Multiple organ dysfunction syndrome (MODS) is a clinical consequence of a dysregulated inflammatory response, triggered by clinically diverse factors and is one of the leading causes of mortality among critically ill patients. Whether MODS should be called a distinct disease is debatable.

Contemporary organ dysfunction scales like sequential organ failure assessment (SOFA) and MOD score evaluate organ dysfunction in six organ systems such as respiratory, renal, cardiovascular, central nervous system, hepatic, and hematologic. Critically ill patients also manifest dysregulated glucose homeostasis termed as stress hyperglycemia and is shown to be associated with poor outcomes. Stress hyperglycemia is a result of hepatic glucose production due to upregulated gluconeogenesis and glycogenolysis. This normally provokes an increase in insulin secretion by the β-cells. However, the increase in counterregulatory hormones such as glucagon, cortisol, catecholamines, and proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α) prevent control of hyperglycemia and contribute to insulin resistance (IR).

Conventionally, IR has been described as a clinical state characterized by impaired glucose disposal in the presence of either normal or elevated serum insulin concentrations. IR contributes significantly to the pathophysiology of type II diabetes and is a hallmark of obesity, dyslipidemias, hypertension, and other components of the metabolic syndrome.

**Methods for Quantifying IR**

Hyperinsulinemic-euglycemic glucose clamp technique is a direct gold standard method for quantifying IR. In this technique, plasma insulin concentration is acutely raised and maintained at 100 μU/mL by a continuous infusion of insulin. Meanwhile, the plasma glucose concentration is held constant at basal levels by a variable glucose infusion. When the steady state is achieved, the glucose infusion rate equals glucose uptake by all the tissues in the body and is therefore a measure of tissue insulin sensitivity. Due to its invasive and resource-intensive nature, it is not practical at the bedside in patients.

Various indirect methods and models like fasting insulin, glucose insulin product, C-reactive peptide, insulinogenic index, homeostatic model assessment (HOMA), and quantitative insulin sensitivity check index (QUICKI) have been studied in small subsets of population but not broadly validated in critically ill patients.

HOMA-IR model of indirect IR estimate was first developed by Mathews et al. from normal population and a cohort of type II diabetics. It is a model used to quantify IR and β-cell functions from basal (fasting) glucose and insulin concentrations. HOMA is based on physiological principles governing closed-loop control of glucose and insulin. It predicts fasting steady-state glucose and insulin concentrations for a wide range of possible combinations of IR and β-cell functions. Insulin levels will depend on the pancreatic β-cell response to glucose concentrations, while glucose concentrations are regulated by insulin-mediated glucose production through the liver. Hence, inadequate β-cell function will reflect failure of appropriate response of β-cell to glucose-stimulated insulin secretion. Similarly, IR is reflected by the diminished suppressive effect of insulin on hepatic glucose production. HOMA describes this glucose-insulin homeostasis by means of a set of simple, mathematically derived nonlinear equations. The approximating equation for IR has been simplified and uses a fasting blood sample. It is derived from the use of the insulin glucose product, divided by a constant.

\[
\text{HOMA-IR score} = \frac{\text{FPI} \times \text{FPG}}{405}
\]

whereas insulin concentration is reported in μU/L and glucose in mg/dL.

**Current Issues with Estimating IR Using HOMA-IR Model**

Although the HOMA model has proved to be a robust clinical and epidemiological tool in descriptions of the pathophysiology of diabetes, HOMA-IR and its correlation with gold standard method is not validated across the subset of critically ill patients. Also lacking is standardization of fasting insulin assessment method and its cutoffs for critically ill population. In a cohort of adolescent nondiseased population, Schwartz et al. showed that the surrogate measures were only modestly correlated with the
Insulin Resistance and Homeostatic Model Assessment in Critically Ill

euglycemic-hyperinsulinemic insulin clamp and do not appear to offer any advantage over fasting insulin alone. The lack of standardized reference range for the HOMA-IR index across different age groups, sex, race, health, and different disease conditions like noncommunicable diseases has limited its clinical application.8-11

There are only a few studies that have evaluated HOMA-IR in the subset of critically ill patients such as trauma, acute pancreatitis, and acute kidney injury. In a small single-center prospective cohort of 37 nondiabetic severe trauma patients without head injury, admission HOMA IR correlated with longer ICU stay.12 A prospective study by Cho et al. with 269 patients of acute pancreatitis evaluated the relation between IR (using an HOMA-IR cutoff of 2.5) and percentage of patients requiring ICU admissions and mortality rate. The area under the curve (AUC) of HOMA-IR matched that of other pancreatitis scoring systems such as CT severity index, Ranson score, and bedside index of severity in acute pancreatitis (BISAP). IR was the only independent significant factor that correlated with either ICU admission or progression to severe acute pancreatitis.13 In a case–control study by Fayed et al.,219 critically ill ICU patients with acute kidney injury (AKI) were compared to matched controls. Statistically significant higher fasting insulin levels and higher levels of HOMA-IR were observed in patients with AKI than patients without AKI.14 However, in these studies with a subset of patients with acute pancreatitis and AKI, HOMA-IR is affected as disease per se has a significant effect on glucose/insulin homeostasis.

The study by Sama et al. in the current issue evaluated admission HOMA-IR in 82 nondiabetic critically ill MODS patients with an average APACHE II score of 17.88.15 They determined that a HOMA-IR cutoff value of 1.61 predicted 28-day mortality. The predictive performances of prognostic test or score are assessed using receiver operating curve (ROC) and AUC of 0.8 is considered as significant. The AUC in this study was of 0.68 with a sensitivity of 36% and specificity of 95.5%. The authors could not recruit the requisite planned sample size of 115. This study may be considered as a proof-of-concept study for use of IR to predict the outcomes in MODS. However, it is unclear from the present study whether HOMA-IR will add any incremental predictive value to current MODS scores.

Future Directions for Research

We need to explore further concept of IR in critically ill patients. Questions needing further exploration are whether its cause or effect of disease? What is the best and validated assessment method for IR in critically ill cohort? What are the appropriate cutoffs of such IR assessments? Should we look at basal IR or delta IR developing over a period of stay in ICU? Does IR has only prognostic value or any potential therapeutic intervention based on IR will affect outcomes?

References

1. Gourid NM, Nikitas N. Multiple organ dysfunction syndrome. J Intensive Care Med 2020;35(12):1564–1575. DOI: 10.1177/0885066619871452. PMID: 31455133.
2. Marshall JC. Med Klin Intensivmed Notfmed 2020;115(Suppl. 1): S15–S20. DOI: 10.1007/s00063-020-00660-9.
3. Van Cromphaut SJ, Vanhoorebeke I, Van den Bergh G. Glucose metabolism and insulin resistance in sepsis. Curr Pharm Des 2008;14(19):1887–1899. DOI: 10.2174/138161208784980563. PMID: 18691100.
4. Hompesch M, Rave K. An analysis of how to measure glucose during clamp studies: are glucose meters ready for research? J Diabetes Sci Technol 2008;2(5):896–898. DOI: 10.1177/193229680800200522.
5. Singh B, Saxena A. Surrogate markers of insulin resistance: a review. World J Diabetes 2010;1(2):36–47. DOI: 10.4239/wjd.v1.i2.36.
6. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28(7):412–419. DOI: 10.1007/BF00280883.
7. Available from: https://www.mdcalc.com/home-ir-homeostatic-model-assessment-insulin-resistance.
8. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004;27(6):1487–1495. DOI: 10.2337/diacare.27.6.1487.
9. Schwartz B, Jacobs DR Jr, Moran A, Steinberger J, Hong CP, Sinaiko AR. Measurement of insulin sensitivity in children: comparison between the euglycemic-hyperinsulinemic clamp and surrogate measures. Diabetes Care 2008;31(4):783–788. DOI: 10.2337/dc07-1376. PMID: 18174496.
10. Uyttendaele V, Chase JG, Knopp JL, Gottlieb R, Shaw GM, Desaive T. Insulin sensitivity in critically ill patients: are women more insulin resistant? Ann Intensive Care 2021;11(1):12. DOI: 10.1186/s13613-021-00807-7.
11. Qu HQ, Li Q, Rentfro RA, Fisher-Hoch SP, McCormick JB. The definition of insulin resistance using HOMA-IR for Americans of Mexican descent using machine learning. PLoS One 2011;6(6):e21041. DOI: 10.1371/journal.pone.0021041.
12. Bonizzi M, Zagli G, Lazzeri C, Degl’Innocenti S, Gensini G, Peris A. Early insulin resistance in severe trauma without head injury as outcome predictor? A prospective, monocentric pilot study. Scand J Trauma Resusc Emerg Med 2012;20:69. DOI: 10.1186/1757-7241-20-69.
13. Cho SK, Huh JH, Yoo JS, Kim JW, Lee KJ. HOMA-estimated insulin resistance as an independent prognostic factor in patients with acute pancreatitis. Sci Rep. 2019 Oct 17;9(1):14894. DOI: 10.1038/s41598-019-51466-5.
14. Fayed A, Soliman A, Badr M, Abdelmoniem M, Drwesh H, Fakher M, et al. Fasting insulin level and Homaster IR as predictors of acute kidney injury in critically ill patients. Bull Natl Res Centre 2020;44:64. DOI: 10.1186/s42269-020-00326-8.
15. Sama S, Jain G, Kant R, Bhadoria AS, Naithani M, Kumar A. Quantifying Insulin Resistance (HOMA-IR) to Predict Mortality in Multiorgan Dysfunction Syndrome. Indian J Crit Care Med 2021;25(12):1364–1369.