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Determining a diagnostic algorithm for hyperinsulinaemia

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Background: Ascertaining Kraft dynamic insulin response patterns following a 3-h 100 g oral glucose tolerance test seems to be the most reliable method for diagnosing hyperinsulinaemia. However, this test may be too resource-intensive for standard clinical use.

Aim: This study aims to see if Kraft patterns can be accurately predicted using fewer blood samples with sensitivity and specificity analyses.

Setting: St Joseph Hospital, Chicago, Illinois, United States and Human Potential Centre, Auckland University of technology, Auckland, New Zealand.

Method: We analysed the results of 4185 men and women with a normal glucose tolerance, who had a 100 g oral glucose tolerance test with Kraft pattern analysis. Participants were dichotomised into normal–low insulin tolerance (Kraft I or V patterns) or hyperinsulinaemia (Kraft IIA–IV patterns). Sensitivity and specificity analysis was applied to available variables (including age, body mass index, fasting insulin or glucose) both individually and in combination.

Results: Out of a maximal combined sensitivity and specificity score of 2.0, 2-h insulin level > 45 μU/mL attained the highest score (1.80). Two-hour insulin also attained the highest sensitivity (> 30 μU/mL, 0.98) and the highest specificity (> 50 μU/mL, 0.99) scores. Combining the 2-h insulin with other variables reduced the sensitivity and/or specificity. Dynamic measures had a better combined sensitivity and specificity compared to fasting or anthropological measures.

Conclusion: People with a 2-h plasma insulin level < 30 μU/mL are unlikely to be hyperinsulinaemic. Given that first-line treatment is lifestyle modification, we recommend that a 2-h plasma insulin level > 30 μU/mL following a 100 g oral glucose tolerance test be used to identify the hyperinsulinaemic individual.

Keywords: type 2 diabetes; insulin resistance; hyperinsulinaemia; Kraft patterns; insulin response patterns; diagnosis.

Introduction

Hyperinsulinaemia contributes to metabolic disease via inflammatory pathways, by increasing cellular growth and proliferation via IGF-1, and being proatherosclerotic via decreased nitric oxide production, impaired fibrinolysis and increasing triglyceride production.[1] The potential prevalence of hyperinsulinaemia is concerning. Our previous work showed that not only should all people with impaired glucose tolerance or type 2 diabetes be considered hyperinsulinaemic by default, but also so are a substantial proportion of the population with normal glucose tolerance.[2] This suggests that early detection of hyperinsulinaemia may aid public health initiatives as this condition is believed to precede other metabolic changes including hypertension.[3] Therefore, hyperinsulinaemia is forecast to impose a considerable global burden to health because of its role in the aetiology of many metabolic diseases.

Diagnosing hyperinsulinaemia is challenging as most studies are based on the poorly defined concept of insulin resistance. Although the World Health Organization (WHO) has defined insulin resistance as 'under hyperinsulinaemic-euglycaemic conditions, glucose uptake below lowest quartile for background population under investigation',[4] insulin resistance has also been defined as 'the inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and utilisation in an individual as much as it does in the general population'.[5]

Note: †, deceased: 1922–2017.

The hyperglycaemic–euglycaemic clamp test is considered to be the 'gold-standard' test for insulin resistance.[6] During this test, insulin is infused into the person at supra-physiological concentrations, while sufficient glucose is simultaneously administered to maintain euglycaemia. As this combination has the effect of preventing gluconeogenesis, once the person reaches steady state (about 2 h), the glucose infusion rate equals the body-wide rate of glucose uptake. This is considered to be the measure of cellular sensitivity to insulin. The hyperinsulinaemic–euglycaemic clamp test is unsuitable for large clinical trials or wide-scale epidemiological studies. Simpler tests based on a fasting insulin and glucose blood test, such as the homeostasis model assessment (HOMA), were developed and validated against the clamp test, so that insulin resistance could be modelled.

There are a number of studies that use fasting insulin to indicate insulin resistance and/or hyperinsulinaemia. However, there are concerns that using a single fasting insulin level may not be sufficiently accurate because of the oscillatory nature of pancreatic insulin release.[7,8,9,10] Fasting insulin levels may not indicate whether first-phase insulin response is present or absent.[2] This phenomenon has been argued to be the better predictor of future risk of type 2 diabetes.[11]

The question remains as to whether insulin resistance tests should be used to determine hyperinsulinaemia. Although the two conditions are fundamentally intertwined, they are intrinsically different conditions.

Under normal physiological conditions, a person can only become hyperinsulinaemic when two conditions are met. The first is when a person has a degree of insulin resistance that may occur acutely or chronically. Acute insulin resistance can occur under a number of conditions, for example when glucose needs to be preferentially shunted to the brain or other body systems that can only rely on glucose for fuel (e.g. red blood cells). This may include fasting, hypoglycaemia or high cortisol levels. Acute insulin resistance may also occur with acute hyperglycaemia, when the GLUT4 transporters are downregulated.[12] It is postulated that the latter occurs to defend the cell against excessive formation of reactive oxidative species and advanced glycation end products. The acute state of insulin resistance is believed to resolve with improvements to the physiological state with no long-term sequelae. Chronic insulin resistance, however, may occur for a variety of reasons, including chronic stress, elevated free-fatty acids, certain medications and hyperinsulinaemia.[1] The latter is under conditions of a carbohydrate load. Insulin is predominantly released from the pancreas in response to elevated blood glucose levels. This means that a person can be chronically insulin resistant, but not become hyperinsulinaemic if they restrict their dietary carbohydrate intake. This phenomenon may be one reason why insulin resistance testing has not been shown to improve disease risk calculations.

Therefore, to effectively understand hyperinsulinaemia, a new method for diagnosis and monitoring needs to be developed. The most promising research has been based around insulin response patterns, formed during an oral glucose tolerance test. In 1975, Kraft demonstrated five distinct insulin response patterns arising during a 3-h 100 g oral glucose tolerance test.[13] These patterns were based on both the magnitude and timing of the insulin peak, and the rate of decay of the response. Using Kraft's 1975 definitions, a normal insulin response is considered to be a fasting insulin < 30 μU/mL along with an insulin peak at 30 or 60 min, followed by a rapid rate of decay such that the sum of the 2-h and 3-h insulin concentration is < 60 μU/mL.[13] A hyperinsulinaemic response occurs with any combination of elevated fasting insulin, a delayed insulin peak at 2 h or later or a slow rate of decay. A hypoinsulinaemic response occurs when every plasma insulin value is ≤ 30 μU/mL. Our previous work examined the Kraft database and both simplified the original algorithm while ensuring that fewer people were left unclassified (Table 1).[2]

Hayashi and colleagues used different insulin response patterns. They measured plasma insulin at baseline and then at 30, 60 and 120 min during a 2-h, 75 g oral glucose tolerance test. By determining the timing of the insulin peak/s, as assessed by the responses, they showed an increased risk of developing type 2 diabetes in people who had an insulin response that peaked at 2 h compared to those who had an insulin peak at 30 or 60 min.[11]

Our previous research suggests that Kraft patterns should be preferred to the Hayashi patterns as Kraft patterns demonstrated less variation.[14] The disadvantages to using insulin response patterns are (1) the sheer number of blood tests that are required, and (2) the duration of time needed for the assessments. Kraft patterns require five blood samples taken over 3 h, while Hayashi patterns are based on four blood tests taken over 2 h.

TABLE 1: Kraft pattern algorithm.[2]

Kraft pattern	Description
Pattern I (normal insulin)	• Fasting insulin ≤ 30 μU/mL • 30-min or 1-h peak • 2-h + 3-h sum < 60 μU/mL
Pattern IIA (borderline)	• Fasting insulin ≤ 50 μU/mL • 30-min or 1-h peak • 2-h + 3-h sum ≥ 60, < 100 μU/mL *or* • Fasting insulin 31–50 μU/mL • 30-min or 1-h peak • 2-h + 3-h sum < 60 μU/mL
Pattern IIB (hyperinsulinaemia)	• Fasting insulin ≤ 50 μU/mL • 30-min or 1-h peak • 2-h + 3-h sum ≥ 100 μU/mL
Pattern III (hyperinsulinaemia)	• Fasting insulin ≤ 50 μU/mL • Delayed peak (2 or 3 h)
Pattern IV (hyperinsulinaemia)	• Fasting insulin > 50 μU/mL
Pattern V (hypoinsulinaemia)	• All values ≤ 30 μU/mL

Source: Crofts C, Schofield G, Zinn C, Wheldon M, Kraft J. Identifying hyperinsulinaemia in the absence of impaired glucose tolerance: An examination of the Kraft database. Diabetes Res Clin Pract. 2016;118:50–57. https://doi.org/10.1016/j.diabres.2016.06.007

It is also plausible that other clinical features influence, or are influenced by, hyperinsulinaemia. For example, Hayashi and colleagues demonstrated that different glucose response patterns were produced depending on the patient's insulin response curve.[11] Therefore, it is plausible that we can predict a patient's insulin response pattern by a clinical profile instead.

Sensitivity and specificity analyses are statistical binary classification measures used to assess the proportions of correctly diagnosed people suspected of having a clinical diagnosis. Sensitivity measures the proportion of correctly identified people with the clinical condition (sick), while specificity measures the proportion of correctly identified people without the clinical condition (healthy) as according to the methods of Altman and Bland.[15] Ideally, a test should have a combined sensitivity and specificity sum as close to 2.0 as possible. In practice, this is less likely to occur, and it must be decided whether to focus on sensitivity or specificity. When sensitivity is maximised, at the expense of specificity, it means that sick people are less likely to be misdiagnosed as healthy, but the proportion of false negatives, that is, when healthy people are misdiagnosed as being sick, is increased. This option should be preferred when the risk associated with missing people is high (e.g. an infectious epidemic) and/or the first-line treatment is of low risk (e.g. lifestyle measures). The reverse occurs when specificity is maximised. This study will use a variety of clinical features gathered during a 3-h 100 g oral glucose tolerance test and apply sensitivity and specificity analyses to determine whether the insulin response pattern can be accurately predicted.

Method

Participants

A total of 15 000 patients and healthy volunteers were referred for an oral glucose tolerance test at St Joseph Hospital, Chicago, IL, USA between 1972 and 1992. Data collected included plasma glucose, plasma insulin, age, gender, height and weight.

Study protocol

Subjects fasted overnight for 10–16 h. A fasting venous blood sample was taken; 100 g of glucose (Glucola, Miles/Ames, Elkhardt, IN, USA) was ingested and venous samples at 30 min, 60 min and each subsequent hour for between 3 and 5 h. The blood specimens were measured for glucose and insulin. Originally, the ferricyanide method (Autoanalyzer, Technicon Corporation, Tarrytown, NJ, USA) was used to analyse glucose, but this was later changed to plasma glucose oxidase method (Autoanalyzer, Technicon Corporation; Vitros, Johnson and Johnson Clinical Diagnostics, Inc., Rochester, NY, USA). According to the methods of Passey and colleagues, glucose samples analysed with the ferricyanide method were adjusted downward by 10 mg/dL to account for the systematic error.[16]

Plasma insulin was determined from the samples stored at –70 °C by a commercial double-antibody solid phase radioimmunoassay, (Pharmacia insulin RIA 100, Pharmacia Diagnostics AB, Uppsala, Sweden). The Phadebas Insulin Test had duplicate procedure precision of 1 standard deviation = ±5 μU in measurements up to 150 μU.

Re-analysis exclusion

Exclusion criteria included a body mass index (BMI) ≤ 17.9kg/m^2 because of the potential confounder of concurrent illness. Women aged between 20 and 45 years were excluded because of the potential confounder of pregnancy.

Re-analysis inclusion

From this data set, we included 2161 men aged older than 20 years and 2024 women aged older than 45 years, who had a normal glucose tolerance as defined by WHO criteria (1999) and also had age, height and weight recorded – a total of 4185 participants (Table 2).

Analysis

This study uses current clinical practices and sensitivity and specificity calculations to logically derive whether Kraft's patterns can be simplified. Area under the curve calculations were performed using the trapezoidal rule. Statistical analysis was performed using Microsoft Excel 2010 or IBM SPSS Statistics 22. Sensitivity and specificity calculations were performed as according to the methods of Altman and Bland.[15]

Variables

The variables to be tested individually and in combination within the sensitivity and specificity calculations included BMI, age, HOMA2 %B, HOMA2 %S, HOMA2 IR, oral glucose insulin sensitivity (OGIS) and plasma glucose or

TABLE 2: Participant characteristics.

Characteristics	Total
N	4185
Female	2024 (48)
Age (years)	
Male	44.9 (15.2)
Female	59.1 (9.4)
BMI (kg/m^2)	25.9 (4.7)
Plasma insulin (μU/mL)	
0 min	13 (13)
30 min	87 (56)
60 min	105 (73)
120 min	77 (62)
180 min	40 (41)
Plasma glucose (mg/dL)	
0 min	86 (10)
30 min	152 (32)
60 min	146 (43)
120 min	101 (22)
180 min	82 (25)

Frequency data are reported as *n* (%), otherwise mean (standard deviation).

insulin levels from each time point (0 min, 30 min, 1 h, 2 h and 3 h). HOMA2 variables and OGIS were calculated using their respective calculators.[17,18]

Inclusion for sensitivity and specificity calculations

Sensitivity and specificity calculations can only be performed with a dichotomised test outcome. Therefore, as depicted in Figure 1, this study separates the Kraft patterns into low-to-normal insulin responses (Kraft I, V) and hyperinsulinaemic responses (Kraft IIa–IV) as per the algorithm listed in Table 1.

Ethical considerations

This study was granted ethical approval by Health and Disability Ethics Committee (New Zealand) on 30 October 2013. Approval reference: 13/CEN/166. AUTEC reference: 13/337.

Results

As depicted in Figure 3, people with fasting insulin levels insulin > 30 µU/mL are automatically diagnosed with hyperinsulinaemia using Kraft's definitions[19]; therefore, these people (n = 238) were excluded from further analysis. As shown in Table 3, a 2-h insulin level > 30 µU/mL attained the highest sensitivity (0.98), a moderate specificity (0.62) and an overall score of 1.6 from a possible 2.0. This means that in a sample of 100 people with hyperinsulinaemia and 100 people with normal insulin tolerance, this test would correctly identify 99 of the people with hyperinsulinaemia as being hyperinsulinaemic. However, of the 100 people with normal insulin tolerance, 38 people would be falsely diagnosed with hyperinsulinaemia.

The highest overall score was 2-h insulin > 45 µU/mL (1.80) and the highest specificity was 2-h insulin > 50 µU/mL (0.99). The 2-h insulin alone achieved high scores for sensitivity, but this score dropped if applied in combination with another variable such as glucose. For example, 2-h glucose > 80 mg/dL achieved scores of 0.9, 0.38 and 1.28 for sensitivity, specificity and the total sum, respectively, and 2-h insulin > 45 µU/mL achieved scores of 0.85, 0.95 and 1.8 for sensitivity, specificity and the total sum respectively. However, the combination of 2-h glucose > 80 mg/dL and 2-h insulin > 45 µU/mL only attained a score of 0.78 for sensitivity, 0.96 for specificity and a combined result of 1.74. Although this is still a very good score, the sensitivity is lower than using 2-h insulin in isolation.

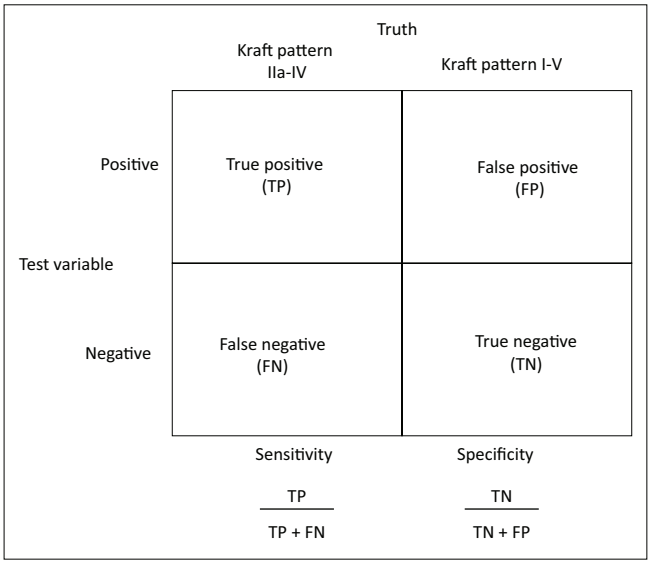

FIGURE 1: Sensitivity and specificity calculation table.

Oral glucose insulin sensitivity < 600 mL/min/m^2 attained the highest score (1.30) of the measures for insulin resistance with a very high sensitivity score (0.95). HOMA2 variables did not score highly overall: HOMA2 %B > 20 scored 1.27, while HOMA2 IR > 0.2 scored 1.32.

A receiver operating characteristic (ROC) curve confirmed these sensitivity and specificity calculations (Figure 2 and Table 4).

TABLE 3: Sensitivity and specificity calculations (further data on file).

Test variable	Sensitivity	Specificity	Sum SS
2-h insulin > 30 µU/mL	0.98	0.62	1.60
OGIS < 600 mL/min/m^2	0.95	0.34	1.30
2-h insulin – fasting insulin > 30 µU/mL	0.90	0.83	1.73
2-h glucose > 80 mg/dL	0.90	0.38	1.28
HOMA2 %B > 20	0.87	0.40	1.27
1-h insulin > 50 µU/mL	0.86	0.49	1.36
2-h insulin > 45 µU/mL	0.85	0.95	1.80
Age > 35 years	0.85	0.24	1.09
2-h insulin – fasting insulin > 35 µU/mL	0.84	0.92	1.76
2-h glucose – fasting glucose > 0 mg/dL	0.83	0.47	1.31
Fasting insulin > 5 µU/mL	0.83	0.46	1.29
1-h insulin > 60 µU/mL	0.80	0.61	1.40
2-h insulin > 50 µU/mL	0.79	0.99	1.78
3-h insulin > 20 µU/mL	0.79	0.85	1.64
2-h insulin > 45 µU/mL and 2-h glucose > 80 mg/dL	0.78	0.96	1.74
OGIS < 500 mL/min/m^2	0.70	0.84	1.54
2-h insulin > 45 and 2-h glucose > 90	0.69	0.97	1.67
2-h glucose – fasting glucose > 10 mg/dL	0.68	0.67	1.35
2-h insulin – fasting insulin > 50 µU/mL	0.65	1.00	1.64
2-h glucose > 100 mg/dL	0.63	0.73	1.35
Age > 50 years	0.61	0.52	1.13
3-h insulin > 30 µU/mL	0.60	0.99	1.58
Fasting glucose > 85 mg/dL	0.56	0.46	1.02
2-h insulin > 45 µU/mL and 2-h glucose > 100 mg/dL	0.55	0.98	1.54
BMI > 25 kg/m^2	0.55	0.61	1.16
BMI > 25 kg/m^2, 2-h insulin > 30 µU/mL	0.54	0.83	1.37
Fasting insulin > 10 µU/mL	0.54	0.79	1.32
HOMA2 IR > 0.2	0.52	0.81	1.32
2-h glucose – fasting glucose > 20 mg/dL	0.50	0.81	1.31
Age > 35 years and BMI > 25 kg/m^2	0.48	0.70	1.17
BMI > 30 kg/m^2	0.16	0.91	1.07
2-h insulin > 20 µU/mL	0.12	0.99	1.11
Fasting glucose > 80 mg/dL and fasting insulin > 20 µU/mL	0.09	0.99	1.08

SS, total sum of sensitivity and specificity.

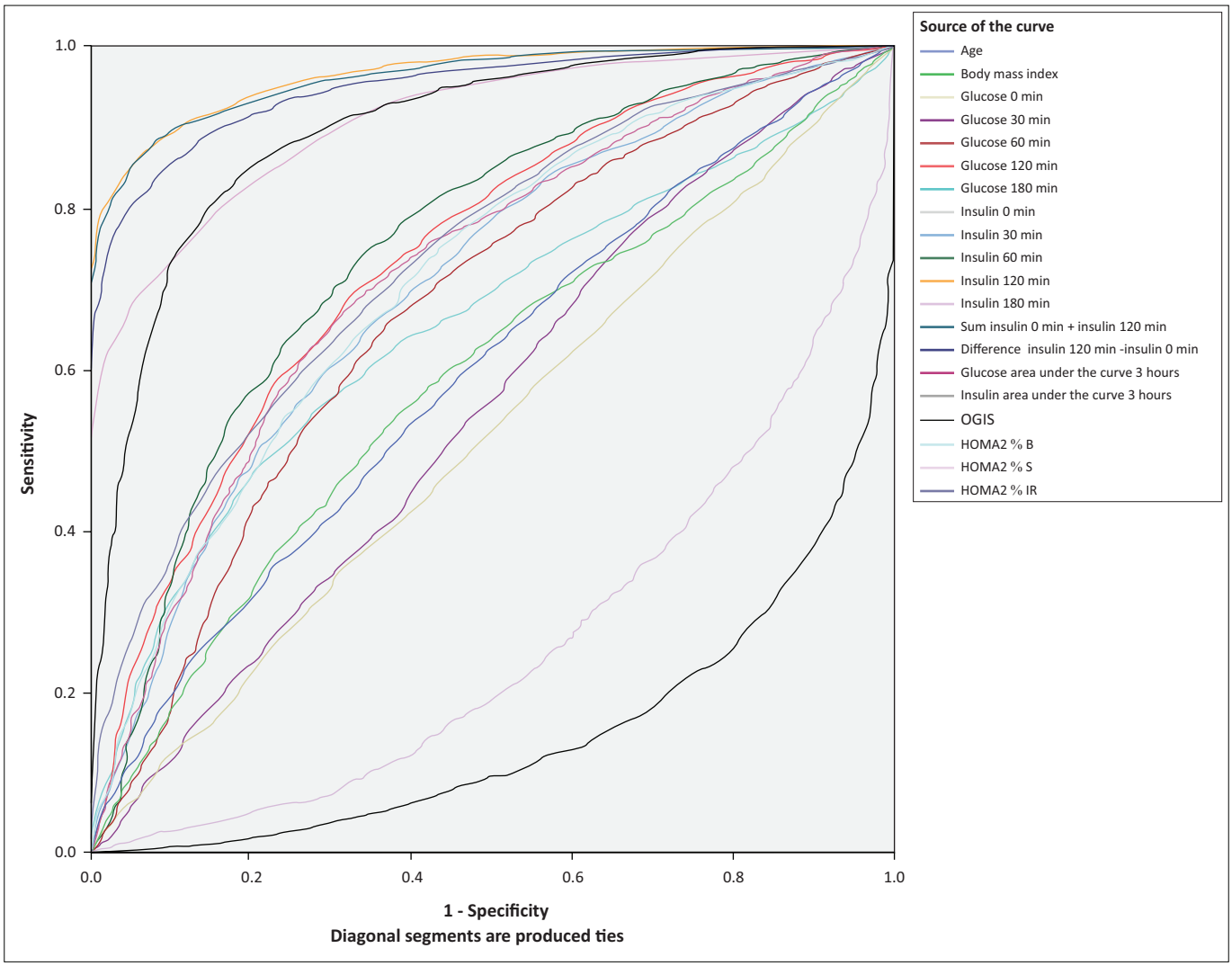

FIGURE 2: Receiver operating characteristic (ROC) curve.

Discussion

This study aimed to determine if there was a test that could simplify the diagnosis of hyperinsulinaemia in people with normal glucose tolerance, as defined by Kraft patterns IIa, IIb, III and IV. We were looking for a test with a high degree of sensitivity that required the least amount of resources, including time. We found that if the fasting insulin was < 30 µU/mL, then a 2-h plasma insulin level > 30 µU/mL following a 100 g, 2-h oral glucose tolerance test (OGTT) provided the highest degree of sensitivity in predicting a hyper insulinaemic pattern.

Although other variable combinations attained a higher combined sensitivity and specificity score, there are a number of reasons why we believe that the combination of a fasting insulin level combined with an OGTT and a 2-h plasma insulin cut-off of 30 µU/mL is the most useful test to recommend for both clinical and research practice.

If a person returned a fasting insulin level of > 30 µU/mL, then this alone should be considered diagnostic for hyperinsulinaemia, but lower levels cannot exclude the condition.[2] Two-hour plasma insulin alone featured prominently in both the ROC analysis and the sensitivity and specificity calculations with different levels attaining the highest sensitivity, specificity and combined score. Furthermore, using a fasting and 2-h level aligns with current OGTT protocols for diabetes diagnosis.

Using the lowest 2-h insulin level that maintained a reasonable sensitivity and specificity seemed the most appropriate clinical decision. Although a 2-h level > 45 µU/mL attained the highest summed score of 1.8, it had a lower sensitivity of 0.85 compared with 0.98 for a 30 µU/mL cut-off. A sensitivity score of 1.0 means that everybody who is tested for the disease, who truly has the disease, will be given a correct diagnosis. When sensitivity scores are decreased to 0.85, this means 15% of people who truly have the disease will be told, falsely, that they have a negative result. A lower specificity score increases the possibility of false negative results, or when people will be told that they have the disease, when they are, in fact, disease free.

The decision to err on the side of sensitivity or specificity also depends on the available management strategies. If the potential treatment is associated with significant risks relative

TABLE 4: Area under the curve calculations for receiver operating characteristic analysis.

Test variable	Area under the curve
Insulin 120 min	0.965
Sum insulin 0 min + insulin 120 min	0.963
Difference insulin 120 min - insulin 0 min	0.948
Insulin 180 min	0.912
Insulin area under the curve 3 h	0.897
Insulin 60 min	0.771
Glucose 120 min	0.740
Insulin 0 min	0.737
HOMA2 %IR	0.736
Glucose area under the curve 3 h	0.720
HOMA2 %B	0.713
Insulin 30 min	0.706
Glucose 60 min	0.673
Glucose 180 min	0.656
Age	0.596
Body mass index (BMI)	0.590
Glucose 30 min	0.550
Glucose 0 min	0.518
HOMA2 %S	0.264
OGIS	0.150

HOMA, homeostasis model assessment; OGIS, oral glucose insulin sensitivity.

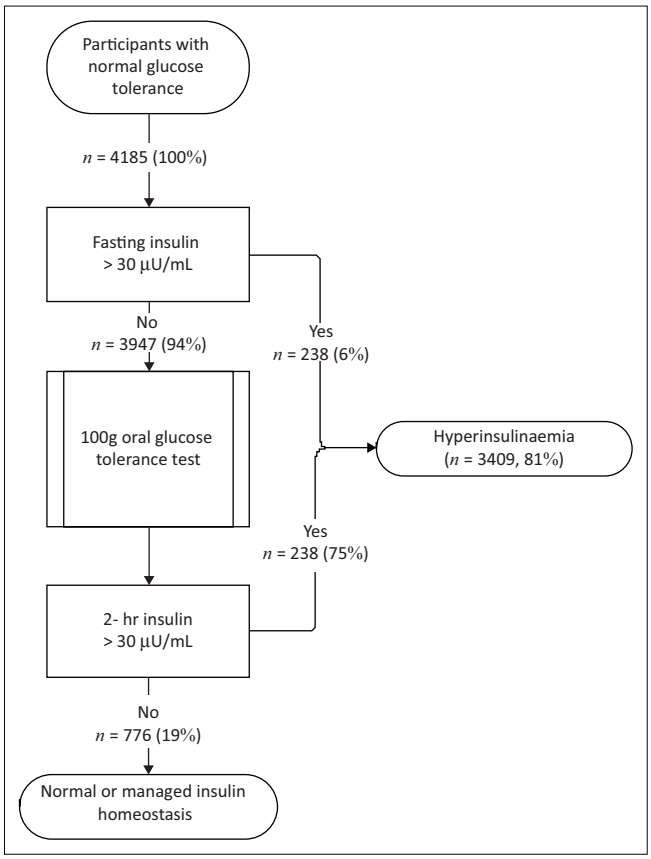

FIGURE 3: Diagnostic algorithm for hyperinsulinaemia.

to benefits, then the decision may be based on specificity. For hyperinsulinaemia, the potential first-line treatments include diet and physical activity.[20,21,22] Given that the risks associated with treatment are low when compared to potential benefits, we have erred on the side of sensitivity.

One criticism of using insulin is that 2-h levels have a high degree of variability. Our previous study showed that the repeatability coefficient of 2-h plasma insulin following a 100 g OGTT was approximately 45 µU/mL (282 pmol/L).[14] Given the limits of sensitivity and specificity ranged between 30 µU/mL and 50 µU/mL, we believe that the variation, as shown by the repeatability coefficient, would not have a significant impact on clinical outcome, but this needs to be confirmed with further research.

Fasting insulin levels ≤ 30 µU/mL were not useful in determining hyperinsulinaemia. Levels at the lowest end of the current reference range had a high sensitivity, but low specificity. We partially agree with current recommendations that neither hyperinsulinaemia nor insulin resistance should be diagnosed on the basis of a fasting insulin test,[23] as a low result does not exclude the condition. In our study, fasting insulin levels only detected hyperinsulinaemia in 238 of the 3409 (7.0%) people with hyperinsulinaemia (Figure 3).

We were disappointed that we could not recommend a single fasting test for hyperinsulinaemia: variables such as BMI, fasting glucose and fasting insulin, either alone or in combination did not attain sufficient sensitivity or specificity. Haemoglobin A1c (HbA1c) was not collected by Kraft, but is likely only useful for determining glucose status as plasma insulin elevation may be detected prior to changes in HbA1c.[24] We also recognise that our database does not capture information that may be useful as a prognostic marker such as ethnicity, or other biometabolic markers such as the triglyceride:high-density lipoprotein ratio, uric acid or liver enzymes.[25,26] Further research is needed to demonstrate the association between these markers and insulin response curves.

A significant limitation to our study is the lack of long-term health outcomes because of the cross-sectional nature of the Kraft database. We cannot, at this stage, evaluate the effectiveness of this test in actually predicting the risk of future disease. Previous work has shown that elevated 2-h insulin levels are associated with increased risk of developing type 2 diabetes[11]; therefore, our conclusions are plausible. However, either new prospective studies or reanalysis of studies that have collected both the 2-h insulin level and long-term outcomes are required.

Conclusion

Hyperinsulinaemia is conclusively linked with many metabolic diseases,[1,27] but this disease may be silent and not be associated with obesity.[2] Identifying the normoglycaemic individual with concurrent hyperinsulinaemia may benefit public health initiatives. We recommend that a fasting level combined with a 2-h plasma insulin level > 30 µU/mL following a 100 g oral glucose tolerance test be used to identify the hyperinsulinaemic individual.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

C.A.P.C. made substantial contributions to the study concept and design, data collection, analysis and interpretation; drafted the article; and performed data and statistical analysis. G.S. made contributions to the article concept and critical revisions. M.C.W. made contributions to the article concept, design, data analysis and interpretation, and critical revisions. C.Z. made contributions to the article concept and critical revisions. J.R.K. was responsible for data collection and made contributions to the article drafting and data analysis.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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