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Review

Diabetes microvascular complications—A clinical update

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ABSTRACT

Background: The purpose of this study is to summarise the empirical evidence addressing diabetes microvascular complications and management. The effects of diabetes mellitus include long–term damage, dysfunction and failure of various organs. Microvascular disease tends to occur predominantly in tissues where glucose uptake is independent of insulin activity because these tissues are exposed to glucose levels that correlate very closely with blood glucose levels. These metabolic injuries cause altered blood flow and changes in endothelial permeability, extravascular protein deposition and coagulation resulting in organ dysfunction which in turn lead to microvascular complications.
Method: A systematic search of the literature from 2000 to 2016 was conducted using four databases (Medline, Pubmed, Cochrane central and Google scholar) using search terms such as diabetic microvascular complications', pathogenesis, screening, risk factors, pharmacological and non-pharmacological interventions and management.
Results: The current evidence supports a direct relationship between blood pressure (BP) and glycaemic control and progression of nephropathy and retinopathy. These are now considered as independent risk factors for microvascular disease progression. New fields of research addressing new drugs as potential therapeutic targets of the future will be presented.
Conclusion: The prevention of microvascular disease involves paying attention to aggravating risk factors and implementing screening programmes to improve early detection.

Contents

1. Introduction

The World Health Organisation estimates the number of people diagnosed with diabetes to reach 366 million by 2030. This is almost double the number of 171 million estimated in 2000 [1].

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The surge in the number of diabetes will have potential implications on both the health care services and patients' quality of lives [2]. The effects of diabetes mellitus include long–term damage, dysfunction and failure of various organs (WHO 1999) [3]. This has been documented widely in the literature [1–3]. A study published by the American Diabetes Association that aimed at quantifying the total economic liability of diabetes caused by increased health resource use and loss of productivity, and to provide a detailed breakdown of the costs attributed to diabetes complications has found that the total estimated cost of diabetes in 2007 is $174 billion, including $116 billion in excess medical expenditures and $58 billion in reduced national productivity [4].

Microvascular disease tends to occur predominantly in tissues where glucose uptake is independent of insulin activity (eg kidney, retina and vascular endothelium) because these tissues are exposed to glucose levels that correlate very closely with blood glucose levels. These metabolic injuries cause altered blood flow and changes in endothelial permeability, extravascular protein deposition and coagulation resulting in organ dysfunction which in turn lead to microvascular complications [5,6]. This report summarises the most empirical evidence addressing diabetes microvascular complications related to pathogenesis, screening, risk factors, management and future directions.

2. Methods

This narrative review is based on a systematic search of the literature from 2000 to 2015 using four databases (Medline, Pubmed, Cochrane central and Google scholar) using search terms such as diabetic microvascular complications', pathogenesis, screening, risk factors, pharmacological and non-pharmacological interventions and management. The details of the major studies included in the review are in Table 1.

2.1. Pathogenesis of microvascular complications

The damage caused by hyperglycaemia is said to target a particular subtype of cells such as capillary endothelial cells in the retina, mesangial cells in the renal glomerulis and neurons and Schawn cells in the peripheral nerves [5]. These cells are exposed to hyperglycaemia as they are unable to reduce the transport of glucose inside the cell once they are exposed to hyperglycaemia. Unlike other cells whose internal glucose remains constant because of their efficient glucose transport mechanism. These cells are more likely to get damaged as a result of constant hyperglycaemia inside them. This has led to the conclusion that what causes microvascular complications is occurring inside the cell rather than outside the cells [5,6].

Several hypotheses have then been proposed to explain the process of developing microvascular complications. These include the following; (1) generation of reactive oxygen species and oxidative stress, (2) stimulation of polyol pathway, (3) production of advanced glycation end products, (4) initiation of flux through the hexosamine pathway, (5) altered expression and action of growth factors, and (6) triggering of protein kinase C [7]. As a result, it was then concluded that the development of complications is a combination of direct glucose-mediated endothelial damage, oxidative stress due to superoxide overproduction, and the production of sorbitol and advanced glycation end-products due to hyperglycaemia. The above mentioned processes are also linked to an extent. A long term exposure to hyperglycaemia in these cell types lead to an increased production of reactive oxygen species as shown in Fig. 1. This is consistent with the early proposal of hyperglycaemia being linked to oxidative cells in the early sixties [7]. Based on these theories, specific interventions targeting each of the above six processes are feasible to prevent the development of diabetic complications even if satisfactory normoglycemic control is not achieved.

2.2. Risk factors

To date, the current evidence supports a direct relationship between blood pressure (BP) and glycaemic control and progression of nephropathy and retinopathy. These are now considered as independent risk factors for microvascular disease progression [8]. Other risk factors include age, glycated hemoglobin, duration of diabetes, and serum triglycerides. The centre for diseases control and prevention conducted a large study on patients' diagnosed diabetes who have risk factors for complications in the United States, in 2010 and have found that a significant proportion of people with risk factors such as smoking (20%), obesity (57%), overweight (85%), physical inactivity (36%), Hypertension(57%) and high cholesterol (58%) developed microvascular complications [9].

Moreover, a recent study by Raman et al., 2012 found that increasing age (odds ratio [OR] = 1.07, 95% CI = 1.04–1.11, $P < 0.0001$), increasing systolic blood pressure (OR = 1.03, 95% CI = 1.01–1.06, P = 0.001), and increasing hemoglobin (OR = 1.39, 95% CI = 1.09–1.79, P = 0.011) are also significant risk factors to developing microvascular complications [10].

A more recent large study by Zoungas et al., 2014 found that diabetes duration is independently associated with microvascular complications and this effect is more significant in the youngest patients [11]. These findings were also consistent with two other early studies by Krolewski et al., 1987 and Jerneld and Algvere who found that microvascular eye lesions were more prominent in people who had been exposed to long duration of hyperglycaemia rather than the age of diagnosis of diabetes [12,13].

2.3. Types of diabetes microvascular complications

2.3.1. Diabetic neuropathy

The most common form of diabetic neuropathy is a distal, symmetrical sensorimotor neuropathy which is asymptomatic in up to 50% of patients with diabetes [14]. Other types of diabetic neuropathy include; Peripheral neuropathy affecting the toes, feet, legs, hands and arms; autonomic neuropathy affecting the heart and blood vessels, the digestive system, the urinary tract, sex organs, the sweat glands, the eyes and the lungs; Proximal neuropathy affecting the thighs, hips, buttocks and legs; and focal neuropathy affecting the eyes, facial muscles, ears, pelvis and lower back, chest, abdomen, thighs, legs and feet [15].

Diabetic neuropathy is diagnosed on the basis of symptoms and physical examination. There are various other tests employed to test for the disease including vibration studies and ultrasound. The latter test is beneficial in cases where there is trauma, as recurrent distress to affected areas usually results in skin breakdown, ulceration and infection. Delay in management of neuropathic pain can result in amputations and death in some circumstances [15,16].

The first step in the management of diabetic neuropathy includes normalisation of glycaemic control [16]. Non-pharmacological treatments includes nerve stimulation, electromagnetic field treatment and Reiki therapy with varying benefits of symptoms (Improvements in sleep quality, sensitivity and stress reduction, impacting on quality of life were reported) [17]. Pharmacological management includes the use of a variety of adjunct analgesics such as tricyclic and non-tricyclic antidepressants, anti-epileptics, serotonin noradrenaline reuptake inhibitors, gabapentin, benzodiazepines and opioids. All have different degrees of benefit on pain control [17,18,19]. Other treatment such as capsaicin, which is an alkaloid derived from red chilli peppers was found to be beneficial in decreasing pain associated

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