Pathophysiology od diabetic foot assignment

Patients afflicted with diabetes are at risk for a variety of pathologies resulting in many complications including foot ulceration and amputation. The multi-factorial etiology of diabetic foot ulcers is evidenced by the numerous pathophysiologic pathways that can potentially lead to this disorder. A multicenter study attributed 63 percent of diabetic foot ulcers to the critical triad of peripheral sensory neuropathy, deformity, and trauma (Reiber, et al. , 1999). The following discusses the pathophysiology of each of the triad in limited detail.

Background: Glucose is liberated from dietary carbohydrate such as starch or sucrose by hydrolysis within the small intestine, and absorbed into the blood. GLUT-2 transporters carry glucose in to beta cells via insulin-independent facilitated diffusion. Through rapid glycolysis, intracellular glucose is immediately phosphorylated and therefore, cannot diffuse out (the transport protein is specific for glucose). Internal glucose (unphosphorylated) concentration remains low providing a large concentration gradient for entry into the cell.

Aerobic metabolism leads to increased ATP/ADP ratios and ATP sensitive K+ channels close. Depolarization activates voltage gated Ca2+ channels and insulin exocytosis. Insulin binds to the insulin receptor and activates a tyrosine kinase second messenger system. Auto phosphorylation of the insulin receptor causes insulin-dependent GLUT transporters to be inserted into the cell membranes of insulin dependent cells like muscle cells. Glucose uptake and utilization promotes the use of glucose and the lowering of blood glucose levels.

Elevated concentrations of glucose in the blood stimulates release of insulin which stimulates increase in number of GLUT transporters at the membrane surface. This in turn increases the diffusion rate while the driving force (phosphorylation) remains the same. Low insulin levels, as in diabetes, decrease the number of glucose transporters at membrane surface. Portions of the membrane with GLUT transporters endocytose, trapping the transport protein in a vesicle. The vesicle cannot refuse with the membrane until insulin levels increase.

The result is an increased level of glucose circulating in the plasma, or hyperglycemia, the triggering event for the pathophysiology of multiple complications. Peripheral sensory neuropathy: The peripheral nervous and microvascular systems are coupled by their physiological codependence. In the simplest terms, blood vessels depend on neural regulation for normal function, and neurons depend on capillaries for nutrients. Neither vascular nor nervous tissue requires insulin for the uptake of glucose. Therefore, hyperglycemia results in elevated intracellular glucose levels that raise havoc in both vascular and nervous tissue.

High nerve glucose concentrations lead to conversion of glucose to sorbitol via the polyol pathway (Oates, 2002) through a series of reactions catalyzed by aldose reductase . Nerve fructose levels are also increased. The excess fructose and sorbitol decrease the expression of the sodium/myoinositol cotransporter, leading to decreases in myoinositol levels, essential for the development and regeneration of peripheral nerve cells (Chau, Lee, Law, et al, 2005). Additionally, this causes decreased levels of phosphoinositide,

which interferes with activation of the Na pump and decreases Na/K ATPase activity.

Activation of aldose reductase depletes its cofactor, nicotinamide adenine dinucleotide phosphate-oxidase (NADPH), which results in decreased levels of nitric oxide and glutathione, which buffer against oxidative injury. Lack of nitric oxide also inhibits vascular relaxation, which can cause chronic ischemia. Finally, this pathological shift favoring vasoconstriction leads to capillary basement membrane thickening and endothelial cell hyperplasia which contribute to diminished oxygen tension, hypoxia, and neuronal ischemia and infarction.

The complicated process results in decreased nerve depolarization as well as decreased cellular nutrient provision. The patient develops numbness and tingling with decreased sensation. Deformity: Resultant increased extracellular glucose in hyperglycemia has a stimulatory effect on collagen production leading to soft tissue changes in the feet of diabetic patients. This contributes to ulcerations through the pathway of altered pressure distributions through the sole of the foot. Such alterations include a reported increased thickness of the plantar fascia with associated limitation of dorsiflexion, decreased thickness of plantar oft tissue, accentuated hardness/stiffness of the skin, and a propensity to develop calluses. Trauma: Decreased sensation coupled with changes in skin thickness leads to an inability to assess injury when it occurs. Ill fitting shoes, blisters, and altered pressure in various areas of the foot may start an ulcerative injury that could go unnoticed. The hyperglycemic vasoconstriction and decreased circulation to the site retards healing. The patient doesn’t notice the injury until it is

sizeable. Indeed, it may begin internally and break the skin at the surface after it is already ample size.

Treatment: Treatment of the wound is first order, trying to promote healing and if severe, amputation to the point of viable tissue. The main treatment must be preventative and involves control of hyperglycemia to improve symptoms and prevent complications while minimizing hypoglycemic episodes. Goals for treatment are maintenance of plasma glucose between 80 and 120 mg/dL (4. 4 and 6. 7 mmol/L) during the day and between 100 and 140 mg/dL (5. 6 and 7. 8 mmol/L) at bedtime and maintenance of HbA1c levels ; 7%. HbA1c levels are a better gauge of long term glucose stability than plasma circulating glucose.

Glucose “ sticks” to the hemoglobin in the erythrocyte (red cells) to make a ‘ glycosylated haemoglobin’ molecule, called hemoglobin A1C or HbA1C. The more glucose in the blood, the more hemoglobin A1C or HbA1C will be present in the blood. Red cells live for 8 -12 weeks before they are replaced. By measuring the HbA1, results can tell how high blood glucose has been on average over the last 8-12 weeks. Plasma glucose will only give results from the most recent food ingestion. A normal non-diabetic HbA1C is 3. 5-5. 5%. In diabetes about 6. 5% is good. References Chau, J. F. L. , Lee, M. K. , Law, J. W. S, Chung, S. K. , ; Chung, S. S.

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