The notion that insulin resistance is associated with a cluster of abnormalities that increase risk of coronary heart disease (CHD) was introduced in 1988, and this view continues to gain traction. The study by Robins et al provides additional support for the link between insulin resistance and CHD, but it also emphasizes that a good deal remains to be learned about this relationship. For example, because high triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C) concentrations are associated with insulin resistance, we evaluated the plasma TG/HDL-C concentration ratios in nonobese individuals before they have obvious disease. Robins et al used the homeostasis model assessment of insulin resistance (HOMA-IR) for this purpose, a surrogate estimate of insulin action based on measurements of fasting plasma glucose and insulin (FPI) concentrations. The correlation \( r \) value between HOMA-IR and a direct measure of insulin action in a nonobese population is not robust, ranging from 0.33 in normal-weight people to 0.60 in obese individuals. However, direct measurements of insulin action are rarely performed in studies of large populations, and HOMA-IR is often the estimate of choice in such studies. Parenthetically, because FPI concentrations vary little as hyperglycemia supervenes in patients with type 2 diabetes, the use of HOMA-IR in these individuals becomes little more than a marker of degree of hyperglycemia. Consequently, the utility of HOMA-IR as an estimate of insulin action is most reliable when used in nondiabetic individuals, whether or not their TG concentrations were higher or their HDL-C concentrations lower than the median value in the population studied.

Given the apparent importance of insulin resistance as a CHD risk factor, as well as the emerging role it seems to play in the pathogenesis of a number of clinical syndromes, it would seem useful to identify insulin-resistant individuals before they have obvious disease. Robins et al used the homeostasis model assessment of insulin resistance (HOMA-IR) for this purpose, a surrogate estimate of insulin action based on measurements of fasting plasma glucose and insulin (FPI) concentrations. The correlation \( r \) value between HOMA-IR and a direct measure of insulin action in a nonobese population is not robust, ranging from 0.33 in normal-weight people to 0.60 in obese individuals. However, direct measurements of insulin action are rarely performed in studies of large populations, and HOMA-IR is often the estimate of choice in such studies. Parenthetically, because FPI concentrations vary little as hyperglycemia supervenes in patients with type 2 diabetes, the use of HOMA-IR in these individuals becomes little more than a marker of degree of hyperglycemia. Consequently, the utility of HOMA-IR as an estimate of insulin action is most reliable when used in nondiabetic individuals. Thus, the decision of Robins et al to exclude patients with diabetes significantly enhances the validity of their conclusions. It should be noted that under these conditions, FPI concentration and HOMA-IR are closely related to a direct measure of insulin action, consistent with a correlation between HOMA-IR and FPI of 0.98 in the study of Robins et al.

The relative insensitivity of HOMA-IR as an estimate of insulin resistance is compounded by the lack of a standardized insulin assay. Robins et al classified individuals as insulin resistant if they were in the upper quartile of HOMA-IR values. Unfortunately, the HOMA-IR value used by Robins et al to define insulin resistance cannot be translated to any other situation unless the FPI concentrations are analyzed in the same laboratory. Put most simply, HOMA-IR, using semiarbitrary cut-points in epidemiological studies, may provide insights as to the role of insulin resistance in disease. However, unless a health-care provider is measuring FPI concentrations in the same laboratory, the actual values of HOMA-IR used to classify individuals as insulin resistant in a given study cannot be applied to an individual patient.

Faced with this dilemma, we have approached it by seeing whether metabolic variables closely related to insulin action, and for which standardized laboratory measurements are available, might be useful in identifying individuals who are insulin resistant. Because high TG and low HDL-C concentrations are both significantly associated with insulin resistance, we evaluated the plasma TG/HDL-C concentration ratio (mg/dL) as a way to identify apparently healthy individuals who are insulin resistant. With this approach, we showed that a ratio \( \geq 3.5 \) was able to identify individuals defined as being insulin resistant on the basis of a specific measure of insulin-mediated glucose disposal with a sensitivity and specificity comparable to that using the Adult Treatment Panel III criteria for metabolic syndrome.

On the other hand, the use of the TG/HDL-C concentration ratio to identify apparently healthy individuals who are insulin resistant is not ideal. The major virtue of using this approach is that the crucial variables are determined with reasonably standardized methods throughout the United States, and a TG/HDL-C ratio that seems to be effective in a given racial group can be applied to a comparable group nationwide. However, it would help to have a method that had greater sensitivity and specificity. Furthermore, somewhat different TG/HDL-C ratios must be used in different racial groups to be maximally effective, and it has been argued that it does not do as well as does HOMA-IR in identifying individuals who develop CHD. On the other hand, 17% of those classified as insulin resistant in the latter study had diabetes, a well-recognized CHD risk factor. Thus, it is not obvious that the putative “superiority” of HOMA-IR...
to identify CHD would be seen in a population of apparently healthy individuals. Regardless, it is obvious from the study by Robins et al that the association between TG and HDL-C concentration and insulin action as assessed by HOMA-IR is present but far from perfect. For example, relatively few people (≤10%) in the highest HDL-C or lowest TG quartiles were insulin resistant; insulin resistance is unlikely in the absence of dyslipidemia. On the other hand, although the prevalence of insulin resistance was highest in the quartile with the highest TG and lowest HDL-C concentrations, it seemed to be present in only 40% to 50% of these individuals. These findings emphasize the need to do better than using lipid concentrations in efforts to identify insulin resistant individuals.

The report by Robins et al provides further support for the link between insulin resistance and CHD, as well as the potential clinical benefits of identifying apparently healthy individuals as being insulin resistant before they develop manifest disease. Unfortunately, the gap between the benefits that could be gained and our ability to accomplish this task continues to widen. A standardized insulin assay would significantly narrow that distance; its availability is long overdue.

References


 Keywords: coronary heart disease, insulin resistance, triglycerides, high-density lipoprotein cholesterol
Wanted!: A Standardized Measurement of Plasma Insulin Concentration
Gerald Reaven

Arterioscler Thromb Vasc Biol. 2011;31:954-955
doi: 10.1161/ATVBAHA.111.224790
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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