vascular, cardiac, immunology and other systemic functions. Intracellular hyperglycaemia increases *diacylglycerol* (DAG) which is important *activating cofactor* for protein isoform β and δ-PKC. PKC may also be activated by various growth factors and radical superoxida ($\bullet O_2$) and formation of AGEs which is induced by hyperglycemia [38].

Increased DAG will trigger micro and macro vascular. Increase in DAG will spur microvaskular and macro vascular complications caused by mitochondria ROS, with the activation of PKC will cause various effects on gene expression with clinical manifestations such as in Figure 1 [16].

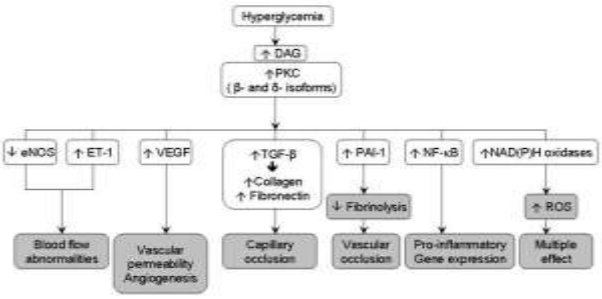

Figure 1. PKC Activation and clinical Manifestation due to Hyperglycaemia [16].

Hexosamine Pathway

Increase of glycose in the cell will undergo glycolysis to form glucose-6 phosphate, and fructose 6-phosphate through *glycolytic pathway*. Increased of fructose 6-phosphate diverts to signalling path in which glutamine GFAT (*fructose-6 phosphate aminotransferase*) and converts fructose-6 phosphate to glucosamine-6 phosphate with *UDPGlcNac (uridine diphosphate N-acetyl glucosamine)* as end product. *N*-acetyl glucosamine reacts with serine and threonine residues of transcription factor causing gen expression modification [14]. For instance, *N*-acetyl glucosamine modifies *transcription factor* Sp1 which causes increase expression of TGF-β1 (*transforming growth factor-β1*) and PAI-1 (*plasminogen activator inhibitor-1*). Both the substances play important roles in atherosclerosis and vascular dysfunction.

According to [35], hyperglycaemia in target cell (such as endothelium) increases ROS production by mitochondria which later causes damage of nuclear DNA strand. This damage will activate poly ADP-ribose polymerase (PARP), a *DNA repair enzyme*, which will modifies and decreases GADPH activates resulting in increase of AGEs production, activation of PKC, as well as activation of hexosamine polyol pathways (Figure 2).[16] These processes explain the pathogenesis of micro vascular complication [35].

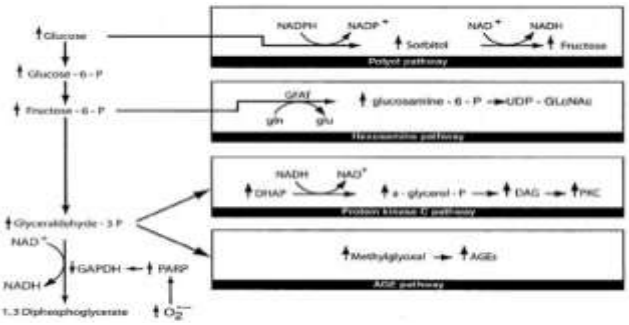

Figure 2. Four Main Mechanisms that Trigger Mitochondrial ROS Formation and Causes Tissue Damage as a result of Hyperglycaemia [16].

C. Endothelium Disfunction and Wound Healing Disturbance

Endothelial cell lines blood vessel. The roles of this cell are vital to attain balanced blood composition and good performance of blood vessel wall at all times. In healthy people layer of endothelial cells are in state of close, thus blood only flows within the blood vessel. In contrast, the presence of trauma changes the cells behaviour in which cells loosen each other causing blood to flow out of the vessel to develop swollen [39].

Endothelial dysfunction may also change the cell function which results in failure of NO availability, thus endothelial dysfunction should be differentiated with endothelial damage which is anatomical. Endothelium position on the vascular diseases is a major barrier against macromolecule and cells that circulate from blood to tissue. Endothelial permeability is regulated by intercellular junction which is complex structure formed by trans membrane adhesion molecule relating to cytoskeletal protein tissue [40]. Endothelium is target organ of damages caused by the diseases of hypertension, diabetes mellitus, and hyperlipidemia [41.

Hyperglycemia is unfavorably condition for wound healing in diabetic people. The wound increases risk of complication including infection and amputation. Pathophysiological there is correlation between DM and wound healing failure. The failure relates to system disturbances of vascular and nerve, immune, and abnormality of blood biochemistry. The chronic state, lack of glucose control and care of the wound would all together worsen the prognosis [42].

DM complication causes disorders related to micro and macro-angiophaty and neuropathy. These trigger angiogenesis, ephytelialisation, collagen deposition problems and other essential processes because of deficiencies of growth factor and cytokinin proangiogenic, matrix deposition and remodeling tissue on wound healing step. Thus, failure of wound healing occurs [43],[44].

In diabetic patients, wound healing takes place slowly. Result shows that inhibitor of p38 MAPK (Mitogen-Activated Protein Kinase) which has anti-inflammatory activity is found on chronic wound. The process starts with inhibition of inflammatory cytokines expression and regulation pathway to the wound resulting in challenged recovery [45].

Discussion

Insulin resistance occurs in diabetic. Beta pancreatic cell fails to produce sufficient insulin to maintain normal blood glucose. This failure arises due to decreased insulin function in energy production process in which insulin acts as glucose transporter to mitochondria. The decrease of insulin function causes glucose obtained from the intake cannot be converted to energy. Therefore, there will be built up glucose in the blood causing hyperglycemia.

Chronic hyperglycemia may cause damage of blood vessel of retina, kidney, and nerve. One important factor involved in the process is oxidative stress. This is as a result of increase of oxidant within or out of the cell. The oxidant increase is triggered by elevated blood glucose. Normally oxidant is used for maintaining immunity, however elevated oxidant causes damages. Damages are not only caused by chronic hyperglycemia but also acute hyperglycemia [46].

Elevated blood glucose also produces *Reactive Oxygen Species* (ROS) in mitochondria, which suppress phase-1 *glucose-induced insulin secretion* through inhibition of *glyceraldehyde 3-phosphate dehydrogenase (*GADPH). The presence of free radical in diabetic decreases *immunity,* causing decrease of *chemotaxis* and *phagocytosis* activities. These activities play major roles in prevention of infection thus prolongs wound healing [47].

Study by El-Osta (2008) concludes that acute hyperglycemia could result in permanent damage of blood vessels. The research was conducted on culture of non-diabetic human blood vessel and mice. The result

showed that acute hyperglycemia triggered permanent expression on gene that causes atherosclerosis. Foam cell is formed in the blood vessel during the atherosclerosis process. The cell grows and thickens blood vessel wall and forms plaque which then oxidizes and thrombus and ruptures in the vessel. The rupture results in damage of blood vessel [48].

In type 2 diabetic negative effect of oxidised LDL is severer. In non-diabetic the LDL contributes to formation of atherosclerosis since the initial process. As type 2 diabetic has higher LDL therefore the formation process occurs more rapidly.

UKPDS (*United Kingdom Prospective Diabetes Study*) has shown that hyperglycaemia is determining risk factor for micro vascular complication but not macro vascular. Risk of occurrence of *micro vascular end point* increases 10 times with rise of HbA_{1c} from 5.5% to 9.5%. The similar case only doubles the risk for macro vascular.

Insulin resistance appears to be more dominant in macro vascular complication pathogenesis. Data from *San Antonio Heart Study* shows that insulin resistance increases cardiovascular risk 2.5 times, this even after adjusting for other risk factors including LDL, HDL, TG, blood pressure, and smoking. Insulin resistance also increases *flux free fatty acid* (FFA) from adipose to artery endothelia cell. The FFA oxidizes in mitochondria and causes increase of ROS which ultimately ends with similar outcome, that is activating pathways of AGEs, PKC, hexosamine (GlcNac) and NFκB [16].

There 4 pathways for hyperglycemia to vasculopathy diabetic. Immediate effect; through endothelial basement membrane, collagen, smooth muscle, and others, are all dysfunctional. Polyol pathway; with the accumulation of sorbitol in the cell, will be obtained and the osmotic effect miosinositol levels and activity of Na/K-ATPase and glucoosilation non-enzymatic process. By changing the physico-chemical properties of the cell and form Advanced glycosylation end-Products (AGEs), which contribute to the chronic complications of diabetes mellitus. This settles AGEs in tissues, the body's proteins that turn-over its slow as: collagen, myelin, crystalline, and elastin, LDL lipoprotein, albumin, IgG. This bond is chemically irreversible [16].

Type 2 diabetic consumes excessive energy from carbohydrate or fat which may block endothelium by formation of plaque. Plaque is fibrous blockage or fat-rich thin connective tissue. Recent study shows that *matrix metalloproteinase* (MMPs) contributes to plaque formation. However, it is also responsible for lowering substances in the fibrous blockage such as collagen, elastin, fibronectin, and proteoglycan. In addition to increased ox-LDL, size of LDL particle is another potential problem for type 2 diabetic. LDL size relates to endothelium damage.

Endothelium dysfunction is a vasculopathy diabetic pathophysiology. Current studies demonstrates that endothelium dysfunction is a predictor for cardiovascular. Endothelium damage releases growth factor which promotes monocyte to move into intima layer of blood vessels. Lipids enters into blood vessels through both active and passive transport and converts monocyte on blood vessel wall into macrophage and phagocytes cholesterol LDL to form foam cells [49]. The process of endothelium damage is shown on Figure 3.

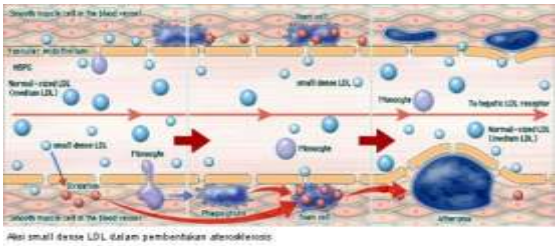

Figure 3. Process of Endothelial Damage as a Result of SDLP and Atherosclerosis Formation

Hyperglycemia also promotes LDL oxidation through several effects of pro-oxidant including protein kinase C activation, glycosylation increase of protein function and glucose auto-oxidant. In addition, hyperglycemia causes endothelium dysfunction following release of oxidative phosphorylation and eNOS [50.

On their 4 or 5 decades, mortality risk of the diabetics increases twice. Blindness, renal failure, and amputation are all related to micro vascular complication and require costly care [28]. When good care is not provided, endothelial dysfunction on diabetic is likely to cause complications which affect whole body function including diabetic retinopathy, neuropathy, nephropathy, coronary heart diseases, and gangrene [51].

Diet is fundamental for diabetic management as unhealthy food habit plays important role on the initial diabetic development. Development of type 2 diabetic may be prevented by good food habit specifically focusing on carbohydrate intake. Blood glucose increase can be well controlled by the diet, physical exercise, and medication [52]. The cause of atherosclerosis on type 2 diabetic is multifactors which involve complex

interaction between these factors: hyperglycemia, hyperlipidemia, oxidative stress, early aging, hyperinsulinemia and/or hyperproinsulinemia and changes in process of coagulation and fibrinolysis.

Recent hypothesis related to the course is that initial development of atherosclerosis lession is indicated by changes in endothelial cel function. Endothelial disfunction may be developed in both type 2 and type 1 diabetic especially when microalbuminemia has occured. Current studies shows that endothelia disfunction may also be developed in individu with insulin resistance (obese) or those who have high risk of developing type 2 dibetic and gestational diabetic [34].

Wound healing process is strongly influenced by nutrition. Nutrient form tissue is synthesized to acute phase protein which promotes the healing. However, the *chronic no resolving inflammation* p38 mitogen in diabetic inhibits the synthesis. Furthermore, there is also failure to antioxidant formation which functions to enhance immunonutrition in the wound healing process. This failure occurs due to decrease of beta pancreatic cell function in which glucose form tissue fails to be converted to glutamine before further formation to glutathione and antioxidant. As acute phase protein and antioxidant formation are inhibited, the wound healing is delayed accordingly [46].

Special treatment should be given to diabetic who has gangrene with hyperglycemia. First step to the treatment is to normalize blood glucose by administration of insulin. This is important in order to prevent hyper osmosis when wound is developed. Insulin administration is also important to help wound heals because insulin can promotes antioxidant formation which diabetic could not produce due to decrease in beta pancreatic cell functions.

Wound healing failure in diabetic is likely the presence of inhibitors. Increased blood glucose causes cell wall to harden so that the blood cannot flow through the wounded blood vessel surface resulting in failure of hemoglobin to distribute oxygen. This affects oxygen and nutrients deficiency of the wound.

When blood glucose is normal wound healing process occurs more rapidly provided that nutrient intakes are adequate. The healing process requires high energy intake and index glycaemia value should be considered in choosing right foods to prevent hyperglycemia. Other consideration includes control of blood pressure, fat intake, and life style. When uncontrolled this may cause perilous endless chain "hyperglycemia–oxidative stress–beta cell dysfunction–hyperglycemia" on diabetic. DM management should be aimed on blood glucose control as optimum as possible to cut the chain down.

3. Conclusion

1. Hyperglycaemia activates pathways of polyol, AGEs, PKC, and hexosamine (GlcNac) resulting in increase of ROS from mitochondria, and endothelial dysfunction.
2. Endothelial dysfunction causes failure formation of *acute phase protein*, *immunonutrition* and antioxidant and oxygen and nutrients deficiency of wounded blood vessels. This results in problem of diabetic wound healing.
3. Diabetic wound healing requires proper diet, high energy intake, and low glycemic index of foods. The management also involves healthy life style to control blood glucose, blood pressure, and plasma lipid.

4. Recomendation

Other factors specifically that associates to nutrition which related to wound healing on diabetics is an interesting area to study. One is how the effect of certain foods on a variety of indicators in the process of wound healing in diabetics especially needs immediate research.

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