Surrogate measures of insulin resistance: of rats, mice, and men

Kieren Mather

Indiana University School of Medicine, Indianapolis, Indiana

To the Editor: In studies of human metabolic physiology a number of surrogate measures of insulin resistance have been proposed, and their relationships to formal measures of whole body insulin sensitivity made by classical insulin-glucose clamp measures have been assessed (2, 8, 11, 13, 20, 22, 23, 30, 32). The most prominent of these at present are the homeostasis model index of insulin resistance [HOMA-IR; \( \text{insulin (in mU/l)} \times \text{glucose (in mmol/l)} / 22.5 \)], and the quantitative insulin check index of insulin sensitivity [QUICKI; \( 1 / (\log(\text{insulin}) + \log(\text{glucose})) \)] (7, 23, 25, 34). These two indexes were independently derived using empirical methods and are mathematically strongly related to each other (27). One notable difference is that the HOMA-IR index incorporates a normalizing factor that is specific to its application in human subjects, having been derived and validated in humans. Other indexes in common use include fasting insulin concentrations (usually analyzed as 1/insulin), and the Matsuda and Stumvoll indexes (22, 30). The addition of dynamic (i.e., OGTT-derived) components can add information about ß-cell responsiveness to the measures of fasting and post-load insulin responses, but with less specificity than would be available from mathematical modeling to separate these components (as is done in modeling the dynamic response to a glucose load in the Bergman minimal model, for example). Ultimately, the simplest and least confounded indexes remain the HOMA and QUICKI models. The strength of these measures as surrogates relies on the strength of the underlying physiological relationship between hepatic insulin responses (i.e., suppression of hepatic glucose production by insulin under fasting conditions) and whole body insulin responses measured with clamp procedure (largely reflecting skeletal muscle insulin responsiveness). Multiple investigators have demonstrated strong correlations (\( r \) values 0.6 – 0.8) between these surrogates and clamp-based measures (3, 7, 9, 11, 16, 20). Furthermore, shifts in these surrogates with interventions that shift clamp-based measurements of insulin resistance (20, 21, 29, 31) confirm their utility in epidemiologic and clinical trial applications in the study of human disease.

The study of metabolic abnormalities in animal models contributes importantly to advances in our understanding of the physiology and pathophysiology of obesity, insulin resistance, and diabetes. In animal models, some aspects of metabolic function are available for direct measurement (e.g., ex vivo measurement of ß-cell function or signaling molecule responses to insulin), but the need for intact system, whole animal measurements of physiology remains. In fact, due to the smaller blood vessel size and smaller blood volume available for sampling, the performance of classical hyperinsulinemic euglycemic clamp studies is arguably more difficult in rodents than in humans. It is therefore not surprising that there is equal interest in surrogate measures in rats and mice as in studies of humans. Although these indexes have begun to be applied in work involving rodent models (1, 5, 6, 10, 12, 14, 15, 18, 19, 24, 26, 28, 33, 35), formal assessments of the relationship of surrogate measures with clamp measures of insulin resistance in rodents are only now coming to light. One such paper was recently published in this Journal, detailing interrelationships of HOMA-IR and QUICKI with formal clamp-derived methods in Sprague-Dawley and Wistar rats (4). Another recently published paper describes analogous comparisons in mice, including standard C57BL6 mice and a selection of transgenic mice with increased or decreased endogenous insulin resistance (17).

The overall result is that HOMA-IR and QUICKI as surrogate measures provide a reasonable and reliable approximation of formal measures of insulin resistance when applied to rats and mice as they do in humans. In both papers, the surrogate indexes proved adequate for demonstrating physiologically relevant differences in insulin resistance, induced by pregnancy in the study of rats and induced by fat feeding and/or transgenes in the study of mice. This is an extremely useful set of observations and validates the continued application of these surrogates in animal studies. Also, the similarities with observations in humans suggest that the relationships between fasting and insulin-stimulated measures of insulin resistance carry well across species, validating the animal models for these applications.

There are interesting subtleties that limit the broad application of these indexes and therefore warrant comment. For instance, the degree of correlation with clamp measures of insulin sensitivity in the two strains of rats evaluated was of the same order as that described for humans (\( r = 0.7–0.8 \)), but these measures were less closely correlated in mice (\( r = 0.4 \) compared against both glucose infusion rate and SIclamp, modestly improved by adjusting for body weight). Differences in the precision of the clamp measures in the smaller animals may have contributed to this observation. The two strains of rats studied exhibited different physiologically normal fasting glucose levels with similar insulin concentrations. Therefore, the absolute value of the “normal” value for the HOMA-IR and QUICKI differed considerably between strains, although linear relationships of indexes with clamp measurements were similar between strains. The study of mice included only one “normal” strain, so it is unclear whether such differences need to be taken into account for mice as well. In the study of rats, a species-specific normal range for HOMA-IR was applied, rather than dividing the glucose-insulin product by the human-specific constant of 22.5. Since this term is in the denominator for the HOMA-IR calculation, the use of incorrect values (or values with incorrect units) will introduce a nonlinear error. This species-specific adjustment is therefore more correct and advisable in the application of the HOMA model to nonhuman species. The QUICKI model does not incorporate such species-specific components and therefore does not require such adjustment.

These points warrant consideration in the design and interpretation of studies applying these surrogate measures of insulin resistance to the study of metabolism in animal models. However they do not detract from the broader observation that, as in humans, HOMA-IR and QUICKI indexes of insulin...
resistance based on fasting measurements of glucose and insulin can serve as useful and reliable surrogates of more difficult and time-consuming clamp-based measurements. The formal clamp-based measures will still provide the most definitive measures where detailed physiological questions are being pursued; but with the above caveats in mind, these surrogates can be more broadly applied in animal studies where clamps are not otherwise needed.

REFERENCES