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بسم الله الرحمن الرحيم

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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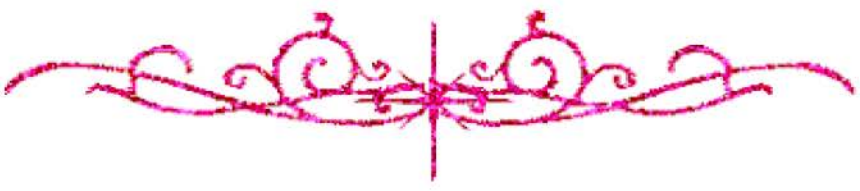

بالرسالة صفحات لم ترد بالأصل

B/N/W°

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Thesis

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INTRODUCTION

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DEFINITION OF DIABETES MELLITUS

Diabetes mellitus is a complex syndrome characterized by: chronic hyperglycemia and disturbances of carbohydrates, fat and protein metabolism associated with absolute or relative deficiencies in insulin secretion and/or insulin action.[1]

DIABETIC NEUROPATHY

Involvement of the nervous system in diabetes has long been recognized. Rollo[2] is creditable to be the first who recorded this association in 1798, and until the middle of the 19th century, diabetes itself was ascribed to be a disorder of the central nervous system.

Marchal de Calve[3] in 1864 first suggested that diabetes might be the cause rather than the effect of neuropathy. Although an increasing bulk of evidences favour the concept that neuropathy is due to diabetes, particularly if it is poorly controlled, it is clear that characteristic symptoms of neuropathy may occur without clinically manifest diabetes.[4] Furthermore, the most infrequent lack of relation between the duration or severity of abnormal glucose metabolism and the presence of neuropathy is consistent with the possibility that peripheral neuropathy may be a concomitant abnormality.[5] Increased blood glucose is frequently noted in patients with peripheral neurologic manifestations but ketosis does not appear to be a factor in the development of symptoms.[5]

METABOLIC BASIS OF NEUROPATHY

In the human, with diabetes, abnormal motor and sensory nerve conduction can be at least partially corrected by the control of hyperglycemia. The rapid deterioration of neural function and its reversal by glycemic control suggests a primary metabolic lesion rather than vascular occlusion as the basis of neuropathy. Over the past decade, there has been considerable interest in excessive shunting of glucose into sorbitol pathway in the presence of hyperglycemia. This pathway, present in many tissues including the mammalian peripheral nerves[6] is one of the many pathways that do not require phosphorylation of glucose, so glucose entry is not dependent on insulin. Levels of intermediates in the sorbitol pathway are correlated with plasma levels of sorbitol, as well as fructose and are significantly elevated in uncontrolled diabetes.[6]

It has been suggested that sorbitol accumulation in the peripheral nerves could lead to osmotic effect, which might be responsible for Schwann's cell damage and demyelination. Inhibitors of sorbitol formation can delay the onset of abnormalities in nerve conduction in the galactose fed rat.[7] The significant increase in water content of diabetic nerve cells superficially seems to support "osmotic shock" as the basis of the neural damage. However, most of the increase in water is confined to the endoneural space rather than to the Schwann's cell or axon, indicating that increased vascular permeability, and leakage rather than osmotic swelling of the cellular structure in the peripheral nerve, may be responsible for initiating the chain of events that leads to neuropathy.[7] Clements et al[8] has summarized the evidences that the axon itself, rather than its

surrounding myelin sheath and Schwann's cell, is the locus of the primary lesion in diabetic neuropathy. The evidences supporting this approach include:

1- Electromyographic data indicating that axonal dysfunction rather than segmental demyelination can precede the development of neuropathy.
2- Pathological findings that axonal degeneration is often the earliest detectable morphologic abnormality in diabetic neuropathy.
3- Biopsy findings showing the loss of both demyelinated and myelinated fibres.

Alterations in myoinositol metabolism have been implicated in the pathogenesis of diabetic neuropathy. This cyclic alcohol is present in great amounts in the normal peripheral nerves. The induction of experimental diabetes results in a fall in the myoinositol content of the peripheral nerves, which can be correlated with changes in the motor nerve conduction time. Intensive insulin therapy as well as oral administration of myoinositol has been shown to correct these abnormalities of nerve conduction in the severely diabetic animal.[9] It has been demonstrated that dietary myoinositol can improve sensory but not motor conduction velocity in diabetic patients with neuropathy.[10] The aldose reductase inhibitor, sorbinil, has been shown to inhibit sorbitol accumulation in streptozotocin induced diabetic rat nerve, as well as to inhibit a fall in myoinositol levels.[11] This was associated with the prevention of changes in nerve conduction velocities. Myoinositol as a dietary supplement also prevented the abnormalities in the nerve conduction velocities without affecting neural sorbitol level, suggesting that myoinositol deficiency was the primary abnormality.[12]