Insulin Resistance

As ENERGY SURPLUS increases from higher calorie intake beyond that which is necessary, storage of those calories shifts increasingly from SUBCUTANEOUS to VISCERAL fat which has a more rapid TURNOVER of triglycerides. Visceral fat is resistant to the anti-lipolytic effects of insulin -> releasing large amounts of free fatty acids (FFA) affecting the liver and muscle. Excess energy/calorie intake results in the overproduction of the LDL as a result of INCREASED FFA UPTAKE by the liver causing elevated triglycerides (TG) and low HDL cholesterol. Low HDL occurs because of increased TG infiltration into HDL resulting in increased HDL catabolism & also by down regulated HDL production in adipose tissue because Apo A1, HDL's main building block, is controlled by insulin levels which have become either less effective &/or eventually decreased. Excess FFA increase the OXYGEN DEMANDS of ischemic heart muscle and reduce the use of glucose as a metabolic fuel by the heart. In the liver, gluconeogenesis occurs because of a lack of effect of insulin, further increasing blood sugar levels. In muscles, nutritional glucose cannot be taken up because of this insulin resistance from the elevated levels of circulating free fatty acids. Enlarged fat cells also become resistant to insulin and the excess fat that is available is then stored in muscle, liver, and pancreatic beta cells = "lipo-toxicity" that damages beta cells, magnifying insulin deficiency. Visceral fat also produces excess steroid DEHYDROGENASE which then converts inactive cortisone to the biochemically active CORTISOL affecting fat distribution causing central obesity which, again, increases insulin resistance. Insulin resistance results in increasing A1C & each 1% increase of AIC precedes the 8% increased CHF & a 17% increase in cardiovascular disease.

Insulin resistance causes HYPERCOAGUABILITY (the LIVER releases more FACTOR II, VII, IX, & X) , impaired fibrinolysis, chronic inflammation, oxidative stress via increased PAI-1 or decreased TPA, increased TNF-a = tumor necrosis factor alpha (down regulates endothelia nitric oxide synthase (eNOS) -> reduced NO -> increased vasoconstriction along with loss of antioxidant capacity, IL-6 = interleukin 6, resistin, and angiotensinogen affecting the endothelium reducing vasodilating nitric oxide (NO) which results in increased CRP that is a direct and important inflammatory agent. TNF-a increases LDL binding to the endothelium. Increased PAI-1 & decreased TPA interfere with fibrinolysis predisposing to new clot formation. Enlarged adipocytes are less responsive to insulin resulting in the beginning of these multiple cascades. Higher fasting insulin levels increase cardiovascular events 550% and are more predictive than high LDL or Apo B, or low HDL. Insulin resistance also results in less of the beneficial adiponectin. Low adiponectin is predictive of the future development of type II diabetes and coronary artery disease. Binding insulin to the insulin receptor recruits PI3K to the plasma membrane which then activates the central mediator of insulin's effects, Akt-1 also called protein kinase B. Protein kinase B inhibits apoptosis, stimulates myocyte hypertrophy/fibrosis, and nitric oxide (NO) production. Lack of insulin effect -> less nitric oxide more apoptosis and alterations in myocardial structure, resulting in a worsened environment for CHF myocardium. NO controls renal function and reabsorbtion or excretion and is a vascular dilator and controls endothelial progenitor cells/repair. Insulin resistance increases intravascular volume as the kidney becomes insulin-resistant and increases sodium re-uptake -> expanded blood volume, potentiating HBP. ANDROGEN changes occur -> hypo in men and hyperandrogen in women via activation of aromatase which converts testosterone into estrogen.

Insulin resistance is ONCOGENIC via IGF-I and is a growth factor itself. PHOSPHTASE AND TENSIN HOMOLOGUE = PTEN is a tumor suppressor and many cancers have a loss of function or mutation of PTEN which regulates proto-oncogenic phosphatidylinositol 3- kinase (PI3K). PI3K interacts with intracellular growth factors

and insulin. As a result a reduction in PTEN -> higher levels of PIP3 favoring cell growth and survival while boosting the metabolic effects of insulin.

Cardiovascular disease rose progressively as fasting plasma glucose and post-load glucose levels rose above 75 mg/dL = 4.2 mmol/liter (Coutinho M, Gerstein HC, Wang Y, Usuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care* 1999;22:233-240).

Excess glucose is oxidized to FRUCTOSE depleting intracellular GLUTATHIONE, increasing susceptibility to oxidative stress. Excess fructose-6 phosphate is transformed and promotes O-linked GLYCOSYLATION of transcription and signaling factors and nuclear proteins altering their function. Excess glucose promotes pro-inflammatory and pro-thrombotic factors including TGF-a, TGF-Beta, & PAI-1. Excess glucose stresses the endoplasmic reticulum activating NF-k B which promotes inflammatory gene expression. Diacyglycerol -> AGE & is increased from high glucose levels -> PROTEIN KINASE C --> reduces nitric oxide synthase and increases endothelin/vascular permeability, inflammatory gene expression and ROS.

59% of cardiomyopathy patients have frank glucose intolerance. Beta blockers that do not worsen insulin resistance (carvedilol/nebivolol) improve function in non-ischemic cardiomyopathy. Higher FFA levels which are associated with insulin resistance inhibit the much greater increase in ATP production from glucose versus FFA. 5 Kg/day of ATP are made. Akt-1 inhibits free fatty acid metabolism by promoting glucose metabolism. When the FFA supply is greater than the heart's of oxidative capacity, the FFA are stored as intramyocardial triglycerides which are associated with lipo-toxicity and worsened heart failure.

Hypertension doubles the risk for the future development of diabetes. ALLHAT showed a 1% increase in risk of future development diabetes for every 1 mm Hg increase in systolic blood pressure. Both angiotensin I- mediated pancreatic vasoconstriction and aldosterone-mediated hypokalemia inhibit glucose-induced insulin release from beta cells. Hypertension in some is associated with increased sympathetic drive (due to increased central sympathetic outflow), endothelial dysfunction, generation of ROS, inflammatory changes in the vascular wall and LVH. Fat cells express adrenergic receptors that are not responsive to insulin. These impaired fat cells are highly responsive to catecholamines -> high levels of hydrolysis of triglycerides and a continuous release of free fatty acids from visceral adipose tissue into the portal circulation. Increased plasma triglycerides are accompanied by excess insulin production progressively and linearly to an oral glucose load. HDL production is down regulated while HDL catabolism increases by an increase transfer of triglycerides into HDL.

Postprandial platelet activation is related to postprandial plasma insulin rather than glucose in patients with type II diabetes

Cadmium and arsenic in the environment are related to the development of diabetes. Arsenic has been found to be in higher concentration in rice and hence the high rice diet of Hispanics may in part explain the high incidence of diabetes in Hispanics.

Boswellia inhibits 5 lipoxygenase which modifies LDL. Minimally modified LDL initiates the fatty streak. Nitric oxide can be modified by the hydrochlorous acid from myeloperoxidases produced from macrophages -> create ROS. Doing this in inhibits cholesterol efflux. Sepsis or the flu can reduce HDL 50 %. Saturated fat increases the expression of ICAM-1 and VCAM-1 at 6 hours compared to fasting. D-4F is an 18 amino acid peptide not broken down by human digestive enzymes. D-4F given BID reduced ASCVD lesions by 79% without changing cholesterol or HDL levels.