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Graduate School

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The clinical importance for the early detection of insulin resistance

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Professor Michael Guerra

For his involvement in all facets of this review; from lectures that inspired my interest to the guidance and proofreading as my advisor.

Thank you!

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The clinical importance for the early detection of insulin resistance

In the early 1970's, a population-based study of approximately 5000 subjects was conducted to assess the clustering and frequency of five atherosclerotic risk factors including cholesterol, triglycerides, systolic blood pressure, obesity, and cigarette smoking (Criqui, Barret-Conner, Holdbrook, Austin, & John, 1980). In a percentile analysis of this study published in 1980, Criqui et al. found subjects at or above the 70^{th} or 90^{th} percentiles for one risk defined in the study were more likely to be at or above similar percentiles for the other risk factors. This clustering was most evident among the subjects in the highest percentiles of the population. Later, in a follow up study published in 1983, the same clustering of atherosclerotic risks was found to be more prevalent in diabetic participants (Wingard, Barrett-Conner, Criqui, & Suarez, 1983). By 1988, Gerald Reaven, an endocrinologist at Stanford School of Medicine had begun recognizing insulin resistance and hyperinsulinemia as a potential pathophysiology linking the clustering of the previously described risk factors. Reaven made many of his observations through combinations of human and laboratory rat studies; describing a cluster of risks he deemed *Syndrome X*. He found these risks to be present not only in the diabetic population, but in individuals with impaired glucose tolerance; concluding that the underlying insulin resistance and subsequent hyperinsulinemia were responsible for atherogenic changes (Reaven, 1988). Today, the term Metabolic Syndrome is used to describe the presence of dyslipidemia, hypertension, and hyperglycemia; commonly associated with obesity. This clustering of cardiovascular risks factors is associated with an increased risk of coronary artery disease and diabetes (Lempiainen, Mykkanen, Pyorala, Laasko, & Kussisto, 1999).

Current understanding of the syndrome is limited to individual precipitating factors, hypertension, abdominal obesity, hypertriglyceridemia, hyperglycemia, and low high-density lipoprotein levels. These precipitating factors negatively impact endothelial function, serum lipids, and increase the risk of CHD, stroke, and diabetes (National Cholesterol Education Program, 2001). A definitive etiology of the cluster has yet to be identified, although insulin resistance has long been suspected. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) established guidelines in 2001 for metabolic syndrome. The diagnosis of metabolic syndrome is made when 3 or more of risk determinants in **Table 1** are present. In their findings, the ATP III recommend metabolic syndrome as a secondary goal of therapy for atherosclerotic risk reduction behind the primary goal of low density-lipoprotein cholesterol reduction; citing the associated increased risk for (CHD) coronary heart disease (Ford, Giles, & Dietz, 2002).

Prevalence

Little information on the prevalence of the metabolic syndrome was available until the establishment of a unifying definition and criteria established in 2001 by the NCEP-ATPIII. Ford et al. (2002) were able to estimate the age-adjusted prevalence of metabolic syndrome to be 23.7% in the United States by the criteria specified by the ATP III and findings of the Third National Health and Nutrition Examination Survey (NHANES III); collected from a sample population of US non-institutionalized civilians between 1988 and 1994.

Ford further noted a positive correlation of increasing prevalence of metabolic syndrome with increasing age; those aged 20-29 years versus those ages 60-69 years demonstrated a prevalence of 6.7% and 43.5%, respectively (Ford et al ., 2002). Among the participants, Mexican Americans displayed the highest age-adjusted prevalence of metabolic syndrome (31.9%) followed by whites and African Americans, 23.8% and 21.6%, respectively. The age-adjusted prevalence for men and women of all ethnicities showed little disparity, 24.0% and 23.4% respectively. Applying these findings to the 2000 census information, approximately 47million (22%) of the US populations would meet diagnostic criteria for metabolic syndrome (Ford et al.). Ford cautions current prevalence rates may actually be higher citing increasing trends of obesity in the US since the NHANES III was conducted. The Behavioral Risk Factor Surveillance Survey (BRFSS) conducted in 2000 found a 61% increase in obesity since 1991 (Cook, Weitzman, Auinger, Nguyen, & Dietz, 2003).

In 2003, Cook et al. determined that the metabolic syndrome was present in 4.2% of the subjects aged 12-19 years-old in the NHANES III study. In the overweight

children of this age range, defined as a BMI equal to or greater than the 95th percentile for age and gender, 28.7% met diagnostic criteria in comparison to 0.1% of those with a BMI below the 85th percentile for their age and gender. Based on these population-weighted estimates, nearly 910,000 adolescents, approximately 4% of all adolescents in the United States, met the criteria for metabolic syndrome (Cook et al.). Current NHANES data suggests 15% of adolescents surveyed in 1999-2000 are overweight (BMI ≥95%); when applied to the 2000 Census data and the prevalence rate established by Cook et al., approximately 1.4 million adolescents aged 12-19 have metabolic syndrome.

Metabolic Syndrome and Insulin Resistance

The association of impaired fasting glucose/impaired glucose tolerance (IFG/IGT) and the metabolic syndrome has long been recognized. Recently, studies have begun to show the association between insulin resistance, metabolic syndrome, and diabetes (Meigs et al., 2003). In the Bruneck Study (Bonora et al., 1998), the purpose was to assess the prevalence of insulin resistance in populations of patients displaying IGT, non-insulin dependant diabetes mellitus (NIDDM), hyperuricemia, hypertension, and dyslipidemia. Insulin resistance in this study was defined using the Homeostasis Model Assessment for Insulin Resistance ($HOMA_{IR}$), calculated by taking the product of fasting serum insulin (U/ml) x fasting plasma glucose (mmol/l), divided by the constant 22.5 (Matthews et al., 1985). Low $HOMA_{IR}$ values are indicative of high insulin sensitivity, whereas lower values suggest insulin resistance; defined in the Bruneck Study as equal to or greater than the lower limit of the upper quintile of $HOMA_{IR}$ distribution values in normal subjects (BMI $\leq$25 kg/m^2 with no metabolic abnormalities). This study demonstrated the prevalence of insulin resistance in IGT and NIDDM subjects was 65.9% and 83.9% respectively. Eighty eight percent of the subjects with low high-density lipoprotein (HDL) levels displayed insulin resistance, as did 84.2% of those with hypertriglyceridemia. The prevalence of insulin resistance in subjects with the combination of all features including IGT, non-insulin dependant diabetes mellitus (NIDDM), hyperuricemia, hypertension, and dyslipidemia was 95.2% (Bonora et al., 1998). In a similar study using the World Health Organization (WHO) criteria (**Table 2**) for metabolic syndrome, similar prevalence rates of IFG/IGT were found (Isomaa et al., 2001). Metabolic syndrome, as defined by the WHO, omits the use of fasting glucose

defined by NCEP as criteria. However, they add the use of a urinary albumin excretion rate as an additional guideline; 2 of the 4 criteria used in the WHO definition are required for diagnosis (Alberti & Zimmer, 1998).

In a 7-year follow up of the San Antonio Heart Study, prediabetic subjects who had converted to NIDDM were compared among each other based on insulin sensitivity and insulin secretion. Insulin resistance was defined as levels at or above the median for $HOMA_{IR}$ in the non-diabetic population of this study. Insulin secretion was measured using an early insulin secretion response to an oral glucose load; calculated by change in insulin/change in glucose through the first 30 min ($\Delta I_{30-0}/\Delta G_{30-0}$). Again, secretory defects were defined by levels at or below the median $\Delta I_{30-0}/\Delta G_{30-0}$ for the non-diabetic population in this study. As a whole, those that had developed NIDDM displayed elevated levels of blood pressure, triglycerides, and low HDL cholesterol over those in the study who did not convert to NIDDM. However, within the converters, subjects found to have decreased insulin sensitivity (insulin resistance) had a stronger risk of atherosclerosis and significantly higher elevated blood pressure, triglycerides, and low HDL cholesterol over their NIDDM counterparts with only an insulin secretory defect (Haffner, Mykkanen, Festa, Burke, & Stern, 2000).

Insulin Action and Endothelial Dysfunction

Impaired insulin action occurs when the body tissues no longer respond to a normal concentration of insulin. The mechanism in which insulin resistance develops is not fully understood, however, increasing evidence indicates it may rely on a multitude of factors including diet (Purnell et al., 2000), inactivity (Pate et al., 1995), genetics (Taylor et al., 1992), and visceral obesity (St-Pierre et al., 2002). Glucose removal by muscle or adipose tissue and the regulation of hepatic glucose production are commonly interrupted pathways of insulin resistance (Reaven, 1988). When plasma glucose levels become elevated, the β-cells in pancreas respond by secreting more insulin to maintain a euglycemic state (James, 1992). With time, the β-cells will no longer maintain these elevated levels of secretion, resulting in impaired glucose tolerance (IGT) and hyperglycemia. Chronically elevated levels of insulin, as in insulin resistance, often result in metabolic abnormalities such as decreased HDL cholesterol, increased triglycerides (TG) levels, and increased levels of smaller, dense LDL cholesterol in addition to endothelial dysfunction.

Inside endothelial target cells, insulin activates multiple pathways including phosphatidylinositol 3-kinase pathway (PI3K) which works in glucose uptake and metabolism in a manner similar to glucose metabolism in the liver, muscle, and fat cells. Additionally, the PI3K pathway has also been shown to regulate insulin-dependant endothelial nitric oxide (NO) production; in this manner insulin acts a vasodilator (Zeng et al., 2000). The presence of vasodilators promotes vascular dilation and provides an antiatherogenic action (Vallance, Collier, & Moncada, 1989). Nitric oxide is known to produce smooth muscle relaxation, vasodilation, and inhibition of VSMC growth,

migration, in addition to prevention of monocyte adhesion (Celermajer, 1997); many of which contribute to atherosclerosis and hypertension. Nitric oxide-mediated endothelial dysfunction has been found in NIDDM as well as obese subjects (Steinberg et al., 1997). The disruption of the PI3K pathway is the potential link of insulin resistance to hypertension, atherosclerosis, hyperglycemia, and associated metabolic abnormalities seen with the metabolic syndrome (Shephard, Withers, & Siddle, 1998).

Cardiovascular Risk Factors

Traditional risk factors for atherosclerosis and endothelial dysfunction have long been studied; including hypertension, increasing age, smoking, and hypercholesterolemia (Celermajer & Sorensen, 1992). In 1998, Haffner et al. showed the associated risk of CHD for subjects with NIDDM to be equivalent to non-diabetic subjects with a prior cardiovascular event (Haffner et al., 1998). More current studies have begun to focused on an alternate subset of risk factors for endothelial dysfunction and CHD, assessing their potential predication of cardiovascular events; this includes hypertriglyceridemia (Lundman, Eriksson, Schenck-Gustafsson, Karpe, & Tornvall, 1997) and elevated levels of free fatty acids (Steinberg et al., 1997). Insulin resistance, as well, has been significantly linked to CHD (Lempiainen et al., 1999) and endothelial dysfunction (Steinberg et al., 1996). Recent evidence supports insulin resistance as an independent predictor of cardiovascular events (Pyorala, Miettinen, Halonen, Laasko, & Pyorala, 2000).

Insulin Resistance and Dyslipidemia

The atherogenic lipid and lipoprotein abnormalities of the metabolic syndrome and associated insulin resistance consists of decreased HDL cholesterol, increased triglycerides (TG) levels, increased levels of smaller, dense LDL cholesterol and elevated levels of apolipoprotein-B. The association of insulin resistance and dyslipidemia in metabolic syndrome has multiple proposed mechanisms. One suggested pathway relates to dyslipidemia based on the presence of insulin resistant adipocytes; decreased insulin sensitivity in these adipose cells is thought to be the initial step of dyslipidemia. Adipocytes are specifically enabled to store abundant amounts of free fatty acids (FFA) in the form of TG (Unger, 2002). Fat cells will remove free fatty acids from plasma concentrations and combined them with glycerol, derived from glucose, to form TG. Additionally, molecules such as TG-rich very low-density lipoprotein cholesterol (VLDL) act as FFA vectors which are taken up, metabolized, and stored within the adipocytes. The decreased action of insulin results in an increase in lipolytic active within the adipocytes, resulting in hydrolysis and the subsequent release of triglycerides raising serum FFA concentrations (Ginsberg, 2000). These acute elevations of FFA have been shown to show decreased glucose uptake in peripheral skeletal muscle (Kelley et al., 2001) and result in further production of TG and VLDL in association with apolipoprotein B from the liver (McFarlane, Banerji, & Sowers, 2001).

VLDL cholesterol elevations precipitate further dyslipidemia and atherosclerotic risks. Triglyceride-rich LDL particles are more readily hydrolyzed by lipoprotein lipase or hepatic lipase, resulting in a smaller, denser, more atherogenic (LDL) particle that has shown to provide independent risk value for CAD (Lamarche et al., 1997). The manner

in which HDL cholesterol is regulated is not fully understood, however, low HDL-C is commonly associated with elevated triglycerides levels and insulin resistance (Zambon, Brown, Deeb, & Brunzell, 2001).

Assessment of Insulin Resistance

The glucose clamp technique developed in 1979 by DeFronzo et al. has been considered the gold-standard for assessment of β-cell response to glucose (hyperglycemic clamp method) and insulin sensitivity (euglycemic clamp method). The euglycemic clamp technique requires a constant insulin infusion with a variable glucose infusion adjusted to maintain a constant level of euglycemia; the rate of glucose infusion equates to the body's tissue-uptake of glucose. This rate of glucose removal provides a quantitative assessment of insulin action in the body (DeFronzo, Tobin, & Andres, 1979).

Although the glucose clamp technique provides the best evaluation of insulin resistance, its application in larger study populations and clinical settings are limited due to its time consuming nature, inherent high cost, and increased level of sophistication. Bergman et al. (1979) developed a slightly more practical assessment of insulin resistance; the technique design involved a frequently sampled intravenous glucose tolerance test (FSIGTT) where a single glucose injection is followed by a single dose of insulin. Plasma glucose concentrations are then repeatedly measured (22 samples) over 3 hours post insulin injection (Bergman, Ider, Bowden, & Cobelli, 1979). Additionally, Bergman later developed the minimal model technique to compliment this method. Minimal model was designed to calculate an insulin sensitivity index based on the dynamic relationship between glucose and insulin during a frequently sampled glucose tolerance test (Bergman, 1989). Comparisons of the glucose clamp technique and FSIGT with minimal model assessment showed the two are similar in their ability to identify insulin resistance in NGT and IGT subjects, however, findings of the study demonstrate

FSIGTT lacks the same sensitivity as the glucose clamp in assessing insulin resistance among NIDDM subjects (Saad et al., 1994).

Simple Tests of Insulin Sensitivity

Recent attempts have been aimed to develop an accurate index to assess insulin resistance using a single fasting blood sample. Some of these techniques include the $HOMA_{IR}$, oral glucose tolerance tests, fasting insulin, insulin-to-glucose ratio, and combinations of assorted values.

- Homeostasis Model Assessment ($HOMA_{IR}$)

Mentioned earlier, the homeostasis model assessment (1985) uses a computer-solved model of insulin and glucose interactions to plot various fasting plasma insulin and glucose combinations; levels that would be expected in various degrees of β-cell dysfunction and/or insulin resistance. This array provides a graph to which measured fasting plasma insulin and glucose levels can be applied, allowing estimations of glucose sensitivity and β-cell function from a single fasting sample. A simple formula for insulin resistance was derived from this model; calculated by taking the product of the [fasting serum insulin] (μU/ml) and [fasting plasma glucose] (mmol/l), divided by 22.5 (Matthews et al. 1985).

- Insulin-to-glucose ratio

Developed by Caro in 1991, the insulin-to-glucose ratio is a formula similar to the $HOMA_{IR}$ equation for insulin resistance; the constant 22.5 in the denominator is omitted. In this model, insulin resistance is defined by any value lower than 6, calculated using the equation fasting plasma glucose (mg/dL) / fasting serum insulin (μU/ml). This ratio is not without its limitations, because it depends on normal function of β-cells, it is not valid in anyone with a secretory defect, such as NIDDM (Caro, 1991).

- Insulin levels

Laakso in 1993 utilized a more simple approach, investigating fasting insulin and insulin samples following an oral glucose tolerance test. Compared with the euglycemic clamp technique, he found that insulin had different correlation values in assessment of insulin resistance between NGT (normal glucose tolerance), IGT, and NIDDM subjects. He eventually determined that for any insulin value, fasting insulin was the most useful in predicting insulin resistance (Laakso, 1993).

- Insulin and Triglycerides

Based on the assessment Laakso in NGT subjects, McAuley et al. (2001) took a different approach to assessing insulin resistance by evaluating fasting insulin levels in combination with various characteristics in normoglycemic patients including blood pressure, waist circumference, lipid profiles, BMI, liver enzymes, and glucose. In the study population of NGT subjects, fasting insulin, fasting triglycerides, aspartate-aminotransferase, waist circumference, and BMI were found to correlate best with insulin sensitivity among the tested variables (McAuley et al., 2001).

Many comparisons have been drawn between Bergman's minimal model, the glucose clamp, insulin indices, and the homeostasis model assessment. One such study (1995) of the insulin sensitivity models was based on association to (correlation), and consistency (coefficient of variable) with the glucose clamp. Compared with $HOMA_{IR}$ and the other indices, minimal model was superior in both association and consistency in this study. Although, $HOMA_{IR}$ and the insulin-to-glucose ratio correlated well in comparison, their respective coefficient of variation was significantly higher than that of the minimal model. Matthews et al. noted this inconsistency within $HOMA_{IR}$ when first

developed the model in 1985 (Matthews et al.). Despite inferior consistency compared with the minimal model, $HOMA_{IR}$ and the similarly derived IG ratio were marginally superior to the remaining insulin indices (Anderson et al., 1995). The single fasting insulin value proved to have a moderate association with the glucose clamp and poor consistency when tried in a population consisting of NGT, IGT, and NIDDM subjects. Findings suggested single fasting insulin levels would yield varying values depending on the glucose tolerance of the subject; providing a higher coefficient of variation and limiting the models use without prior knowledge of glucose tolerance status in the subject (Anderson et al.).

These findings were confirmed in a similar study in 1998 by Howard et al, suggesting that although some of these methods may provide alternatives for use in studies and trials, they do not provide a reasonable alternative for clinical assessment of insulin resistance in the general population (Howard et al., 1998). The findings associated with combining fasting insulin and fasting triglycerides were not yet published and not assessed in these studies.

Clinical assessment of insulin resistance

Results of earlier studies found that the $HOMA_{IR}$ correlated well with the standard glucose clamp but was highly variable in its results, making the model unsuitable for clinical application. In 1999, Emoto et al. used a log-transformed version of the $HOMA_{IR}$ equation (Log-$HOMA_{IR}$) in their study, resulting in increased correlation with the euglycemic clamp over the standard $HOMA_{IR}$ model (Emoto et al., 1999). Later that year, the log-transformed $HOMA_{IR}$ was assessed against the minimal model applied with a FSIGT, again, displaying a higher correlation than the original $HOMA_{IR}$ (Fukushima et al., 1999).

Recognizing this utility of a log-transformed equation, Katz et al. (2000) developed a related model to similar to Log $HOMA_{IR}$, a quantitative insulin sensitivity check index (QUICKI) (Katz et al., 2000). In his study, QUICKI ($1/ [\log (I_0)] + [\log (G_0)]$) was tried against the glucose clamp, a FSIGTT with minimal model analysis, and the older version of $HOMA_{IR}$ across NGT, IGT, and NIDDM subjects. The results showed that QUICKI correlated better with the glucose clamp ($r = 0.78$) compared to the minimal model ($r = 0.57$) and the $HOMA_{IR}$ ($r = 0.6$) values found in this study (Katz et al.). Later, it was recognized that measuring FFA as a component of the equation would improve the reliability of QUICKI as a screening tool. In this population of non-obese, normoglycemic subjects, results nearly doubled in the correlation of the index with euglycemic clamp ($r = 0.51$ from $r = 0.27$) (Perseghin, Caumo, Caloni, Testolin, & Livio, 2001). This study also demonstrated that inclusion of FFA component improved the sensitivity of QUICKI to lower levels of insulin resistance in normoglycemic subjects.

These benefits were later confirmed and expanded to include the IGT populations as well (Rabasa-Lhoret et al., 2003).

In a comparison of log-transformed $HOMA_{IR}$ and the original formula for QUICKI to the glucose clamp, both models performed similarly (Mather et al., 2001). The findings of the study suggest that both indices correlate highly to the glucose clamp in obese and NIDDM subjects, but comparatively weak among the lean subjects ($r = 0.35$-0.4). This study suggests that although improvements are still needed, these current approaches would be appropriate surrogate measures of insulin sensitivity. Additionally, when compared to models based on fasting insulin alone, indices with inclusion of glucose measures such as Log-$HOMA_{IR}$ and QUICKI provide a more generalized and superior method for assessment of insulin resistance (Mather et al.).

Conclusions

The metabolic syndrome, although poorly defined until recently, has been recognized and studied since the early 1970's. Recognition and identification of these clustering risk factors has demarcated a population with greater risk for development of CAD and diabetes. The underlying pathophysiology of the metabolic syndrome is not well under understood at this time. Insulin resistance has long been considered to play an integral role; research conducted in the past decade has provided plausible mechanisms for IR which may explain associated physiologic changes.

The clinical importance and need for routine insulin resistance screening is clearly apparent by the increasing morbidity and mortality for those who develop CAD and diabetes, as well as the growing population of those meeting metabolic syndrome criteria. Unfortunately, recent attempts to identify IR through the use of computer models, calculations, and measured ratios have proven unsuccessful in large, general populations. Until a simple, cost-effective measure of insulin sensitivity is developed the best screening for IR is the clinical application of NCEP criteria.

Once identified as insulin resistant by NCEP guidelines, treatment should be aggressive for these patients; current ATP III guidelines suggest LDL-C treatment to goal as primary therapy. The identification of the metabolic syndrome and IR, defined by 3 of 5 NCEP criteria should be considered a more progressive disease state. Treating LDL-C in these patients equivocates to symptomatic therapy, leaving the underlying resistance to insulin unchanged. For this reason, the potential use of insulin sensitizers, such as thiazolidinediones, may prove to be more beneficial in treating the underlying

pathophysiology and should be further investigated for their use in the metabolic syndrome population.

Table 1 Diagnostic Criteria for Metabolic Syndrome, Guidelines of National Cholesterol Education Program: Adult Treatment Panel III (Ford et al ., 2002)

Diagnosis of metabolic syndrome requires any 3 of the following:	
Abdominal obesity	Waist circumference
• Men	>102 cm (>40 in)
• Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dl
HDL cholesterol	
• Men	<40 mg/dl
• Women	<50 mg/dl
Blood pressure	≥130/≥85 mmHg
Fasting glucose	≥110 mg/dl and <126 mg/dL

Table 2 Diagnostic Criteria for Metabolic Syndrome, Guidelines of World Health Organization [23]

Diagnosis of metabolic syndrome requires any 2 of the following:	
Abdominal obesity	Waist circumference
• BMI	≥30 kg/m^2
• Waist: Hip Ratio	>0.90 in men, >0.85 in women
Dyslipidemia defined as one/both of:	
• Triglycerides	≥1.7 mmol/l
• HDL cholesterol	<0.9 mmol/l in men, <1.0 mmol/l in women
Blood pressure	≥160/≥90 mmHg or antihypertensive Tx
Microalbuminuria	Urinary Albumin Excretion Rate (AER) ≥20 μg/min

To convert mmol/l of HDL cholesterol to mg/dl, multiply by 38.67.

To convert mg/dl of HDL cholesterol to mmol/l, divide by 38.67.

To convert mmol/l of triglycerides to mg/dl, multiply by 88.57.

To convert mg/dl of triglycerides to mmol/l, divide by 88.57.

References

Alberti, KG., & Zimmer, PZ. (1998). Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabetic Medicine, 15,* 539-553.

Anderson , R. L., Hamman, R. F., Savage, P. J., Saad, M. F., Laws, A., Kades, W. W., et al. (1995). Exploration of simple insulin sensitivity measures derived from frequently sampled intravenous glucose tolerance (FSIGT) tests. *American Journal of Epidemiology, 147,* 724-732.

Bergman, R. N. (1989). Toward physiological understanding of glucose metabolism. *Diabetes, 38,* 1512-5127.

Bergman, R. N., Ider, Y. Z., Bowden, C. R., & Cobelli, C. (1979). Quantitative estimation of insulin sensitivity. *Amercian Journal of Physiology: Endodcrinology and Metabolism, 5,* E667-E677.

Bonora, E., Kiechl, S., Willeit, J., Oberhollenzer, F., Egger, G., Targher, G., et al. (1998). Prevalence of insulin resistance in metabolic disorders. *Diabetes, 47,* 1643-1649.

Caro, J. F. (1991). Clinical review 26: Insulin resistance in obese and nonobese man. *The Journal of Clinical Endocrinology and Metabolism, 73,* 691-695.

Celermajer, D. S. (1997). Endothelial dysfunction: Does it matter? Is it reversible? *Journal of the American College of Cardiology, 30,* 325-333.

Celermajer, D. S., & Sorensen, K. E. (1992). Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet, 340,* 1111-1115.

Cook, S., Weitzman, M., Auinger , P., Nguyen, M., & Dietz, W. H. (2003). Prevalence of a metabolic syndrome phenotype in adolescents: Findings from the Third National Health and Nutrition Examination Survey, 1988-1994. *Archives of Pediatrics and Adolescent Medicine, 157*(8), 821-827.

Criqui, M. H., Barret-Conner, E., Holdbrook, M. J., Austin, M., & John, D. T. (1980). Clustering of Cardiovascular Disease Risk Factors. *Preventive Medicine, 9,* 525-533.

DeFronzo, R. A., Tobin, J. D., & Andres, R. (1979). Glucose clamp technique: A method for quantifying insulin secretion and resistance. *American Journal of Physiology: Endocrinology and Metabolism, 237,* E214-E223.

Emoto, M., Nishizawa, Y., Maekawa, K., Hiura, Y., Kanda, H., Kawagishi, T., et al. (1999). Homeostasis Model Assessment as a clinical index of insulin resistance in type 2 diabetic patients treated with sulfonylreas. *Diabetes Care, 22,* 818-822.

Ford, E. S., Giles, W. H., & Dietz, W. H. (2002). Prevalence of the metabolic syndrome among US adults: Findings from the Third National Health and Nutrition Survey. *Journal of the American Medical Association, 287,* 356-359.

Fukushima, M., Taniguchi, A., Sakai, M., Doi, K., Nagasaka, S., Tanaka, H., et al. (1999). Homeostasis Model Assessment as a clinical index of insulin resistance . *Diabetes Care, 22,* 1911-1912.

Ginsberg, H. N. (2000). Insulin resistance and cardiovascular disease. *The Journal of Clinical Investigation, 106,* 453-458.

Haffner, S. M., Lehto, S., Ronnemaa, T., Pyorala, K., & Laasko, M. (1998). Morbidity from coronary heat disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *New England Journal of Medicine, 339,* 229-234.

Haffner, S. M., Mykkanen, L., Festa, A., Burke, J. P., & Stern, M. P. (2000). Insulin-resistant prediabetic subjects have more atherogenic risk factors than insulin-sensitive prediabetic subjects: Implications for preventing coronary heart disease during the prediabetic state. *Circulation, 101,* 975-980.

Howard, G., Bergman, R., Wagenknecht, L. E., Haffner, S. M., Savage, P. J., Saad, M. F., et al. (1998). Ability of alternative indices of insulin sensitivity to predict cardiovascular risk: Comparison with the "Minimal Model". *American Journal of Epidemiology, 8,* 358-369.

Isomaa, B., Almgrn, P., Tuomi, T., Forsen, B., Lahti, K., Nissen, M., et al. (2001). Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care, 24,* 683-689.

James, D. E. (1992). Cellular and molecular biology of the beta cell. *Diabetologia, 35*(Suppl 2), S41-S48.

Katz, A., Nambi, S. S., Mather, K., Baron, A. D., Follmann, D. A., Sullivan, G., et al. (2000). Quantitative insulin sensitivity check index: A simple, accurate method for assessing insulin sensativity in humans. *Journal of Clinical Endocrinology and Metabolsim, 85,* 2402-2410.

Kelley, D. E., Williams, K. V., Price , J. C., McKolanis, T. M., Goodpaster, B. H., & Thaete, F. L. (2001). Plasma fatty acids, adiposity, and variance of skeletal muscle insulin resistance in type 2 diabetes mellitus. *Journal of Clinical Endocrinology and Metabolism, 86,* 5412-5419.

Laakso, M. (1993). How good a marker is insulin level for insulin resistance? *American Journal of Epidemiology, 137,* 959-965.

Lamarche, B., Tchernof, A., Moorjani, S., Cantin, B., Dagenais, G. R., Lupien, P. J., et al. (1997). Small, dense low density lipoprotein particles as a predictor of the risk of ischemic heart disease in men: Prospective results from the Quebec Cardiovascular Study. *Circulation, 95,* 69-75.

Lempiainen, P., Mykkanen, L., Pyorala, K., Laasko, M., & Kussisto, J. (1999). Insulin resistance syndrome predicts coronary heart disease events in elderly nondiabetic men. *Circulation, 100,* 123-128.

Lundman, P., Eriksson, M., Schenck-Gustafsson, K., Karpe, F., & Tornvall, P. (1997). Transient triglycerides decrease vascular reactivity in young, healthy men without risk factors for coronary heart disease. *Circulation, 96,* 3266-3268.

Mather, K. J., Hunt, A. E., Steinberg, H. O., Paradisi, G., Hook, G., Katz, A., et al. (2001). Repeatability characteristics of simple indices of insulin resistance: implications for research applications . *Journal of Clinical Endocrinology and Metabolism, 86,* 5457-5464.

Matthews, D. R., Hosker, J. P., Rudenski, A. S., Naylor, B. A., Treacher, D. F., & Turner, R. C. (1985). Homeostasis model assessment: Insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia, 28,* 412-419.

McAuley, K. A., Wlliams, S. M., Mann, J. I., Walker, R. J., Lewis-Barned, N. J., Temple, L. A., et al. (2001). Diagnosing insulin resistance in the general population. *Diabetes Care, 24,* 460-464.

McFarlane, S. I., Banerji, M., & Sowers, J. R. (2001). Insulin resistance and cardiovascular disease. *The Journal of Clinical Endocrinology and Metabolism, 86,* 713-718.

Meigs, J. B., WIlson, P. W.F., Nathan, D. M., D'Agostino, R. B, Sr, Williams, K., & Haffner, S. M. (2003). Prevalence and characteristics of the metabolic syndrome in the San Antonio Heart and Framingham Offspring studies. *Diabetes, 52,* 2160-2167.

National Cholesterol Education Program (2001). Executive summary of the third report of the National Cholesterol education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *Journal of the American Medical Association, 285*, 2486-2497.

Pate, R. R., Pratt, M., Blair, S. N., Haskell, W. L., Macera, C. A., Bouchard, C., et al. (1995). Physical activity and public health: A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *Journal of the American Medical Association, 273,* 402-407.

Perseghin, G., Caumo, A., Caloni, M., Testolin, G., & Livio, L. (2001). Incorporation of the fasting plasma FFA concentration into QUICKI improves its association with insulin sensitive in nonobese individuals. *The Journal of Clinical Endocrinology and Metabolism, 88,* 4776-4781.

Purnell, J. Q., Kahn, S. E., Albers, J. J., Nevin, D. N., Brunzell, J. D., & Schwartz, R. S. (2000). Effect of weight loss with reduction of intra-abdominal fat on lipid metabolism in older men. *The Journal of Clinical Endocrinology and Metabolism, 85,* 977-982.

Pyorala, M., Miettinen, Heikki, Halonen, P., Laasko, M., & Pyorala, K. (2000). Insulin resistance syndrome predicts the risk of coronary heart disease and stroke in healthy middle-aged men: The 22-year follow-up results of the Henlsinki Policeman Study. *Arteriosclerosis Thrombosis Vascular Biology, 20,* 538-544.

Rabasa-Lhoret, R., Bastard, J. P., Jan, V., Ducluzeau, P. H., Andreelli, F., Guebre, F., et al. (2003). Modified quantitative insulin sensitivity check index is better correlated to hyperinsulinemic glucose clamp than other fasting-based index of insulin sensitivity in different insulin-resistant states. *The Journal of Clinical Endocrinology and Metabolism , 88,* 4917-4923.

Reaven, G. M. (1988). Role of insulin resistance in human disease. *Diabetes, 37,* 1595-1607.

Saad, M. F., Anderson, R. L., Laws, A., Watanabe, R. M., Kades, W. E., Chen, Y. D., et al. (1994). A comparison between the minimal model and the glucose clamp in the assessment of insulin sensitivity across the spectrum of glucose tolerance. *Diabetes, 43,* 1114-1121.

Shephard, P. R., Withers, D. J., & Siddle, K. (1998). Phospoinositide 3-kinase: The key switch mechanism in insulin signaling. *Biochemical Journal, 333,* 471-490.

Steinberg, H. O., Chaker, H., Leaming, R., Johnson, A., Brechtel, G., & Baron, A. D. (1996). Obesity/insulin resistance is associated with endothelial dysfunction. *Journal of Investigative Medicine, 97,* 2601-2610.

Steinberg, H. O., Tarshoby, M., Monestel, R., Hook, G., Cronin, J., Johnson, A., et al. (1997). Elevated circulating free fatty acid levels impair endothelial-dependant vasodilation. *The Journal of Clinical Investigation, 100,* 1230-1239.

St-Pierre, J., Lemieux, I., Vohl, M. C., Perron, P., Tremblay, G., & Despres, J. P. (2002). Contribution of abdominal obesity and hypertriglyceridemia to impaired fasting glucose and coronary artery disease. *The American Journal of Cardiology, 90*(1), 15-18.

Taylor, S. I., Cama, A., Accili, D., Barbetti, F., Quon, M. J., De La Luz Sierra, M., et al. (1992). Mutations in the insulin receptor gene. *Endocrine Review, 13,* 566-595.

Unger, R. H. (2002). Lipotoxic Disease. *Annual Review in Medicine, 53,* 319-336.

Vallance, P., Collier, J., & Moncada, S. (1989). Effects of endothelial-derived nitric oxide on peripheral arteriolar tone in man. *Lancet, 334,* 997-1000.

Wingard, D. L., Barrett-Conner, E., Criqui, M. H., & Suarez, L. (1983). Clustering of heart disease risk factors in diabetic compared to nondiabetic adults. *American Journal of Epidemiology, 117,* 19-26.

Zambon, A., Brown, G. B., Deeb, S. S., & Brunzell, J. D. (2001). Hepatic lipase as a focal point for the development and treatment of coronary artery disease . *Journal of Investigative Medicine, 49,* 112-118.

Zeng, G., Nystrom, F. H., Ravichandran, L. V., Cong, L. N., Kirby, M., Mostowski, H., et al. (2000). Roles for insulin receptor, PI3-kinase, and Akt in insulin-signaling pathways related to production of nitric oxide in human vascular endothelial cells. *Circulation, 101,* 1539-1545.

Objective: Insulin resistance is considered a potential etiology underlying endothelial dysfunction and dyslipidemia associated with metabolic syndrome. Metabolic syndrome increases the risk for CAD and diabetes. Early identification of metabolic syndrome may prevent progression and complications associated with these diseases.

Methods: An on-line review of published literature through various search engines including Medline, MD Consult, CINAHL, Google, and PubMed of subjects applying but not limited to search terms: metabolic syndrome, insulin resistance, syndrome x, dyslipidemia, and diabetes was conducted to compare and contrast simplicity and accuracy of various IR detection models.

Results: None of the currently reviewed models are practical for clinical application in identifying insulin resistance in large, general populations.

Conclusion: The use of newly established guidelines set by the National Cholesterol Education Panel for metabolic syndrome is currently the most effective clinical screening method available for identifying insulin resistance.