Journal of Insulin Resistance
ISSN: (Online) 2519-7533, (Print) 2412-2785

Interpreting quantification: Is this the Achilles heel of insulin diagnostics?

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How to cite this article:
Zinn C, Crofts C. Interpreting quantification: Is this the Achilles heel of insulin diagnostics? J. insul. resist. 2022;5(1), a70. https://doi.org/10.4102/jir.v5i1.70

With the re-establishment of the *Journal of Insulin Resistance*, it is time to pause, look back and appraise where we have come from and how we have progressed with diagnosing insulin resistance and hyperinsulinaemia. These metabolic states are becoming increasingly better established as underpinning a range of chronic health conditions. What is not well established is the difference between these two states. Whilst they generally do occur concurrently, insulin resistance occurs at the target cell, whereas hyperinsulinaemia results from excessive secretion of insulin. Both states can occur acutely and chronically based on the physiological context but have different downstream physiological outcomes. Whilst these might appear to be technical subtleties, the two conditions are not one and the same and need to be considered as separate entities.

The understanding of these two separate entities and how they coexist, alongside their diagnostic interpretations, might very well be the Achilles heel of the field.

Let us step back in time to see how history has shaped our understanding of insulin dynamics.

Insulin was first discovered 100 years ago, but it was much later, that is, 40 years after its discovery, that it was first quantified. Yallow and Berson established the radioimmunoassay technique, which later won them a Nobel Prize in 1977 and which progressed the understanding and utility of insulin via laboratory explorations.

Joseph R. Kraft progressed this work and was one of the first pathologists to use the radioimmunoassay technique in clinical practice. By measuring insulin in the blood in the 1970s, he was able to recognise the presence of hyperinsulinaemia in the normoglycaemic state and to develop an understanding of the relationship between hyperinsulinaemia and type 2 diabetes. His work culminated in the establishment of the 'Kraft patterns' but it took until recently for this work to show academic and clinical traction.

Fast forward to today, there is a plethora of diagnostic techniques that measure insulin resistance and a few for hyperinsulinaemia. Diagnostic technologies have advanced and all modern techniques accurately quantify intended markers, especially insulin. What is missing is the collective ability to effectively interpret findings of these two metabolic states in a translational way that is meaningful in clinical practice. Several of the techniques are more suitable to research, such as the hyperinsulinaemic-euglycaemic clamp, the gold standard test for insulin resistance, which uses a glucocentric methodology and the oral glucose insulin sensitivity (OGIS) index, a more insulinocentric model addressing dynamic measures of insulin resistance. Both have little application in the real world of clinical practice as they are executed under stringent laboratory conditions and may induce supraphysiological states. Techniques more commonly used in clinical practice include the single fasting insulin measure, which may also be included in other methodologies, such as Homeostatic Model Assessment (HOMA) and quantitative insulin-sensitivity check index (QUICKI). All measures based on fasting insulin are flawed because of insulin's highly oscillatory and reactive nature. The use of insulin as a diagnostic variable is further complicated by the lack of a universal laboratory reference interval and imprecise unit conversion factor. Furthermore, the single fasting insulin measure may fail to diagnose people with hyperinsulinaemia or insulin resistance, with Hayashi et al.'s[1] work showing patients who have lost their first phase insulin response, which may not be identified by fasting insulin measures, have a 30% chance of developing type 2 diabetes in 5–10 years.

The current gold standard for diagnosing hyperinsulinaemia involves measuring insulin over a 5-h or a 2-h period after consuming a glucose bolus.[2,3] Whilst a useful tool in research, its application in the clinical setting (despite being applied by some) is still impractical from being adopted across the board.

Where to from here?

We have learnt a great deal about insulin dynamics over the last 100 years and dramatically improved technologies for its quantification. However, there is still no single practical test that we can currently recommend with confidence for diagnosing either insulin resistance or hyperinsulinaemia. There is also much more work to be done in order to refine the translation of quantified insulin into meaningful interpretation of metabolic states. We look to the future to improve our understanding and development of diagnostic techniques that direct us to a more accurate and real-world application model, which will benefit translational research and practice.

Key directions for future research include the following: (1) a shift from a glucocentric to an insulinocentric model for diagnostics and treatment; (2) an expansion of the reductionist lens with which we approach a concept, to a more holistic approach, whereby a simultaneous interplay of hormones and the normal state of play of the human body is considered; (3) an investigation into the role that other hormones such as glucagon, gastric inhibitory polypeptide (GIP) or glucagon-like peptide-1 (GLP-1) play in the diagnostics of metabolic disease; and (4) a drilling down on the specific contexts of insulin dynamics and assessing the differences between acute and chronic and normal and pathological states.

Overall, with consistency in terminology, semantics and understanding, we will be able to develop effective interpretation and translation of existing and new diagnostic outputs into real-world outcomes. This is what is needed to overcome the Achilles heel and advance metabolic health improvements.

Acknowledgements

Competing interests

The authors have declared that no competing interest exists.

Authors' contributions

C.Z. conceptualised the vision and direction of the editorial. Both authors (C.Z. and C.C.) discussed the content to be included. C.Z. wrote the editorial and C.C. contributed to its refinement.

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