

High Risk Foot - supporting notes.

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2	Aims
8	<p>Veins have a slightly different structure, with their walls consisting mainly of muscle and elastic tissue. Larger veins have a series of valves to help maintain venous return. There are also deep and superficial venous systems with inter-connecting vessels known as perforating vessels. This allows blood to flow from superficial to deep systems and allow efficient drainage.</p> <p>A series of muscle pumps maintains the movement of blood in the right direction.</p> <p>Low pressure system, act as capacitance vessels containing around 70% of total blood volume</p> <p>Vessels, particularly in lower limbs, have valves.</p> <p>Thin walls</p>
11	<p>Oxygen is carried about at high concentrations bound to haemoglobin. The bound oxygen molecule can then be carried from the lungs to the tissues such as the muscle tissues and heart where it is needed for respiration.</p> <p>The blue spheres are the oxygen molecule binding to the heme group. Binding causes a small distortion of the heme ring plane and this changes the overall structure of the protein. This in turn results in changes in the binding affinity of oxygen.</p> <p><i>Oxyhemoglobin</i> is formed during respiration when oxygen binds to the heme component of the protein. This process occurs in the pulmonary capillaries adjacent to the alveoli of the lungs. The oxygen then travels through the blood stream to be dropped off at cells where it is utilized in aerobic glycolysis and in the production of ATP by the process of oxidative phosphorylation. It does not help to counteract a decrease in blood pH. Ventilation, or breathing, may reverse this condition by removal of carbon dioxide, thus causing a shift up in pH.</p>

	<i>Deoxyhemoglobin</i> is the form of hemoglobin without the bound oxygen.
12	Rather than in hypoxia, a more general term denoting a shortage of oxygen (usually a result of lack of oxygen in the air being breathed), ischemia is an absolute or relative shortage of the blood supply to an organ ie a shortage of oxygen & glucose and other blood bourne fuels. Relative shortage means the mismatch of blood supply (oxygen/fuel delivery) and blood request for adequate metabolism of tissue. Ischemia results in tissue damage because of a lack of oxygen and nutrients. Ultimately, this can cause great damage because of the potential for a build-up of metabolic wastes.
14	<p>What is homocysteine - an amino acid normally found in blood. A high level of blood serum homocysteine is considered to be a marker of potential CV disease. A current area of research is whether high serum homocysteine itself is a problem or merely an indicator of existing problems.</p> <p>Most patients have underlying atherosclerosis. The major risk factors for atherosclerosis include hypertension, elevated levels of low-density lipoprotein, reduced levels of high-density lipoprotein, cigarette smoking, diabetes mellitus, obesity, male sex, elevated homocysteine levels, and family history of premature atherosclerosis.</p>
15	<p>Sustained elevation of blood homocysteine, by damaging endothelial cells, predisposes to premature atherosclerosis of the aorta and its branches, the peripheral arteries, the cerebral arteries, and possibly the coronary arteries. Although homocysteine levels are usually elevated in association with other risk factors, they can be modified by diet and vitamin B supplements.</p> <p>The endothelium begins to change, becoming more permeable and allowing adhesion of cells such as monocytes and leukocytes. The adherent monocytes will also begin to move through the endothelium and into the intima</p>
18	The Brain and spinal cord make up the CNS. The PNS can be split into the Sympathetic and Parasympathetic Systems which are opposing actions that basically keep a check on each other to

	<p>provide a balance. Example of this would be heart rate, this is speeded up by the Sympathetic System and slowed down by the Parasympathetic System.</p> <p>Gathers information from the outside world and from inside the body SENSORY FUNCTION Transmits the information to the processing are of the brain and spinal cord Processes the information to determine the best response INTEGRATIVE FUNCTION Sends information to muscles glands and organs so they can respond correctly MOTOR FUNCTION</p> <p>The PNS consists of Neurons NOT included in the Brain and Spinal Cord. Some Peripheral neurons collect information from the body and transmit towards the CNS- AFFERENT neurones, or sensory neurones Others transmitting away from the CNS- EFFERENT neurones, or motor neurones</p>
22	<p>Disorders in the immune system can result in disease. Immunodeficiency diseases occur when the immune system is less active than normal, resulting in recurring and life-threatening infections. Immunodeficiency can either be the result of a genetic disease, such as severe combined immunodeficiency, or be produced by pharmaceuticals or an infection, such as the acquired immune deficiency syndrome (AIDS) that is caused by the retrovirus HIV.</p> <p>In contrast, autoimmune diseases result from a hyperactive immune system attacking normal tissues as if they were foreign organisms. Common autoimmune diseases include rheumatoid arthritis, diabetes mellitus type 1 and lupus erythematosus. Immunology covers the study of all aspects of the immune system which has significant relevance to human health and diseases. Further investigation in this field is expected to play a serious role in promotion of health and treatment of diseases.</p>
34	<p>Ketosis - a state in metabolism occurring when the liver converts fat into fatty acids and ketone bodies which can be used by the</p>

	<p>body for energy.</p> <p>Adipose tissue consists of highly specialized cells which store energy in the form of a triglyceride and release it upon hydrolysis in a process known as lipolysis, yielding three fatty acids and one glycerol molecule. These ketone bodies are a by-product of the lipid metabolic pathway after the fat is converted to energy.</p> <p>Ketoacidosis, by contrast, is the accumulation of excessive keto acids in the blood stream (specifically acetoacetate and beta-hydroxy butyrate).</p>
35	<p>Type 1 diabetes could be a virally induced autoimmune response. In the proposed scenario, pancreatic beta cells in the Islets of Langerhans are destroyed or damaged sufficiently to abolish endogenous insulin production. This aetiology makes type 1 distinct from type 2 diabetes mellitus. It should also be noted that the use of insulin in a patient's diabetes treatment protocol does <i>not</i> render them as having type 1 diabetes, the type of diabetes a patient has is determined only by disease aetiology. The autoimmune attack may be triggered by reaction to an infection, for example by one of the viruses of the Coxsackie virus family or German measles, although the evidence is inconclusive.</p> <p>This vulnerability is not shared by everyone, for not everyone infected by these organisms develops Type 1 diabetes. This has suggested a genetic vulnerability and there is indeed an observed inherited tendency to develop Type 1 . It has been traced to particular HLA phenotypes, though the connection between them and the triggering of an auto-immune reaction is poorly understood.</p>
37	<p>Pima indians - a group of American Indians living in an area consisting of what is now central and southern Arizona and Sonora in Mexico. The USA group have the highest prevalence of type 2 diabetes on Earth, much more than is observed in other U.S. populations. The Pima people have been the subject of intensive study of diabetes, in part because they form a homogeneous group. The general increased diabetes prevalence among Native Americans has been hypothesized as the result of</p>

	<p>the interaction of genetic predisposition (the thrifty phenotype, suggested by anthropologist Robert Ferrell in 1984) and a sudden shift in diet from traditional agricultural goods towards processed foods in the past century.</p> <p>For comparison, genetically similar Pimas in Mexico have virtually no type 2 diabetes.</p> <p>It has been suggested that in poor nutritional conditions, a pregnant female can modify the development of her unborn child such that it will be prepared for survival in an environment in which resources are likely to be short, resulting in a thrifty phenotype. Individuals with a thrifty phenotype will have a smaller body size, a lowered metabolic rate and a reduced level of behavioural activity - adaptations to an environment that is chronically short of food.</p> <p>Those with a thrifty phenotype who actually develop in an affluent environment may be more prone to metabolic disorders, such as obesity and type II diabetes, whereas those who have received a positive maternal forecast will be adapted to good conditions and therefore better able to cope with rich diets. This idea, which is also known as the Barker hypothesis is now widely (if not universally) accepted and is a source of grave concern for societies undergoing a transition from sparse to better nutrition.</p>
38	<p>One of the biggest challenges facing diabetes management today, and a problem which is likely to increase. This was first noticed in the 1960's, but not until 1988 did Reaven propose the concept of metabolic syndrome. He suggested that insulin resistance was the cause of glucose intolerance, hyperinsulinaemia, increased VLDL, decreased HDL, and hypertension, although in his original paper obesity was not included.</p>
49	<p>AGE - If proteins are exposed to glucose over a long period of time the glucose will become attached to the protein through a mechanism which doesn't require any enzyme action. Early glycation products are reversible, but eventually they become permanent and the protein-glucose complex becomes the AGE.</p>

AGE proteins accumulate in direct proportion to the levels and extent of hyperglycaemia. In time they promote ECM accumulation, and the generation of ROS, and together these promote further cell dysfunction. Methods to try and inhibit AGE product are largely unsuccessful, mainly because of the high quantity of dietary AGE products that result from cooking process.

Sorbitol - While most cells require the action of insulin for glucose entry, the cells of the retina, kidney and nervous tissues are insulin independent, so glucose moves freely across the cell membrane, regardless of the action of insulin. The cells will use glucose for energy as normal, and any glucose not used for energy will enter the polyol pathway.

When blood glucose is normal (about 100 mg/dl or 5.5 mmol/l), this interchange causes no problems. Unused glucose enters the polyol pathway when aldose reductase reduces it to sorbitol. Sorbitol dehydrogenase then oxidizes the sorbitol to fructose. Hexokinase can return the molecule to the glycolysis pathway by phosphorylating fructose to form fructose-6-phosphate. (aldose reductase has a low affinity for glucose at normal concentrations).

In a hyperglycemic state, the affinity of aldose reductase for glucose rises, causing much sorbitol to accumulate, and using much more NADPH, leaving less NADPH for other processes of cellular metabolism. This change of affinity is what is meant by activation of the pathway. The sorbitol can not cross cell membranes, and when it accumulates, it produces osmotic stresses on cells by drawing water in. Fructose does essentially the same thing. The amount of sorbitol that accumulates, however, may not be sufficient to cause osmotic influx of water. Also called the **sorbitol-aldose reductase pathway**, the polyol pathway appears to be implicated in diabetic complications, especially in microvascular damage to the retina, kidney and nerves.

In cells unused glucose enters the polyol pathway when aldose reductase reduces it to sorbitol. This is then converted to fructose. This can be returned to the glycolysis pathway, but in

	<p>uncontrolled diabetics who have high blood glucose - more than the glycolysis pathway can handle - there is increased production and accumulation of sorbitol. This affects the production of Myo-inositol, required for normal nerve function. Sorbitol may also glycate nitrogens on proteins, such as collagen, and the products of these glycations are referred-to as AGEs - advanced glycation endproducts.</p> <p>Nerve cell hypoxia is also caused by PVD, etc.</p>
73	<p>Early lesions of calciphylaxis appear as nonspecific violaceous mottling; as livedo reticularis; or as erythematous papules, plaques, or nodules. More developed lesions have a stellate purpuric configuration with central cutaneous necrosis (fig 1). Multiple lesions of variable age may be present, following the path of the vasculature (fig 2). Less commonly, lesions may manifest as either bullae (fig 3), or distinct subcutaneous, erythematous nodules suggestive of erythema nodosum. The lesions are very painful, and extremely firm.</p>
74	<p>The distribution of the lesions may be characterized as proximal or distal;</p> <p>Ninety percent of lesions of calciphylaxis occur on the lower extremities.</p> <p>Distal lesions are those that occur below the knee (Figs 4 & 5); proximal lesions occur on the thighs or the trunk (Fig 6).</p> <p>Proximally distributed lesions occur in 44-68% of patients, with lesions developing predominantly on the thighs, the buttocks, and the lower part of the abdomen.</p> <p>Distal and visceral involvement are not uncommon.</p> <p>The patient in the lower picture still had a peripheral pulse.</p> <p>An intact peripheral pulse (as was the case in Fig 6) helps to distinguish acral calciphylaxis from atherosclerotic peripheral vascular disease. Ulceration is considered a late finding and is associated with a higher mortality rate.</p>
82	<p>Joint involvement is usually symmetrical and peripheral, although more of the major joints become involved with the progression of the disease.</p> <p>Occurs world-wide</p>

	<p>prevalence of 0.5 - 1% worldwide, but 1-3% in western countries. female to male ratio of 3:1 onset common 30 - 40 years of age</p> <p>Current thinking suggests an altered immune response in people with a genetic predisposition. In support of this there have been found to be high levels of immune complexes at sites of involvement. ?Strep infections.</p> <p>Stress is also thought to contribute - commonly occurring after the birth of a child, but remember that onset of the disease is also most common in the 30-40 age group, so it's difficult to separate things.</p>
84	<p>These are the common clinical features seen with RA. Onset is usually insidious, with rest pain and early morning stiffness common. Typically, the small joints are affected, with a progression towards the trunk. Hips are not usually affected, unless the disease is severe or there is secondary OA.</p> <p>In 10%, it starts as a acute polyarthritis, with systemic symptoms such as fever and malaise. These attacks can last from a few hours to a few days.</p> <p>As progression continues, pain, muscle spasm and joint destruction lead to loss of mobility, instability, and deformity. Characteristic deformities such as flexion contractures of the small joints will occur.</p>
85	<p>Hip joints tend to remain unaffected primarily. Features can include :</p> <ul style="list-style-type: none"> • apparent limb length shortening • gluteal muscle atrophy • rheumatoid nodules • loss of knee extension • knee ligament laxity • popliteal cysts <p>In the foot :</p>

	<ul style="list-style-type: none"> • subluxation of the digits • HAV • loss of fibro fatty padding • vasculitis • bursae development • nodules • sinus development • dorsal lesions • ankle joint pain <p>Commonly, we see subcutaneous nodules on the plantar surface and also the elbows. These nodules consist of a central area of damaged collagen, surrounded by proliferating mononuclear cells, and a loose capsule of fibrous tissue.</p> <p>Similar lesions may also occur in the lung and the pericardium. It is not uncommon for these lesions to ulcerate on the plantar surface, usually due to pressure build up.</p>
86	<p>Patients become prone to infection, and also have tissue viability problems, especially in relation to some of the drug therapies.</p> <p>Neurologically, joint disarrangement commonly leads to entrapment neuropathies. Cervical cord compression also occurs, which can lead to death if the neck is inadvertently manipulated. In less dramatic cases there is limb weakness and difficulty in holding the head up.</p>
91	<p>Often occur on the hands, elbows, and in the lungs, but commonly seen by pods on the foot. Correct term is palisading granuloma.</p> <p>Histological examination of nodules shows that they consist of a shell of fibrous tissue surrounding a centre of fibrinoid necrosis. Small nodules have one centre, larger ones tend to be multilocular, with many onnected necrotic centres. Individual necrotic centres may contain a cleft or several centres of necrosis may all open on to a large bursal pocket containing synovial fluid.</p> <p>The boundary between the necrotic centre and the outer fibrous shell is made up of the characteristic feature of the nodule, which is known as a cellular palisade. The palisade is a densely packed layer of macrophages and fibroblasts which tend to be</p>

	<p>arranged radially, like the seeds of a kiwi fruit. Further out into the fibrous shell there is a zone that contains T lymphocytes and plasma cells in association with blood vessels. The overall histological picture is essentially identical to that of rheumatoid synovitis with the main differences being that the palisade replaces the synovial intima (they may blend imperceptibly in bursae) and an almost total absence of B lymphocytes.</p> <p>Treatment of rheumatoid nodules is rarely a priority for people with rheumatoid arthritis. However, surgical removal is often successful, even if there is a tendency for nodules to regrow. Of the drug therapies commonly used in rheumatoid arthritis, methotrexate has the disadvantage of tending to make nodules worse. TNF inhibitors do not have a very reliable effect on nodules. B cell depletion with rituximab often leads to disappearance of nodules but this is not guaranteed.</p>
92	<p>Foot ulceration in RA patients is much less well understood than it is in DM pts, and the risk factors are as yet undertermined. Increased tissue stress of prominent deformity is important, but not the only factor. In previous studies there have been comparisons between RA and DM pts, and although the RA pts had high plantar pressures than the DM, none had a previous history of ulceration, compared to 32% of the DM group.</p> <p>The neuropathy that occurs in RA does not include LOPS, and studies suggest that it is the loss of LOPS that differentiates between the differences in prevalence of foot ulceration in these groups.</p> <p>What should also be taken into account with RA patients is the affect of their long-term medication of skin viability and ability to heal, particularly with the biologic agents, where spontaneous ulceration can occur.</p> <p>Sometimes ulcers in RA pts are iatrogenic, with either under or over-debridement, as can the affect of self-treatment by desperate pts.</p>
94	<p>Immunosuppression involves an act that reduces the activation or efficacy of the immune system. Some portions of the immune</p>

	<p>system itself have immuno-suppressive effects on other parts of the immune system, and immunosuppression may occur as an adverse reaction to treatment of other conditions.</p> <p>Deliberately induced immunosuppression is generally done to prevent the body from rejecting an organ transplant, treating graft-versus-host disease after a bone marrow transplant, or for the treatment of auto-immune diseases such as rheumatoid arthritis or Crohn's disease. This is typically done using drugs, but may involve surgery (splenectomy), plasmapheresis, or radiation.</p>
95	<p>Barbiturates - suppress bone marrow activity, also involved in inhibition of T cell proliferation, differentiation, and cytokine synthesis. Modulate lymphocyte and leucocyte function.</p> <p>Excessive alcohol intake can harm the body's immune system in two ways. First, it produces an overall nutritional deficiency, depriving the body of valuable immune-boosting nutrients. Second, alcohol, like sugar, consumed in excess can reduce the ability of white cells to kill germs. High doses of alcohol suppress the ability of the white blood cells to multiply, inhibit the action of killer white cells on cancer cells, and lessen the ability of macrophages to produce tumor necrosis factors. One drink (the equivalent of 12 ounces of beer, 5 ounces of wine, or 1 ounce of hard liquor) does not appear to bother the immune system, but three or more drinks do. Damage to the immune system increases in proportion to the quantity of alcohol consumed. Amounts of alcohol that are enough to cause intoxication are also enough to suppress immunity</p> <p>The immune system guards the body against disease, debris and aberrant "mutant cells." B and T-lymphocytes are well-known players in this system but another type of lymphocyte - the natural killer cell (NK) - is important for removing mutant cells in the early stages of cancer. NK cells also produce cytokines - small proteins that play a role in immunity, inflammation, and the production of blood cells. Heavy alcohol use disables this front line immune defence. Chronic alcohol consumption decreases the number of NK cells and T-lymphocytes in the body - mainly through destruction in the spleen. Additionally, alcoholism is</p>

known to shut down the production of a key cytokine called IL-15.

Research shows that women's and men's immune systems function differently. During the reproductive years, women have a stronger immune response than men, controlled by differences in the blood levels of oestrogen, which stimulates immune responses, testosterone, which is immunosuppressive. In both males and females, alcohol exposure suppresses immune responses. Chronic exposure to alcohol alters the production of these hormones and hence alcohol's effects on immunity could involve an indirect mechanism in which alcohol alters hormone levels and, in turn, the hormones regulate immune responses. In addition, it takes less time and lower doses of alcohol exposure to cause liver damage in females than in males.

Some experts suspect that alcohol exerts an "allornone" effect on immune response—that is, the presence or absence of alcohol, rather than its amount, dictates the immune response. Other researchers believe that low doses of alcohol—the amount equivalent to a glass of wine—can confer health benefits, including protection against damage to the cardiovascular and immune systems. Such benefits, if they are present, may be attributable to antioxidants in alcoholic beverages such as red wine. In any case, health experts agree that the beneficial effects of antioxidants in some alcoholic beverages are lost if the level of alcohol consumption is elevated.

Overdosing on sugar: Eating or drinking 100 grams (8 tbsp) of sugar which is the equivalent of about two cans of soda, can reduce the ability of white blood cells to kill germs by forty percent. The immune-suppressing effect of sugar starts less than thirty minutes after ingestion and may last for five hours. In contrast, the ingestion of complex carbohydrates, or starches, has no effect on the immune system.