Insulin Resistance and Coronary Heart Disease in Nondiabetic Individuals

Gerald Reaven

Abstract—The goal of this review was to summarize evidence supporting the view that insulin resistance/compensatory hyperinsulinemia play an important role in the pathogenesis of coronary heart disease (CHD) in nondiabetic individuals. Results of case–control and epidemiological studies in nondiabetic individuals will be reviewed to examine the link between insulin resistance/compensatory hyperinsulinemia, associated abnormalities, and CHD. The primary focus of the review will be on the central role that dyslipidemia plays in the link between insulin resistance/compensatory hyperinsulinemia and CHD. Additional issues to be addressed include the following: (1) the relationship among obesity, insulin resistance, and CHD; (2) a listing of other abnormalities that contribute to risk of CHD in insulin-resistant individuals; and (3) discussion of the importance of differential tissue insulin sensitivity in the development of abnormalities that increase CHD risk in insulin-resistant, nondiabetic individuals. The information will reflect the author’s decision as to what issues are believed to be of particular relevance or less well appreciated concerning the complex relationship between insulin resistance and CHD. Resistance to insulin-mediated glucose disposal and hyperinsulinemia is a common finding in apparently healthy individuals and is associated with a number of abnormalities that greatly increase risk of CHD. 

Key Words: insulin ■ insulin resistance ■ coronary heart disease ■ hyperinsulinemia ■ atherogenic lipoproteins

To begin with, the phrases “insulin resistance” and “insulin sensitivity,” unless otherwise specified, will refer to the relative ability of insulin to mediate disposal of an infused glucose load; the more efficient the process, the more insulin the relative ability of insulin to mediate disposal of an infused glucose load; the more efficient the process, the more insulin must be secreted. This coupled biological activity will be referred to by the phrase insulin resistance/compensatory hyperinsulinemia. Third, because essentially all patients with type 2 diabetes mellitus (2DM) are insulin resistant, it is difficult to assess the role of this abnormality in the genesis of coronary heart disease (CHD) in these individuals. The decision to exclude consideration of patients with 2DM from this review simplifies to only a modest degree the complexity of the relationship between insulin resistance/compensatory hyperinsulinemia and CHD (online-only Data Supplement). Finally, there is no shortage of potential mechanisms to account for the association between insulin resistance and CHD, and this review will be limited to the author’s judgment of relevant studies that have been performed in human beings. Omission from consideration and/or emphasis in this review of links between insulin resistance and CHD that are deemed central by the reader is unintentional and obviously a function of the author’s biases.

A Bit of History

Seventy-five years ago, The Lancet published a manuscript by Harold Himsworth entitled “Diabetes mellitus: Its differentiation into insulin-sensitive and insulin-insensitive types.” He described a functional test “for distinguishing these two types of diabetes,” and concluded that “the insulin-sensitive type appears to be caused by a deficiency of insulin,” whereas the insulin-insensitive type is “apparently due not to a lack of insulin.” Despite Himsworth’s standing as a preeminent clinical scientist, and his publications over the next few years in the world’s most distinguished medical journals, his findings seemed to have had little long-term impact. In 1970, we published what we believed to be the first experimental method to directly quantify insulin-mediated glucose uptake in humans, leading to the conclusion that insulin resistance was a characteristic finding in patients with 2DM. This method, aptly called the insulin suppression test, will be referred to often in this review and is based on infusing individuals with octreotide...
Insulin Resistance: Not a Simple Concept

The physiological effect of insulin varies dramatically from tissue to tissue, and this complexity is crucial to understanding the adverse impact of insulin resistance/compensatory hyperinsulinemia in human disease. At the simplest level, modulations of various aspects of renal function by insulin remain intact at the same time that there is a marked defect in insulin-mediated glucose disposal. This effect is referred to as the compensatory hyperinsulinemia in nondiabetic individuals that prevents gross decompensation of glucose homeostasis enhances sodium retention and decreases uric acid clearance, leading to hyperuricemia. The sympathetic nervous system also retains normal insulin sensitivity in the face of muscle insulin resistance, and its activation by hyperinsulinemia, along with enhanced renal sodium retention, likely contributes to the increased prevalence of essential hypertension in insulin-resistant individuals. In addition, profound differences in dose-response characteristics can exist in tissues that are both resistant to the action of insulin. For example, the dose-response curves of insulin’s ability to stimulate glucose disposal in muscle versus inhibiting adipose tissue lipolysis differ dramatically; plasma insulin concentrations that approximate half-maximally inhibit plasma-free fatty acid (FFA) concentrations have a relatively minimal impact on stimulating muscle glucose uptake. However, insulin stimulation of muscle glucose uptake and inhibition of adipose tissue lipolysis are highly correlated when these actions are quantified at the appropriate dose-response curve. Finally, although less well understood, it seems highly likely that different pathways within the same tissue can vary in their degree of insulin resistance (eg, insulin resistance in the glucose regulatory pathway), with insulin remaining able to exert its normal activity as a growth factor. In light of these considerations, it is clear that many of the adverse effects of insulin resistance are secondary to compensatory hyperinsulinemia acting on tissues that remain insulin sensitive, and that care is exercised in thinking about how insulin resistance and differential tissue insulin sensitivity interact in the pathogenesis of human disease.

Obesity, Insulin Resistance, and CHD

This relationship has recently been extensively reviewed and will only be briefly addressed in this presentation. Although obesity is often considered to be synonymous with insulin resistance, it accounted for only ~25% of the 6- to 8-fold variability of insulin-mediated glucose disposal observed in a study enrolling both Pima Indians and individuals of Europeans ancestry. There is also evidence that one third of the most insulin-sensitive individuals in a population of apparently healthy obese individuals had a very low CHD.
Table 1. Cluster of Components Constituting Syndrome X

- Resistance to insulin-mediated glucose disposal
- Hyperinsulinemia
- ± Glucose intolerance
- Increased plasma triglyceride concentrations
- Decreased high-density lipoprotein cholesterol concentrations
- Elevated blood pressure

risk profile. Consequently, it could be postulated that the association between obesity and CHD is a function of the fact that being obese increases the likelihood of being insulin resistant and displaying the cluster of abnormalities related to insulin resistance/compensatory hyperinsulinemia. In support of this general view are results of 2 population-based outcome studies showing that obesity, per se, does not appear to be an independent predictor of CHD. In support of this general view are results of 2 population-based outcome studies showing that obesity, per se, does not appear to be an independent predictor of CHD.18,19 Thus, Ninomiya et al18 analyzed data from the Third National Health and Nutrition Examination Survey and concluded that obesity, estimated from waist circumference, was not an independent predictor of myocardial infarction, whereas syndrome X components, insulin resistance, hypertension, low HDL-C, and hypertriglyceridemia were independently and significantly related. The Emerging Risk Factors Collaboration examined records from prospective studies of 221,934 individuals from 17 countries19 and concluded that BMI, waist circumference, and waist-to-hip ratio, whether assessed singly or in combination, do not importantly improve cardiovascular disease risk prediction in developed countries when additional information is available for systolic blood pressure, history of diabetes mellitus, and lipids. Both these large studies provide compelling evidence that the importance of obesity as a risk factor for CHD is related to its adverse impact on insulin resistance and associated CHD risk factors.

Insulin Resistance and CHD

Several large population–based studies have shown that hyperinsulinemia, a surrogate marker for insulin resistance, predicts incident CHD.20–22 Although these data support the view that insulin resistance/compensatory hyperinsulinemia is a risk factor for CHD in apparently healthy individuals, there is no accepted view of the magnitude of insulin resistance/hyperinsulinemia that provides an estimate of the proportion of apparently healthy individuals who are sufficiently insulin resistant/hyperinsulinemic to be at the greatest risk of CHD. Because SSPG concentrations during an insulin suppression test (described earlier) range >6-fold in a group of apparently healthy individuals,23 it is essential to know what proportion of these individuals are at significantly increased risk of CHD.

We have approached this dilemma by obtaining follow-up clinical information from apparently healthy subjects in whom estimates of insulin action were made at baseline.24–26 Figure 2A presents the incidence of CHD in ≈600 apparently healthy individuals, divided at baseline into quartiles of insulin resistance based on their plasma insulin response to oral glucose.24 These individuals were followed for ≈13 years, and the results suggest that ≈25% of an apparently healthy population is sufficiently insulin resistant to be at significantly increased risk of CHD. Figure 2B displays results of a somewhat similar study, although in this case insulin-mediated glucose disposal was quantified by baseline determinations of SSPG concentrations during the insulin suppression test.25 This apparently healthy population was nonobese, had a mean age of 50 years, and was followed for an average of ≈5 years. They were divided into tertiles on the basis of their degree of insulin sensitivity at baseline; Tertile I being the most insulin sensitive and Tertile III the most resistant. It is obvious that adverse outcomes occurred almost entirely in the most insulin-resistant third, with essentially no events in the most insulin-sensitive third. A subsequent study26 yielded essentially similar results. Thus, it appears that somewhere between one-fourth and one-third

Figure 2. A. The percent of apparently healthy individuals who develop coronary heart disease (CHD) over time as a function of baseline degree of insulin resistance as estimated by the magnitude of their plasma insulin response to an oral glucose challenge. CHD developed to a greater degree in subjects in Quartile IV when compared with those in Quartile I (P=0.03), Quartile II (P=0.04), or Quartile III (P=0.07). Subjects in Quartile I were the most insulin sensitive, and those in Quartile IV the most insulin resistant. B. The per-cent of apparently healthy individuals who developed CHD over time as a function of baseline degree of insulin resistance as quantified by the insulin suppression test. CHD developed to a greater degree in subjects in Quartile III when compared with those in Quartile I (P=0.01) or Quartile II (P=0.06). Subjects in Tertile I were the most insulin sensitive, and those in Tertile III the most insulin resistant.
of an apparently healthy population are sufficiently insulin resistant to be at increased risk of adverse cardiac events.

**Potential Links Between Insulin Resistance/ Hyperinsulinemia and CHD**

Perhaps the most insightful way to address this issue would be the iconic quote from the movie *Casablanca*—"round up the usual suspects." There are multiple abnormalities associated with insulin resistance/compensatory hyperinsulinemia that likely contribute to the increased prevalence of CHD, but it is easier to list them as in Table 2 than to assess the magnitude of their adverse impact.5-8,11,27,28 Because it is impossible within the space constraints of this review to address all potential links between insulin resistance/compensatory hyperinsulinemia and CHD, focus will be on the relationship among insulin resistance/compensatory hyperinsulinemia, dyslipidemia, and CHD.

The decision to focus on this link is not entirely arbitrary, given ample evidence that insulin-resistant/hyperinsulinemic subjects have a highly atherogenic lipoprotein profile, and given ample evidence that insulin-resistant/hyperinsulinemic patients eating the 60% carbohydrate diet result in an increase in hypertriglyceridemia, per se, as an independent risk factor for CHD; and (2) the causal relationships among insulin resistance, hyperinsulinemia, hepatic VLDL-TG secretion, and fasting TG concentrations; the issue to be addressed in this section. One view is that resistance to insulin regulation of muscle and adipose tissue leads to higher plasma insulin and FFA concentrations, and this combination stimulates hepatic VLDL-TG secretion, leading to the increase in plasma TG concentration.28-32 Alternatively, it has been argued that hypertriglyceridemia occurs in insulin-resistant, nonobese individuals because of a defect in the ability of insulin to inhibit hepatic VLDL-TG secretion (ie, the liver is insulin resistant with regard to lipoprotein metabolism).33 Evidence in support of this view is derived primarily from acute experiments.34 For example, the acute infusion of insulin has also been shown to suppress hepatic VLDL-TG secretion in humans, in association with a substantial decrease in plasma FFA concentration. An obvious explanation for the ability of an acute insulin infusion to decrease VLDL-TG secretion is the profound decrease in adipose tissue lipolysis secondary to even modest increases in plasma insulin concentrations.12-14,27-32 Another metabolic milieu in which a decrease in VLDL-TG is not surprising. Furthermore, Aarsland et al33 measured VLDL-TG secretion rates 1 and 4 days after subjects began a high-carbohydrate, hypercaloric diet, an intervention resulting in a 6-fold elevation of plasma insulin concentration that persisted throughout the study. VLDL-TG secretion rate was, if anything, lower after 1 day of hyperinsulinemia without any change in plasma TG secretion. By day 4, however, there were significant increases in both hepatic VLDL-TG secretion and plasma TG concentrations. These data demonstrate that the acute effects of exogenous hyperinsulinemia do not necessarily reflect the chronic effects of endogenous hyperinsulinemia.

The changes in TG and insulin concentrations after ingestion of high-carbohydrate diets provide another way to examine this controversy. If anything, such diets are associated with enhanced insulin sensitivity.35 Furthermore, when nondiabetic subjects consumed a 60% carbohydrate diet, they had much higher fasting and daylong insulin and TG concentrations when compared to those following a 40% carbohydrate diet.36 The fact that increases in elevated circulating insulin concentrations in subjects eating the 60% carbohydrate diet resulted in an increase in plasma TG concentration is not compatible with the notion that hypertriglyceridemia is a consequence of insulin resistance. The fact that hypertriglyceridemia in the face of chronic endogenous hyperinsulinemia is attributable to a defect in the ability of insulin to suppress hepatic TG secretion.

Perhaps the most compelling evidence that hypertriglyceridemia is not the consequence of an inability of insulin to overcome hepatic insulin resistance is the effect of insulin deficiency on FFA and TG metabolism. If a physiologic role of insulin is to inhibit VLDL-TG secretion, the combination of low levels of insulin and extremely high plasma FFA concentrations should lead to a massive increase in hepatic VLDL-TG secretion. In fact, just the opposite is seen—a decrease in hepatic VLDL-TG secretion.32

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**Fasting Plasma Triglyceride Concentration**

An association among insulin resistance, compensatory hyperinsulinemia, and elevated fasting plasma triglyceride (TG) concentrations was first demonstrated in 1967,29 and the following quantitative relationships were published in 1974:30 insulin resistance → ↑ insulin response to oral glucose (r=0.74) → ↑ hepatic very-low-density lipoprotein (VLDL)-TG secretion (r=0.74) → ↑ fasting plasma TG concentration (r=0.88). These studies were carried out over a wide range of plasma TG concentrations (≈7-fold), but essentially similar findings were seen in individuals whose TG concentrations ranged from 37 to 174 mg/dL.31

In addition to being the first component of the atherogenic lipoprotein profile now known to characterize insulin-resistant/hyperinsulinemic individuals, fasting hypertriglyceridemia also contributes to the development of the other members of the quartet. Because controversy exists as to why insulin-resistant/hyperinsulinemic individuals develop hypertriglyceridemia, this particular issue will be discussed in some detail.

Although there is agreement with the relationships shown above, controversy exists regarding the following: (1) the role of fasting hypertriglyceridemia, per se, as an independent risk factor for CHD; and (2) the causal relationships among insulin resistance, hyperinsulinemia, hepatic VLDL-TG secretion, and fasting TG concentrations; the issue to be addressed in this section. One view is that resistance to insulin regulation of muscle and adipose tissue leads to higher plasma insulin and FFA concentrations, and this combination stimulates hepatic VLDL-TG secretion, leading to the increase in plasma TG concentration.28-32 Alternatively, it has been argued that hypertriglyceridemia occurs in insulin-resistant, nonobese individuals because of a defect in the ability of insulin to inhibit hepatic VLDL-TG secretion (ie, the liver is insulin resistant with regard to lipoprotein metabolism).33 Evidence in support of this view is derived primarily from acute experiments.34 For example, the acute infusion of insulin has also been shown to suppress hepatic VLDL-TG secretion in humans, in association with a substantial decrease in plasma FFA concentration. An obvious explanation for the ability of an acute insulin infusion to decrease VLDL-TG secretion is the profound decrease in adipose tissue lipolysis secondary to even modest increases in plasma insulin concentrations.12-14,27-32 Another metabolic milieu in which a decrease in VLDL-TG is not surprising. Furthermore, Aarsland et al33 measured VLDL-TG secretion rates 1 and 4 days after subjects began a high-carbohydrate, hypercaloric diet, an intervention resulting in a 6-fold elevation of plasma insulin concentration that persisted throughout the study. VLDL-TG secretion rate was, if anything, lower after 1 day of hyperinsulinemia without any change in plasma TG secretion. By day 4, however, there were significant increases in both hepatic VLDL-TG secretion and plasma TG concentrations. These data demonstrate that the acute effects of exogenous hyperinsulinemia do not necessarily reflect the chronic effects of endogenous hyperinsulinemia.

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**Table 2. Abnormalities Associated With Insulin Resistance/ Hyperinsulinemia That May Contribute to Coronary Heart Disease Risk**

<table>
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<th>Abnormality</th>
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<tr>
<td>Dysglycemia</td>
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<td>Dyslipidemia</td>
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<td>Elevated blood pressure</td>
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<tr>
<td>Procoagulant state</td>
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<tr>
<td>Inflammation</td>
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<tr>
<td>Endothelial dysfunction</td>
</tr>
<tr>
<td>Hyperuricemia</td>
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<tr>
<td>Enhanced sympathetic nervous system activity</td>
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<tr>
<td>Increased renal tubular sodium reabsorption</td>
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Postprandial Lipemia
Although there is evidence that fasting TG concentrations are an independent predictor of CHD, it now appears that nonfasting TG concentrations, particularly TG-rich remnant lipoproteins, are more likely to be the responsible particle. On the other hand, the 2 aspects of VLDL metabolism are related in nondiabetic individuals, and the higher the fasting TG concentration, the greater the postprandial accumulation of TG-rich lipoproteins (VLDL, VLDL remnants, chylomicrons, and chylomicron remnants). In addition to the relationship between fasting TG concentration and postprandial lipemia, the daylong increase in TG-rich remnant lipoproteins is significantly correlated with the magnitude of their insulin resistance/compensatory hyperinsulinemia. Furthermore, postprandial lipemia is enhanced when insulin-resistant/hyperinsulinemic individuals are matched for degree of fasting hypertriglyceridemia with insulin-sensitive persons. Thus, although questions may continue as to whether fasting or postprandial TG concentrations are most closely linked to CHD, it appears that both these measures of VLDL metabolism are closely associated with insulin resistance/compensatory hyperinsulinemia.

LDL Particle Diameter
Analysis of LDL particle size distribution has identified multiple distinct LDL subclasses. This has led to the characterization of individuals as having a predominance of either larger LDL particles (diameter >255 Å, pattern A) or smaller LDL particles (<255 Å, pattern B) particles, and persons with pattern B are at increased risk of CVD. The presence of the pattern B LDL-particle phenotype is closely linked to the fasting plasma TG concentration, and the prevalence of small, dense LDL particles increases substantially as fasting plasma TG levels rise above 150 mg/dL. Because fasting hypertriglyceridemia is secondary to the ability of hyperinsulinemia to stimulate hepatic TG synthesis and secretion, it should not be surprising that healthy volunteers with a predominance of small, dense LDL particles (pattern B) are relatively insulin resistant, hyperinsulinemic, hypertriglyceridemic, and have lower HDL-C concentrations.

High-Density Lipoprotein Cholesterol
A low-plasma HDL-C concentration is a well-established risk factor for CHD, often associated with hypertriglyceridemia. Despite the common occurrence of the combination of a high TG and a low HDL-C concentration, both changes seem to be independently related to insulin resistance/hyperinsulinemia. A low HDL-C concentration is the third member of the atherogenic lipoprotein phenotype associated with insulin resistance/hyperinsulinemia that is at least partly secondary to the increased VLDL-TG pool size. Specifically, the larger the VLDL pool, the greater the transfer, catalyzed by cholesteryl ester transfer protein, of cholesterol from HDL to VLDL in exchange for TG, resulting in lower HDL-C and higher HDL-TG concentrations. Thus, the greater the increase in hepatic VLDL-TG synthesis and secretion that characterizes insulin-resistant/hyperinsulinemic individuals, the lower will be the HDL-C concentration. In addition, hyperinsulinemia in insulin-resistant, nondiabetic individuals is associated with increases in the fractional catabolic rate of apoprotein A-1, and the higher the apoA-1, the lower the HDL-C concentration. Irrespective of which mechanism is most responsible, there is clearly evidence that a low HDL-C is a characteristic of insulin-resistant/hyperinsulinemic individuals.

Concluding Comments
The role that differences in insulin sensitivity play in human disease has grown enormously in the 75 years since Himsworth first demonstrated its crucial importance in the pathogenesis of 2DM. This presentation has briefly summarized some salient issues of the relationship among insulin resistance, dyslipidemia, and CHD. Although outside the purview of this presentation, what must not be overlooked is the increasing number of clinical syndromes, in addition to 2DM and CHD, now known to be linked to insulin resistance. The list continues to grow, and some of the more important examples are briefly discussed in the online-only Data Supplement.

Disclosures
None.

References


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Supplemental Material

I. Exclusion of patients with type 2 diabetes (2DM)

Patients with 2DM were excluded from this review for several reasons. At the simplest level, plasma glucose concentrations are normal, or only +/- abnormal [1, 2] in insulin resistant, nondiabetic individuals, as contrasted to the frank hyperglycemia that characterizes patients with 2DM. Given the uncertain state of hyperglycemia as a risk factor for CHD, exclusion of patients with 2DM diminishes substantially the possibility of it playing a major role in CHD in these individuals. Secondly, essentially all patients with 2DM are insulin resistant, with relatively little differences in degree between them [1, 3]. Thirdly, excluding patients with 2DM avoids the confounding effect of “glucotoxicity” as a modulator of insulin sensitivity [4]. That having been said, there is considerable similarity in CHD risk factors in insulin resistant, nondiabetic individuals and patients with 2DM, but discerning the role of insulin resistance/compensatory hyperinsulinemia, per se, in this risk is confounded in patients with 2DM.

II. Relationship between insulin resistance/compensatory hyperinsulinemia and associated abnormalities (other than dyslipidemia) contributing to CHD risk.

A. Dysglycemia: The magnitude of the relationship between insulin resistance and fasting plasma glucose concentration is quite modest, ranging from r-values of 0.2 -0.4, varying with degree of adiposity [5]. In addition, a significant proportion of insulin resistant, nondiabetic individuals have normal glucose tolerance [1, 2]. Furthermore, daylong plasma glucose concentrations in response to meals are only marginally elevated (at best) in patients with prediabetes [6, 7]. Indeed, increments in plasma glucose concentrations following test mixed-meals are not different in subjects with
prediabetes as compared to those of individuals with normal glucose tolerance when measured daylong [7]. None of these considerations rules out the possibility that dysglycemia is a major link between insulin resistance and CHD, but seem to question that notion.

B. Elevated Blood Pressure: As emphasized in Section III, tissue insulin sensitivity can vary widely in a given individual. Of particular relevance to blood pressure is the coexistence of normal insulin sensitivity in the sympathetic nervous system and kidney in the face of significant muscle insulin resistance and compensatory hyperinsulinemia [8-11]. The inevitable consequence of the hyperinsulinemia is enhanced renal sodium retention accompanied by increased sympathetic nervous system activity, making it more difficult to maintain normal blood pressure regulation.

C. Procoagulant State: Elevation of plasma concentrations of plasminogen activator inhibitor-1 (PAI-1) provides a good example of the link between insulin resistance/compensatory hyperinsulinemia, a procoagulant state, and CHD. Thus, population-based studies [12, 13] have indicated that elevations of plasma insulin concentration, as a surrogate estimate of insulin resistance, are associated with increases in plasma concentrations of both PAI-1 and fibrinogen, although the relationship is stronger with PAI-1. In addition, there is evidence clearly documenting the fact that plasma PAI-1 concentrations are higher in insulin resistant individuals, associated with the compensatory hyperinsulinemia and dyslipidemia characteristic of these subjects [14].

D. Inflammation: There is substantial evidence of an association between insulin resistance and inflammation. For example, obese, insulin resistant women had higher concentrations of C-reactive protein (CRP) than equally obese women who were insulin
sensitive, and both insulin sensitivity and CRP concentration declined when the obese
insulin resistant women lost weight [15]. On the other hand, insulin resistance and
inflammation do not necessarily always coexist. Thus, insulin resistance was present in
young, lean offspring of patients with 2DM as compared to insulin sensitive offspring,
whereas the two groups did not differ in plasma concentration of resistin, TNF-
alha, interleukin-6, or adiponectin [16]. Similarly, insulin resistance and associated
dyslipidemic changes was demonstrated in young, lean, apparently healthy individuals,
despite “no differences in plasma TNF-alpha, IL-6, adiponectin, resistin, retinol protein,
or intraabdominal fat volume” as compared to the insulin sensitive control group [16].
There is also evidence that there are no differences in plasma concentrations of TNF-
alha, TNF-alpha receptor 2, as well as TNF-alpha polymorphisms in apparently
healthy individuals classified as being either insulin resistant or insulin sensitive [17].
Consequently, it seems apparent that insulin resistance can exist in the absence of
evidence of enhanced inflammation. Perhaps, as suggested by Savage, et al [18]
inflammatory changes are unlikely to be the primary abnormality in the development of
insulin resistance, but “inflammatory cell recruitment and changes in cytokine production
may be secondarily involved in maintaining /exacerbating the insulin resistant state
associated with obesity.”

Finally, it should be remembered that atherogenesis is an inflammatory process, and
it could be argued that the increase in inflammatory markers described in insulin
resistant states and CHD could represent a secondary role for inflammation, i.e., insulin
resistance/compensatory hyperinsulinemia lead to a variety of adverse changes that
increase atherogenesis, and the increased evidence of inflammation is a consequence of the vascular changes.

**E. Endothelial Dysfunction:** There is evidence on several levels of an association between insulin resistance and endothelial dysfunction. At the simplest, impaired flow-mediated vasodilatation has been described in a number of clinical syndromes related to insulin resistance and CHD[19, 20], and insulin resistance/hyperinsulinemia have been shown to be independently related to a similar defect in apparently healthy individuals [21]. In addition, evidence has been published [22] showing that the more insulin resistant an individual, the greater is their plasma concentration of asymmetric dimethylarginine (ADMA)--an endogenous inhibitor of nitric oxide synthase. Consequently, higher circulating ADMA concentrations would be anticipated to decrease plasma nitric oxide (NO) concentrations, and there is evidence that this is the case in apparently healthy, individuals in whom hyperinsulinemia is used as a surrogate estimate of insulin resistance [23]. Furthermore, it has been shown that increased circulating ADMA concentrations are independently associated with decreased flow-mediated vasodilatation in individuals at otherwise low global CVD risk, as well as with elevated plasma insulin concentrations [24]. Finally, there is also evidence that soluble adhesion molecules, produced by endothelium, are significantly related to insulin resistance in apparently healthy individuals [25]. Specifically, degree of insulin resistance was significantly correlated with concentrations of sE-selectin, sICAM-1, and sVCAM-1. Furthermore, mononuclear cell binding correlated significantly with concentrations of sE-selectin and sICAM-1. Based on these considerations, there seems to be little doubt that insulin resistance and various measures of endothelial...
dysfunction are significantly associated, and can contribute to risk of CHD. What is not established is to what degree the endothelial dysfunction is secondary to insulin resistance, or the cause of it.

**F. Hyperuricemia:** An increase in the prevalence of elevated uric acid concentrations in insulin resistant individuals is a consequence of the ability of the kidney to retain normal insulin sensitivity in the presence of muscle insulin resistance [8, 9]. In this instance, the compensatory hyperinsulinemia, secondary to the insulin resistance, acts on the kidney to decrease uric acid clearance, resulting in an increase in plasma uric acid concentration. The more insulin resistant/hyperinsulinemic an individual is, the greater their decrease in uric acid clearance, and the higher their plasma uric acid concentration. It should also be noted that apparently healthy individuals with elevated uric acid concentrations are also at increased likelihood to be glucose intolerant, hyperinsulinemic, with increased blood pressure, and a high plasma triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C) concentration [26]. The fact that high uric acid concentrations are associated with increased CVD risk does not tell us whether hyperuricemia is a bystander, a reflection of the effect of insulin resistance/compensatory hyperinsulinemia on the kidney, or has an independent impact on CVD; a question that continues to be controversial [27].

**G. Enhanced Sympathetic Nervous System Activity:** As indicated above, the sympathetic nervous system is another example of tissues/organs that retain normal insulin sensitivity in the face of muscle insulin resistance [10, 11]. Thus, the philanthropic increase in insulin secretion associated with insulin resistance leads to enhanced sympathetic nervous activity. As is often true when considering the
relationship between insulin resistance/compensatory hyperinsulinemia, associated abnormality, and CHD risk, the usual “chicken and egg” dilemma appears. Thus, it is possible to outline a proposal, in which insulin resistance is the primary defect, the associated abnormalities, including in this instance, enhanced sympathetic nervous system activity, as being secondary consequences, and all of them contributing to the increased risk of CHD [11]. Alternatively, an argument has been made that the primary abnormality is increased sympathetic nervous system activity, with insulin resistance, hyperinsulinemia, glucose intolerance, dyslipidemia, and high blood pressure being secondary consequences, with the same factors serving to increase CHD risk [28].

H. Increased Renal Tubular Sodium Reabsorption: Perhaps the clearest indication that the kidney retains normal insulin sensitivity despite muscle insulin resistance is the changes in weight and sodium excretion when apparently healthy individuals are exposed to diets varying dramatically in sodium content [29]. Thus, increasing a low sodium diet 8-fold led to varying degree of weight gain and increases in urinary sodium excretion. Neither insulin action nor insulin concentrations varied in response to the two diets. Baseline insulin resistance and insulin concentration were directly related to weight gain, and inversely related to urinary sodium excretion. Concentrations of plasma renin activity and aldosterone decreased and plasma atrial natriuretic peptide increased in response to the high sodium diet, but these changes did not correlate with either weights gain or sodium excretion. Insulin resistance was also an independent predictor of the increase in blood pressure in response to the high sodium diet. These data are consistent with the notion that compensatory hyperinsulinemia in insulin
resistant subjects acts on a normally insulin sensitive kidney to increase salt and weather retention to a high sodium diet.

III. Additional clinical syndromes associated with insulin resistance /compensatory hyperinsulinemia.

The notion that insulin resistance/compensatory hyperinsulinemia play important roles in the pathogenesis of 2DM and CHD is well-appreciated, and this awareness tends to detract from consideration of the other clinical syndromes closely associated with insulin resistance/hyperinsulinemia. An example of this has been a major focus [30] on the “best” diagnostic criteria to identify individuals with an entity called the “metabolic syndrome,” the components of which are all associated with insulin resistance [1-3]. In this section a few comments will be addressed to these additional serious clinical syndromes associated with insulin resistance/hyperinsulinemia (Table 1) in the Supplemental Files:

A. Essential hypertension: Approximately 50% of patients with essential hypertension can be classified as being insulin resistant [31], and insulin resistance can be discerned in non-hypertensive first degree relatives of patients with hypertension [32, 33]. Furthermore, hyperinsulinemia, as a surrogate marker for insulin resistance, predicts the development of essential hypertension [34-36]. Finally, both risk factors for CHD, as well as the actual development of CHD, appear to be greatly enhanced in the sub-set of patients with essential hypertension who are also insulin resistant/hyperinsulinemic [31, 37, 38].

B. Idiopathic dilated cardiomyopathy/heart failure: A recent review has summarized the extensive evidence of an association between 2DM and heart failure, but also pointed
out that the association between heart failure and insulin resistance in nondiabetic individuals is not widely appreciated [39]. Consistent with this view are data showing that the plasma glucose and insulin responses to oral glucose were significantly elevated in the approximately 20% of subjects in a university heart failure center who had idiopathic dilated cardiomyopathy (IDCM), in the absence of diabetes and other comorbid conditions[40]. Finally, and most compelling, is the report by Ingelsson and colleagues[ 41] showing that baseline direct measures of insulin sensitivity with the “clamp” technique in 1187 individuals was an independent predictor of developing heart failure, independent of other risk factors, including diabetes. Furthermore, they concluded that the previously described association between obesity and heart failure “may be mediated largely by insulin resistance. “

**C. Polycystic ovary syndrome (PCOS):** Although an association between insulin resistance and elevated plasma concentrations of testosterone in women with PCOS has been known for some time [42], PCOS does not seem to be a simple function of insulin resistance. At the simplest level, not all insulin resistant/hyperinsulinemic women develop PCOS, nor are all women with PCOS insulin resistant and hyperinsulinemic [43]. Indeed, there is significant interaction between insulin resistance/hyperinsulinemia and the diagnosis of PCOS [43]. Specifically, it has been shown in a study of equally overweight women, with a history of PCOS or normal ovulation, that the highest plasma testosterone concentrations are seen in women with PCOS, who are also insulin resistant. However, although plasma testosterone concentrations are lower in women with PCOS, who are insulin sensitive, their values are still higher as compared to insulin resistant women, with a history of normal ovulation. This demonstration of significant
interaction between the presence of PCOS and insulin resistance is consistent with the notion of ovarian hypersensitivity to insulin stimulation of testosterone production in women with PCOS as proposed by Baillargeon and Nestler [44].

**D. Nonalcoholic Fatty Liver Disease (NAFLD):** There is ample evidence that patients with NAFLD are insulin resistant and hyperinsulinemic, and the presence of increased hepatic fat content in insulin resistant/hyperinsulinemic patients who are neither alcoholic nor have any viral infection is well-recognized.[45, 46]. Furthermore, these changes have been shown to be independent of obesity. It has also been pointed out that NAFLD is commonly seen in subjects diagnosed as having the metabolic syndrome [47, 48]; i.e. the abnormalities in glucose, lipoprotein metabolism, and blood pressure associated with insulin resistance. However, it has also been pointed out in a group of apparently healthy individuals, without known disease, and normal liver function tests, that hyperinsulinemia, as a surrogate estimate of insulin resistance, predicted both hepatic fat content and concentration of alanine transaminase [49]. Furthermore, the relationship between insulin concentration and hepatic fat content was independent of differences in degree of obesity, blood pressure, and plasma glucose, TG, and HDL-C concentrations [49].

Although it seems quite clear that there is a relationship between insulin resistance/hyperinsulinemia, associated CHD risk factors, and NAFLD, the manner in which they are related continues to be debated. For example, both fatty liver and increased CHD risk could represent epiphenomena of the insulin resistance/hyperinsulinemia. Thus, since insulin resistance/compensatory hyperinsulinemia appear to stimulate hepatic TG synthesis and secretion (see Section VI in the review
article), it could be argued that the development of fatty liver would be the expected consequence. Furthermore, the other abnormalities associated with insulin resistance listed in Table 2 of the review would also contribute to risk of CHD. On the other hand, it has been argued [50] that NAFLD “may be actively involved in the pathogenesis of CHD by increasing the “release of pro-atherogenic facts from the liver, including fibrinogen, PAI-1 and other inflammatory cytokines.” In contrast, others have suggested [51] that the presence of NAFLD does not add anything unique to the risk of developing CHD beyond that associated with well-recognized and conventional risk factors. Which of these various points of view are most “correct” remains to be seen

**E. Certain forms of cancer:** Perhaps studies of breast cancer provide the most compelling evidence of a link between insulin resistance/hyperinsulinemia and neoplastic disease. Reports have been published of higher plasma C-peptide and/or insulin concentrations in both pre- and postmenopausal women with breast cancer, as well as evidence that fasting insulin concentration predicts outcome in women with early breast cancer [52-54]. Indirect support for a relationship between insulin resistance/hyperinsulinemia and breast cancer can be found in reports of increased prevalence of breast cancer in association with hypertriglyceridemia, obesity and type 2 DM [55-57]. In this context, the recent report that non-fasting TG concentrations were associated with increased risk of cancer provides further support for a relationship between insulin resistance/hyperinsulinemia and cancer [58, 59]. Reports have also been published suggesting a relationship between insulin resistance/hyperinsulinemia and both colorectal and prostate cancer. As with breast cancer, the evidence consists of reports that both cancers are more likely to occur in individuals who are overweight
and/or have type 2DM, as well as the presence of higher plasma insulin concentrations in patients with colorectal or prostate cancer [60-68].

**F. Sleep Disordered Breathing:** It has been known for many years that subjects with obstructive sleep apnea (OSA) tend to be overweight/obese. Overweight/obese individuals also tend to be insulin resistant [69], and the prevalence of OSA is increased in clinical syndromes [70-72], such as CHD and 2DM, in which both overweight/obesity and insulin resistance are common. What remains unclear is the relationship between obesity-associated insulin resistance, OSA, 2DM, and CVD. It is generally assumed to be as follows: obesity→sleep disordered breathing/OSA→insulin resistance/2DM→CHD. Defects in both insulin action and insulin secretion have been described in patients with OSA [73]; metabolic abnormalities that increase the likelihood of developing 2DM and CVD [74]. The view that sleep disordered breathing leads to the down-stream metabolic abnormalities and clinical syndromes is supported by experimental evidence that insufficient sleep and poor sleep quality can decrease insulin sensitivity [75]. On the other hand, there is evidence that insulin resistance and/or hyperinsulinemia can predict the development of OSA [76], similar to the results of previous studies of the link between insulin resistance/hyperinsulinemia and 2DM and CHD [74, 77-80].

Evidence of the association between sleep disordered breathing, OSA, 2DM, and CHD risk (metabolic syndrome) has been summarized in three excellent review articles [81-84], providing extensive proof of the clustering of these syndromes. These reviews also identify limitations of current understanding as to the significance of this clustering, and again serve to emphasize that understanding of the causal relationships among these variables, as with the other syndromes discussed in his section, is lacking. As
emphasized by Levy, et al [84], “Interventional studies are clearly needed to address the question of causality.” Until such time, the associations described in this and the other clinical syndromes listed in Table 1 of the Supplemental File will remain associations.
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Supplemental Table I

Clinical Syndromes beyond Type 2 Diabetes and Coronary Heart Disease
Associated with Insulin Resistance

- Essential Hypertension
- Idiopathic Dilated Cardiomyopathy/Heart Failure
- Polycystic Ovary Syndrome
- Nonalcoholic Fatty Liver Disease
- Certain Forms of Cancer
- Sleep Disordered Breathing