Literature review: diabetes, inflammation and obesity

LITERATURE REVIEW

DIABETES

The metabolic disease diabetes mellitus is marked by high blood glucose concentration as a result of impairment in insulin secretion and/or insulin action. The primary cause of high blood glucose concentration is most of the time not obvious as to be a result of either defects in insulin secretion or insulin action on target tissues since both impairments often occur in the same patient. Numerous factors may result in the formation of diabetes mellitus ranging from autoimmune destruction of the pancreatic β-cells leading to a decrease of insulin production to anomalies that cause insulin resistance. Impairment of insulin action on target tissues is the root of aberration in fat, protein and carbohydrate metabolism. The long-lasting effect of hyperglycemia in diabetics results in a range of organs to suffer from a decrease in function, long-term damage and failure. The organs being the most affected are the heart, eyes, kidneys, blood vessels and nerves. Chronic high blood glucose concentration may also result from growth impairment and vulnerability to certain infections (Diabetes Care 2004).

There are two main types of diabetes; type 1 diabetes and type 2 diabetes. Type 1 diabetes is caused by a high decrease of insulin secretion while type 2 diabetes is caused by an amalgam of insulin resistance and an ineffective response to secrete more insulin to recompense (Diabetes care 2004).

TYPE 1 DIABETES

Previously called as insulin-dependent diabetes, type 1 diabetes is a consequence of cellular-mediated autoimmune destruction of pancreatic β-

cells. Islet cell autoantibodies, antibodies to insulin, antibodies to glutamic acid decarboxylase (GAD_{65}) and antibodies to the tyrosine phosphatases, IA-2 and IA-2β are markers for the immune destruction of the pancreatic β-cells. About 5-10% cases of diabetes are that of type 1 diabetes. This type of immune mediated diabetes is more pronounced in children and adolescence and at an advanced phase of this disease there is little or no insulin secretion (Diabetes Care 2004).

TYPE 2 DIABETES

Previously called as non-insulin-dependent diabetes, type 2 diabetes is probably bring about by many different causes which are yet not well known but is certainly not caused from autoimmune pancreatic β-cell destruction and insulin secretion is relatively deficient rather than absolutely deficient compared to type 1 diabetes. Type 2 diabetes is caused by insulin resistance and an ineffective response to secrete more insulin to compensate.. About 90-95% cases of diabetes are that of type 2 diabetes and it is more pronounced in adults and increases with age, obesity and insufficient physical activity. Unlike in type 1 diabetes, most patients with type 2 diabetes are obese and this obesity can cause further insulin resistance (Diabetes Care 2004).

DIABETES STATISTICS

In 2012, the estimated number of peoples with diabetes worldwide was more than 371 million out of which more than 4. 8 million people died from this non-communicable disease (International Diabetes Federation 2012). This number has since increased in 2013 with more than 372 million people with diabetes worldwide out of which more than 5. 1 million people died.

According to International Diabetes Federation (IDF), in less than 25 years, the number of people with diabetes is estimated to go beyond 592 million (International Diabetes Federation 2013). As for Mauritius diabetes prevalence was 14. 76% in 2012 (International Diabetes Federation 2012) and the same prevalence was recorded in 2013 (International Diabetes Federation 2013). Mauritius is no longer found in the top 10 countries/territories worldwide for prevalence of diabetes in 2013 (International Diabetes Federation 2013). It has been estimated that diabetic patients have two to four times more chance of dying from cardiovascular disease compared to non-diabetic patients (Gerich, 2007) and the main cause of death in people with type 2 diabetes mellitus is cardiovascular disease but also blindness, lower limb amputations and renal failure (King *et al* . 1998 and The Diabetes Atlas 2006). Among all the patients assigned with diabetes mellitus in Mauritius, about 40% died from heart disease and 30% from strokes (Ministry of Health and Quality of Life, 2011). There is also a high warning that diabetes may cause a major hindrance to global development according to latest figures (International Diabetes Federation 2013).

INFLAMMATION

IMMUNE SYSTEM

The immune system is very diverse and helps to protect the body against infectious factors and the harm that they cause to the body as well as protection from other harmful substances like insect toxins (Kumar 2014 and Murphy 2012, p. 3). The immune system is composed of many different types of effector cells and molecules and yet many more remains to be

discovered since the study of immune system is relatively a new section of physiology and medicine (Kumar 2014 and Murphy *et al* . 2012, p. 3). The immune system is classified into two major groups which are innate immunity and adaptive immunity and both innate and adaptive immune responses are dependent on the functions of white blood cells/leukocytes (Kumar 2014 and Murphy *et al* . 2012, p. 4). Innate immunity consists of innate immune cells such as macrophages, dendritic cells, neutrophils, eosinophils, basophils, mast cells, platelets and natural killer cells and its humoral part, the complement system. Adaptive immunity consists of B-cell mediated humoral Immunity and T-cell mediated cellular immunity (Kumar 2014). When bacteria and other pathogens such as viruses, parasites and fungi cross the physical barrier such as the skin and/or chemical barrier such as the mucosal layer, the immune system comes into play to destroy the pathogens. Initially the first branch that comes into play is the innate immunity response. The pathogens are detected by the receptors on macrophages such as those found in tissues that attach to common constituents of several types of bacterial surfaces. Binding to these receptors cause the macrophage to engulf the pathogens as well as to digest it internally. Moreover, this binding also causes secretion of cytokines and chemokines which are proteins that transfer essential messages to other immune cells. Cytokines are any type of proteins secreted by cells and that alters the behavior of neighboring cells which have the suitable receptors. Chemokines are proteins that are secreted and function as chemoattractants which attract cells possessing chemokine receptors, such as monocytes (macrophage precursor) and neutrophils, from the bloodstream to the site of infection. The cytokines and chemokines secreted from activated

macrophages begin the process called as inflammation (Murphy *et al* . 2012, p. 10).

INFLAMMATORY RESPONSE

Infection triggers an inflammatory response. Inflammation is a helpful process to fight against infection through the use of proteins and cells from the bloodstream to the site of infected tissues resulting in the pathogens to be directly destroyed. The recruitments of those proteins and cells from the bloodstream are helped by cytokines which increase permeability of blood vessels. Moreover, an inflammatory response also causes more microbes and antigen-presenting cells to travel from the site of infected tissue to neighboring lymphoid tissues by increasing the lymph flow. The attraction of microbes and antigen-presenting cells into the lymphoid tissues are helped by chemokines and this cause the activation of lymphocytes and the stimulation of adaptive immune response. Furthermore, as soon as the adaptive immune response is activated, inflammation causes the mobilisation of the effector components of the adaptive immune response such as effector T-cells and antibody molecules to the site of infected tissues. Local inflammation and phagocytosis can also be activated as a consequence of the activation of a series of plasma proteins known conjointly as complement. The surfaces of bacteria lead to the activation of the complement system. This process causes the bacterial surfaces only and not the surfaces of own body cells to be layered with complement fragments through a series of proteolytic reactions. These complement-coated pathogens are then bound to specific complement receptors found on the

surface of macrophages and neutrophils and eventually engulfed by phagocytosis and digested internally (Murphy *et al* . 2012, p. 10-11).

In the early phase of an inflammatory response, the main cell types that converge to the infected tissue sites are macrophages and large amounts of neutrophils followed by the convergence of monocytes to the infected tissues and there they swiftly mature into macrophages. In the later phase, if inflammation persists, the microbes are destroyed by the convergence of eosinophils in the inflamed tissues. Monocytes, macrophages, neutrophils and eosinophils are also called as inflammatory cells (Murphy *et al* . 2012, p. 11).

Inflammation is clinically named by the Latin words *calor* , *dolor* , *rubor* and *tumor* , which mean heat, pain, redness and swelling respectively. The increase in local blood flow and movement of fluid and blood proteins into tissues is due to an increase in blood vessels circumference and permeability respectively which caused the heat, redness and swelling and ultimately this process is caused by the effect of cytokines. Pro-inflammatory cytokines which are produced by endothelial cells in response to an infection alter the stickiness of endothelial cells, inducing mobile leukocytes to adhere to and pass in between the endothelial cells to the infected tissue sites attracted by chemokines (Murphy *et al* . 2012, p. 11). Examples of those adhering molecules that helps leukocytes to pass in between the endothelial cells are selectins (E-selectin, P-selectin), cell adhesion molecules [intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1)], and integrins (Devaraj *et al* . 2008). The movement of leukocytes in between

the endothelial cells and their action is what cause pain (Murphy *et al* . 2012, p. 11).

C-REACTIVE PROTEIN

Examples of pro-inflammatory cytokines that are released by macrophages during an infection are the molecules tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and iterleukin-6 (IL-6). These molecules have an important function in triggering an acute-phase response in the liver and to trigger fever also (Murphy *et al* . 2012, p. 98-101). The liver cells, hepatocytes, are operated by these cytokines in the acute-phase response and the hepatocytes react by altering the profile of proteins that they produce and release into the bloodstream, where the blood levels of some proteins decreases while others increases. The proteins that are produced and secreted only by the action of TNF-α, IL-1β and IL-6 on hepatocytes and that have also a similar effect like antibodies are referred as acute-phase proteins (Murphy *et al* . 2012, p. 109). C-reactive protein (CRP) is an acute-phase plasma protein (Black *et al* . 2004) and is formed from five identical subunits, thus forms part of the pentraxin protein family (Murphy *et al* . 2012, p. 110).

BIOLOGICAL FUNCTIONS OF CRP

C-reactive protein is also a multipronged pathogen recognition molecule. It adheres to the phosphocholine unit of some bacterial and fungal cell-wall lipopolysaccharides (LPS), such as pneumococcal C polysaccharide, therefore the name C-reactive protein (Murphy *et al* . 2012, p. 56, 110). However, C-reactive protein cannot bind to the phosphocholine unit of mammalian cell membrane phospholipids. When C-reactive protein adheres to a bacterial cell

wall, it makes the bacterium more susceptible to phagocytosis (act as an opsonin) and it also turns on the complement cascade by adhering to C1q, the first molecule involved in the complement system activation (Murphy *et al* . 2012, p. 110).

EPIDEMIOLOGY OF CRP

C-reactive protein is a non-specific and very stable used marker for acute inflammatory processes (Anzai *et al.* 1997 and Paffen and deMaat 2006). Several evidences has put forward that the levels of the biomarker of inflammation, C-reactive protein, is linked with several problems related to cardiovascular diseases (Bisoendial *et al* . 2010) such as acute myocardial infarction, unstable angina pectoris (Lagrand *et al* . 1999), atherosclerosis (Libby and Ridker 2004), atherothrombosis (Pepys and Hirschfield 2001) and also hypertension (Sesso *et al* . 2003). However, there have also been reports on no relationship between C- reactive protein and myocardial infarction after establishment of risk factors associated with cardiovascular diseases such as smoking and age (Doggen *et al* . 2001). High levels of C-reactive protein have also been linked with diabetes (Calle and Fernandez 2012) and obesity (Tracy *et al* . 1997).

INFLAMMATION, OBESITY AND DIABETES

Chronic inflammations, whereby higher levels of inflammatory markers such as tumor necrosis factor-α and interleukin-6 occur have been linked with metabolic disorders (Fasshauer and Paschke 2003). It has been observed that the innate immune system of obese peoples is often activated and this cause a low-grade inflammation of white adipose tissue and subsequently make an increase in the level of certain biological markers of inflammation

such as C-reactive protein, tumor necrosis factor-α and interleukin-6 (Bastard *et al* . 2006). The innate immune cells contain receptors on their surfaces that identify molecular prototypes present on pathogens known as pattern-recognition receptors (Cawthorn and Sethi 2008). One of the most well known pattern-recognition receptors is the toll-like receptors (TLR) such as TLR2 and TLR4 that can identify fatty acids and trigger the production of pro-inflammatory cytokines by macrophages (Murphy et al. 2012, p. 85-86 and Shi et al. 2006). Upon binding of the molecular prototype of pathogens and pattern-recognition receptors, nuclear factor-kappa-B (NF-kB) signaling pathways are triggered resulting in an inflammatory response (Cawthorn and Sethi 2008). Low-grade inflammation can consequently give rise to diseases such as insulin resistance, impaired glucose tolerance and also diabetes (Bastard *et al* . 2006). According to a study done by Barzilay *et al* . (2001) it has been found that obese peoples with higher C-reactive protein levels have two times more risk of having type 2 diabetes within three to four years.

Insulin sensitivity is altered in many different ways through changes in different steps of the pathway of insulin signaling (Calle and Fernandez 2012). One of the many steps alteration include the phosphorylation of the serine residues of the insulin receptor substrate-1 (IRS-1) rather than the tyrosine residues due to elevated levels of tumor necrosis factor-α and interlukin-6. This causes the cessation of insulin signaling thus causing insulin resistance (Fasshauer and Paschke 2003). Moreover, the phosphorylation of serine residues of the insulin receptor substrate-1 can also be caused by high levels of free fatty acids (FFAs) which cause elevated inflammation by activation of toll-like receptors and activation of Jun N-

terminal kinase (JNK) thus leading to type 2 diabetes (Hotamisligil 2008). In turn, hyperglycaemia triggers iterleukin-6 production from endothelium and macrophages but also stimulates the action of suppressor of cytokine signaling (SOCS) therefore exacerbating insulin resistance (Rønn *et al* . 2007).