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Identifying hyperinsulinaemia in the absence of impaired glucose tolerance: An examination of the Kraft database

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ABSTRACT

Objective: Hyperinsulinaemia is associated with development of chronic metabolic disease and is emerging as a health risk independent to that of insulin resistance. However, little is known to what extent hyperinsulinaemia occurs with normal glucose tolerance in lean subjects.
Method: Oral glucose tolerance tests with concurrent insulin assay were conducted during the 1970s–1990s. Participants were classified according to glucose tolerance and insulin response pattern. Analysis of variance compared differences in plasma glucose, plasma insulin, and demographic and metabolic risk factors between groups.
Results: Participants with normal glucose tolerance comprised 54% ($n = 4185$) of the total cohort. Of these, just over half ($n = 2079$) showed hyperinsulinaemia despite normal glucose clearance. Obesity had a modest association with hyperinsulinaemia in people with normal glucose tolerance. Fasting insulin had limited value in diagnosing hyperinsulinaemia. The majority of participants (93%) with impaired glucose tolerance or diabetes had concurrent hyperinsulinaemia.
Conclusion: Hyperinsulinaemia in the absence of impaired glucose tolerance may provide the earliest detection for metabolic disease risk and likely occurs in a substantial proportion of an otherwise healthy population. Dynamic insulin patterning may produce more meaningful and potentially helpful diagnoses. Further research is needed to investigate clinically useful hyperinsulinaemia screening tools.

1. Introduction

Hyperinsulinaemia is emerging as a risk factor for subsequent metabolic disease that is independent to insulin resistance [1,2]. Although the two conditions have an intertwined pathophysiology, quantifying insulin resistance has failed to translate to clinical benefit [3]. Insulin resistance cannot mechanistically explain the subsequent pathologies, including hypertriglyceridaemia and hypertension. Hyperinsulinaemia contributes a common pathway to the aetiology of many non-communicable diseases including cardiovascular disease type 2 diabetes, cancer and dementias [4–6]. This may be via mechanisms such as arterial wall damage, microthrombi and vasoconstriction [7]; enhancing cellular growth

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and proliferation, increasing the risk of deranged DNA [8,9]; or changed regulation of beta-amyloid and tau protein and decreased synaptic plasticity [10,11].

Hyperinsulinaemia is becoming recognised as the earliest symptom of metabolic diseases, including that of metabolic syndrome. For example, elevated fasting insulin occurs up to 24 years prior to the onset of hyperglycaemia and is also posited to precede obesity [12–14]. There are clear, direct links (biological and epidemiological) between hyperinsulinaemia, hypertriglyceridaemia, hypertension and non-alcoholic fatty liver disease [15]. This means that we need to broaden our understanding of hyperinsulinaemia independent to insulin resistance as an early metabolic risk factor.

Currently, hyperinsulinaemia is not clinically used for diagnosing or monitoring metabolic risk as we do not have a clinically reliable reference interval from an easy to implement measure. Fasting insulin levels have a wide coefficient of variation and are unreliable for predicting individual disease risk [3,16]. It is also unknown whether other measures of insulin resistance can accurately predict compensatory hyperinsulinaemia. We also have very little understanding of the extent to which hyperinsulinaemia affects people with differing degrees of glucose tolerance, especially in people with normal glucose tolerance. For example, we do not know the extent, in populations, at which hyperinsulinaemia occurs in the absence of impaired glucose homeostasis.

During the early 1970s to mid-1990s Dr. J.R. Kraft pioneered some of this work. Dr. Kraft collected oral glucose tolerance test data with concurrent insulin assay from more than 10,000 individuals [17]. The participants were able to be classified into one of five insulin patterns ranging from normal insulin response (Kraft I) through to hyperinsulinaemic responses (Kraft II–IV) and a hypoinsulinaemic response (Kraft V). However, Kraft's work has a number of limitations. His peer-reviewed paper in 1975 described the algorithm that defined insulin patterns, but the glucose response was described in the archaic Wilkerson points system [17]. This algorithm was also unable to ascertain the pattern if the fasting insulin ranged between 31 and 50 μU/ml. Kraft proposed a second algorithm to define the insulin patterns in a lay publication [18]. While this algorithm did not exclude any results, the degree of similarity or difference between the two patterns has not been examined. Neither have analyses of Kraft's insulin patterns focussed on people with normal glucose tolerance, nor examined insulin response in relation to demographic, or other risk, factors including (BMI).

This study will explore the incidence of hyperinsulinaemia in the presence of both impaired and normal glucose metabolism by re-analysis of Kraft's original database using a modern perspective, including the WHO definitions of glucose tolerance. It aims to understand the relationship of hyperinsulinaemia to age, gender or BMI in the presence of normal glucose tolerance.

2. Subjects and methods

2.1. Subjects

15,000 patients and healthy volunteers were referred for an oral glucose tolerance test at St Joseph Hospital, Chicago. IL. U.S.A. between 1972 and 1992. St Joseph Hospital is a large, non-profit, teaching hospital based near downtown Chicago. Data collected included plasma glucose, plasma insulin, age, gender, height, and weight.

2.1.1. *Reanalysis inclusion*

From this database, we included 3953 men aged older than 20 years, and 3802 women aged greater than 45 years who also had age, height and weight recorded; a total of 7755 participants (Table 1).

2.1.2. *Reanalysis exclusion*

Exclusion criteria included a BMI > 17.9 kg/m^2 due to the potential confounder of concurrent illness. Women aged between 20 and 45 years were excluded due to the potential confounder of pregnancy.

2.2. Materials and methods

2.2.1. *Study protocol*

Subjects fasted overnight for 10–16 h. A fasting venous blood sample was taken, followed by ingestion of 100 g of glucose solution (Glucola, Miles/Ames, Elkhardt, IN.). Subsequent venous samples were collected at 30 min, 60 min, and each successive hour for between three and five hours as determined by the patient's physician. The blood specimens were measured for glucose and insulin. Originally the ferricyanide method (Autoanalyzer, Technicon Corporation) was used to analyse glucose, but this was later changed to plasma glucose oxidase method (Autoanalyzer, Technicon Corporation, Tarrytown, N.J., Vitros, Johnson and Johnson Clinical Diagnostics, Inc., Rochester, N.Y.). Precision was not reported for either glucose analysis; however, another study using both methods reported a within-run precision for both ferricyanide (CV < 5%) [19] and plasma glucose oxidase (CV < 3%) methods [38]. Glucose samples analysed with the ferricyanide method were adjusted downward by 10 mg/dl to account for the systematic error, according to the methods of Passey and colleagues [19].

Plasma insulin was determined from the samples stored at −70 °C by the Phadebus Insulin Test, (Pharmacia insulin RIA 100, Pharmacia Diagnostics AB, Uppsala, Sweden). Precision was reported as SD = 5 μU/ml up to 150 μU ml [17].

2.2.2. *Ethics*

Data re-analysis 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.

2.3. Analysis

2.3.1. *Participant classification*

2.3.1.1. Glucose tolerance. Glucose tolerance was defined using WHO criteria [20]. There is no consensus for defining hyperinsulinaemia. Previous research generally classifies participants into groups based on quantiles derived from fasting insulin levels. Recommendations for normal fasting insulin range from 2 μU/ml to 30 μU/ml [21–24]. However, earlier research suggested that fasting insulin levels had no relationship to

Table 1 – Participant characteristics.

	Total	Men	Women	p	Cohen's d
n	7755	3953	3802		
Diabetes mellitus	1666 (21%)	820 (20%)	846 (22%)		
Impaired glucose tolerance	1762 (23%)	895 (23%)	867 (24%)		
Impaired fasting glucose	142 (2%)	77 (2%)	65 (2%)		
Normal glucose tolerance	4185 (54%)	2161 (55%)	2024 (52%)		
Age (years)	55.2 (14.0)	50 (15.4)	60.6 (9.9)	<0.001	0.75
BMI (kg/m^2)	26.9 (5.2)	26.7 (4.5)	27.0 (5.9)	0.044	0.02
Glucose 0 min (mg/dl)	98 (34)	98 (34)	98 (35)	0.443	–
Glucose 30 min (mg/dl)	172 (54)	172 (46)	174 (50)	0.027	0.08
Glucose 60 min (mg/dl)	190 (78)	190 (76)	190 (80)	0.781	–
Glucose 120 min (mg/dl)	157 (92)	155 (90)	159 (94)	0.03	0.07
Glucose 180 min (mg/dl)	120 (85)	112 (80)	127 (88)	<0.001	0.20
Insulin 0 min (μU/ml)	15 (19)	16 (22)	15 (16)	0.018	0.06
Insulin 30 min (μU/ml)	74 (57)	73 (57)	76 (58)	0.035	0.05
Insulin 60 min (μU/ml)	105 (74)	103 (73)	106 (75)	0.040	0.05
Insulin 120 min (μU/ml)	103 (81)	100 (79)	107 (83)	<0.001	0.09
Insulin 180 min (μU/ml)	61 (63)	55 (68)	68 (70)	<0.001	0.21
$AUC_{glucose}$ (mg h/dl)	471 (212)	464 (205)	477 (219)	0.006	0.06
$AUC_{insulin}$ (μU h/ml)	253 (169)	245 (164)	262 (174)	<0.001	0.11
Glucose 120 min – glucose 0 min (mg/dl)	59 (69)	56 (68)	62 (70)	0.001	0.07

Frequency data are reported as n (%), otherwise mean (SD).
Effect sizes for Cohen's d are interpreted as: Large > 0.5, moderate 0.3–0.5, small ⩽ 0.2.

subsequent insulin response pattern, especially $AUC_{insulin}$, and vice versa [17]. Because of this, we believed that a dynamic pattern would best define normal insulin homeostasis. Using the principles of glucose homeostasis, where glucose returns to near fasting levels in healthy people after two hours, this study continues to define normal insulin metabolism as Kraft I. As insulin secretion first increases, then decreases as β-cell dysfunction progresses towards diabetes [25], we further define normal insulin metabolism occurring only in the presence of normal glucose tolerance.

2.3.1.2. Insulin tolerance. Insulin tolerance was defined using Kraft patterns [17]. The algorithm for determining the 1975 Kraft patterns was determined to be overly complex and failed to accurately classify any participant with a fasting insulin between 31 and 49 μU/ml inclusive ($n = 440$). Conversely, while the 2008 algorithm captured every participant, it was deemed to be overly simplistic as there was little difference for many cases between a "normal" insulin pattern (Kraft I) and a "severely hyperinsulinaemic" pattern (Kraft IV) when the insulin response curves were plotted. These algorithms were combined, along with additional information, such as that from Hayashi and colleagues [26] to form the 2014 algorithm as outlined in Table 2 and depicted in Fig. 1.

A hypoinsulinaemic response (Kraft V) either indicated pancreatic gland dysfunction as shown by an elevated glucose response or assumed to be due to a "low carbohydrate diet" [17]. If the latter, then the test was repeated after two weeks of a "high carbohydrate diet", which resulted in a Kraft I–IV pattern. Therefore, participants with Kraft V pattern were excluded from sub-analyses on people with normal glucose tolerance on the assumption that they had a repeated test; the results of which were included in Kraft patterns I–IV.

2.3.2. Calculations and statistical analysis

Area under the curve calculations were performed using the trapezoidal rule. Statistical analysis was performed using Microsoft Excel 2010 or IBM SPSS Statistics 22. Two group comparisons were done using independent t-tests. Comparisons between more than two groups were done with one-way analysis of variance. When the omnibus F-test was significant, post hoc analysis were used to effect pair-wise comparisons using either normal glucose tolerance or Kraft I pattern as the reference. Sidak–Bonferroni's test was used when equal variance was assumed (Leven's test > 0.5) or Dunnett's T3 when equal variance was not assumed. Statistical significance was set at $p < 0.05$, two-tailed tests were used throughout. The standardised difference between the means was calculated by Cohen's d. Effect size references were defined as: Large > 0.5, moderate 0.3–0.5, small ⩽ 0.2.

3. Results

3.1. *Hyperinsulinaemia and impaired glucose metabolism*

These results demonstrate that people with impaired glucose metabolism, overall, have higher insulin levels when compared to people with normal glucose metabolism. Analysis of variance identified significant mean differences between people with normal glucose tolerance, impaired fasting glucose, impaired glucose tolerance and diabetes for fasting insulin (13, 17, 16, and 21 μU/ml respectively, $p < 0.001$) and 2-h insulin (77, 78, 145, and 128 μU/ml $p < 0.001$) (Table 3). There was a significant difference in $AUC_{insulin}$ analysis across groups: normal glucose tolerance; impaired fasting glucose; impaired glucose tolerance; and diabetes (216, 229, 317, and 281 μU h/ml, $p \leqslant 0.001$). The majority of participants with either diabetes mellitus (90%) or impaired glucose

Table 2 – Kraft pattern criteria 2014.

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-h or 3-h)
Pattern IV (Hyperinsulinaemia)	• Fasting insulin > 50 μU/ml
Pattern V (Hypoinsulinaemia)	• All values ⩽ 30 μU/ml

tolerance (96%) had a hyperinsulinaemic pattern (Kraft IIA, IIB, III, or IV) (Table 3).

3.2. *Hyperinsulinaemia and normal glucose tolerance*

From Table 4 it can be noted that only 24% of participants with a normal glucose pattern had a Kraft I pattern. In other words, the majority of people presenting with normal glucose tolerance also demonstrated elevated insulin commensurate with hypersecreting insulin. Using Kraft I participants as a reference, mean BMI increased within participants with Kraft II–IV patterns. The increase was statistically significant ($p < 0.001$), but only had a modest effect size. Although there is a mean age difference between the genders, reflecting the respective cohorts, there was no clinical difference between the genders for mean BMI (male = 26.7 kg/m^2, women = 27.0 kg/m^2). The Kraft pattern could not be determined for most people based solely on their fasting insulin (Table 4) as there was no clinically meaningful difference for mean insulin between Kraft patterns I–III at baseline. Both the difference between plasma glucose at 120 min and fasting glucose and the $AUC_{glucose}$ showed that although these cohorts all had normal glucose tolerance, those with hyperinsulinaemia, had greater $AUC_{glucose}$ and a longer delay in plasma glucose returning to baseline ($p < 0.001$). All patterns showed a large effect size (Cohen $d > 0.5$), suggesting clinical significance, with the exception of Kraft IIA, which had a moderate effect size.

4. Discussion

This study examined the presence of hyperinsulinaemia in a large cohort of healthy volunteers and people suspected of having impaired glucose homeostasis, using the previously defined Kraft I pattern as the definition of normal insulin tolerance. These results show that, overall, hyperinsulinaemia affected more than 80% of the study population. This included > 90% of participants with diabetes or impaired glucose tolerance and nearly 75% of people with normal glucose tolerance.

This study is unique in that it features a study design that focuses purely on the analysis of the results from approximately 20 years of medical data that was collected in accordance with the best medical practice of the time. The complete database reflected a population sampling of Chicago I.L. with no preselection as to age, gender or ethnicity. The large sample size and the extended time period over which the data were collected reinforce the value of this study. The lack of ethnicity information, co-morbidities, other metabolic information, or long-term outcomes are a limitation to the study. It is also unknown what proportion of people were referred for the test for clinical reasons or as healthy volunteers. Nonetheless, since this information was not collected, they may be considered study delimitations and should not detract from our principal findings. A further potential limitation was that we were unable to differentiate between people with type 1 and type 2 diabetes based on plasma glucose levels. However, a key feature of type 1 diabetes is a hypoinsulinaemic response to a glucose load and likely to be depicted as a Kraft pattern V or, more rarely, pattern I. People with type 1 diabetes are also believed to contribute to a minority of cases of diabetes mellitus and this may be reflected with Kraft pattern V cases comprising about 8% of the cases of diabetes.

Although BMI was associated with hyperinsulinaemia in people with normal glucose tolerance, the effect size was modest. What was most notable, was that the majority of people with a hyperinsulinaemic pattern had a BMI < 30 kg/m^2, i.e., were not obese. Neither age, nor gender showed an association. The clinical significance of this observation is uncertain, but suggests that the hypothesis that obesity triggers insulin resistance [27] should be revisited. While not denying that obesity exacerbates insulin resistance and hence hyperinsulinaemia, elevated fasting insulin levels have been shown to precede weight changes in Pima Indian children [28]. Furthermore emerging research suggests that insulin changes are associated with, and may precede, weight change [13,14]. This suggests that the relationship between obesity and hyperinsulinaemia may not be unidirectional, but that each condition influences the other in a feedback loop. Therefore, elevated post-prandial insulin levels may be the first symptom of metabolic disease.

The influence of post-prandial hyperinsulinaemia is reinforced by the observation that, with the exception of people with a Kraft IV pattern (fasting insulin ⩾ 50 μU/ml), there was little clinical difference in the fasting insulin levels

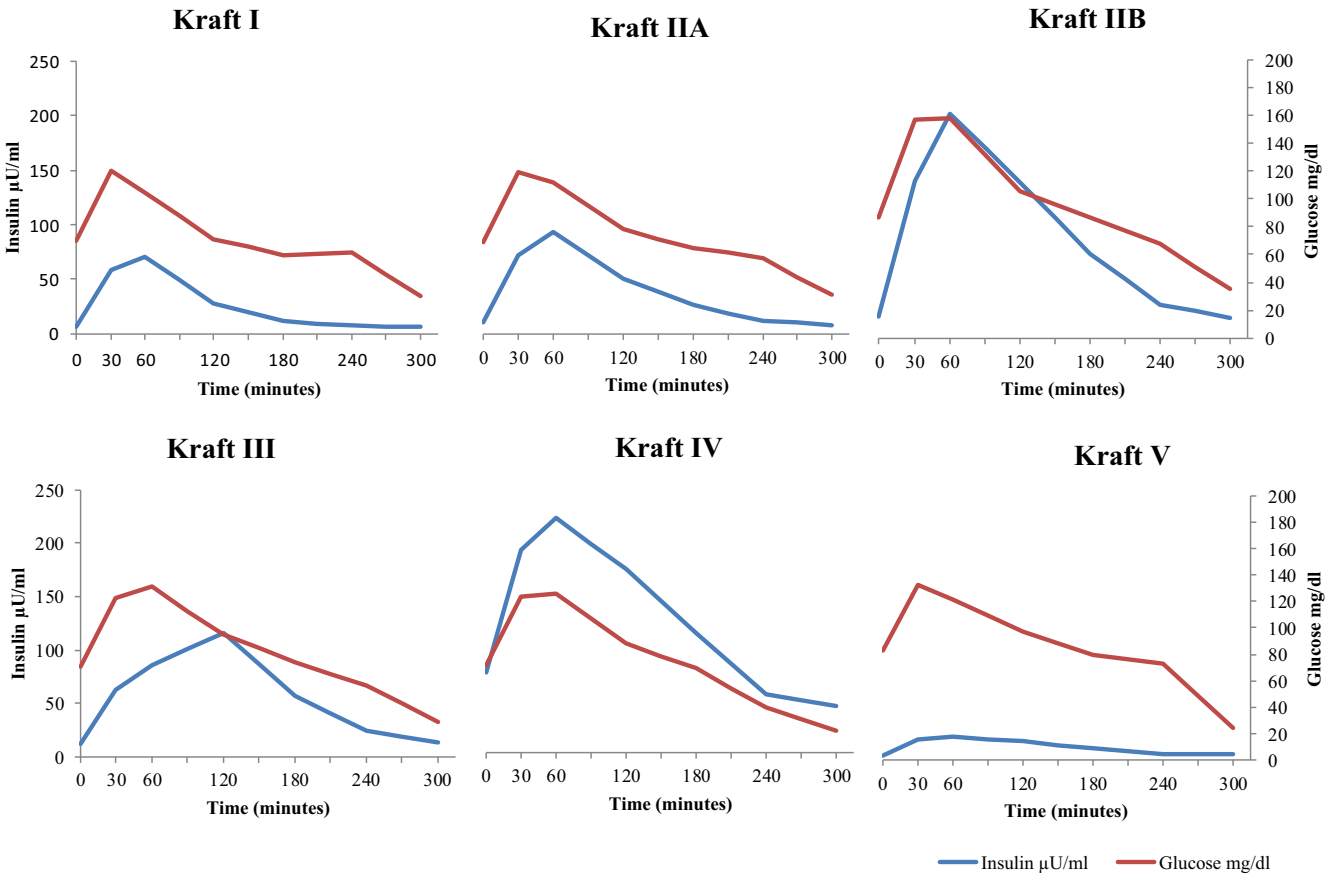

Fig. 1 – Kraft patterns with glucose response in people with normal glucose tolerance.

Table 3 – Diabetes classification by Kraft pattern.

	Kraft I	Kraft IIA	Kraft IIB	Kraft III	Kraft IV	Kraft V	Total
Normal glucose tolerance	990 (24%)	961 (23%)	1208 (29%)	807 (19%)	64 (2%)	155 (3%)	4185
Impaired fasting glucose	34 (24%)	22 (15%)	46 (32%)	32 (23%)	6 (4%)	2 (2%)	142
Impaired glucose tolerance	44 (2%)	94 (5%)	389 (22%)	1170 (67%)	44 (2%)	21 (1%)	1762
Diabetes mellitus	32 (2%)	54 (3%)	120 (7%)	1237 (75%)	86 (5%)	137 (8%)	1666
Total	1100 (14%)	1131 (15%)	1763 (23%)	3246 (41%)	200 (3%)	315 (4%)	7755

between the different Kraft patterns. This was especially noticeable in people with normal glucose tolerance (Table 4). This study shows that fasting insulin should not be relied upon to diagnose hyperinsulinaemia as it has no relationship to post-prandial insulin levels. Future research should consider post-prandial insulin levels, or other metabolic markers that have a clear relationship with post-prandial levels; especially in non-obese people with normal glucose tolerance.

There is a paucity of studies investigating insulin patterns with respect to hyperinsulinaemia in the literature. Hayashi and colleagues investigated the ability of insulin patterns to predict the risk of developing type 2 diabetes over ten years in a cohort of Japanese American men [26]. There are several distinct differences between the two sets of patterns. Hayashi patterns were based on a 75 g, 2-h oral glucose tolerance test with plasma insulin and glucose sampled at baseline, 30, 60, and 120 min. The pattern algorithm is based on the timing of the insulin peaks and troughs. By contrast, Kraft's patterns are based on a 100 g, 3-h oral glucose tolerance test with similar sampling patterns but the pattern algorithm is based on a combination of the magnitude and the timing of the peaks, plus the rate of decay of the plasma insulin concentration. Despite these differences, there are some notable similarities between the two patterns. Hayashi and colleagues noted that there was a significantly increased risk of developing type 2 diabetes if the insulin peak was at 2 h, compared to an insulin

Table 4 – Participant characteristics: Normal glucose tolerance.

	Kraft I	Kraft IIA	Kraft IIB	Kraft III	Kraft IV	Total
n (%)	990 (24)	961 (24)	1208 (30)	807 (20)	64 (2)	4030
Female sex (%)	402 (41)	474 (49)	633 (52)	409 (51)	26 (41)	1944 (48)
Age (years)						
Male	42.0 (14.6)	45.1 (14.9)	45.5 (15.7)	48.3 (15.5)	46.3 (12.8)	2086
Female	57.1 (8.7)	58.7 (9.4)	60.0 (9.6)	60.6 (9.9)	58.4 (7.6)	1944
BMI (kg/m^2)	24.9 (4.0)	25.3 (4.2)[a]	27.0 (5.1)[b]	26.3 (5.1)[a]	29.0 (4.7)[c]	26.0 (4.7)
Plasma insulin during OGTT (μU/ml)						
0 min	7 (5)	11 (7)[a]	16 (10)[c]	12 (8)[b]	77 (39)[c]	13 (13)
30 min	59 (39)	74 (41)[a]	113 (64)[c]	62 (40)	193 (89)[c]	81 (56)
60 min	70 (48)	95 (51)[b]	161 (76)[c]	86 (55)[a]	224 (96)[c]	109 (72)
120 min	28 (11)	52 (14)[b]	112 (57)[c]	116 (71)[c]	175 (98)[c]	79 (61)
180 min	12 (8)	27 (12)[b]	61 (44)[c]	57 (49)[c]	114 (84)[c]	41 (41)
Plasma glucose during OGTT (mg/dl)						
0 min	86 (10)	87 (10)	87 (11)	85 (10)	84 (13)	86 (10)
30 min	150 (33)	152 (31)	157 (30)[a]	149 (31)	149 (32)	152 (32)
60 min	130 (44)	142 (41)[a]	158 (42)[c]	159 (42)[c]	152 (40)[d]	147 (43)
120 min	86 (21)	99 (18)[c]	108 (18)[c]	115 (17)[c]	104 (24)[c]	102 (22)
180 min	72 (20)	81 (24)[b]	87 (25)[c]	88 (27)[c]	80 (25)	82 (25)
Glucose 120 min – glucose 0 min (mg/dl)	0 (22)	11 (19)[b]	21 (20)[c]	30 (19)[c]	20 (25)[c]	15 (22)
AUCg (mg h/dl)	317 (57)	342 (55)[b]	370 (55)[c]	374 (54)[c]	354 (62)[c]	351 (60)
AUCi (μU h/ml)	118 (52)	176 (55)[b]	324 (136)[c]	243 (139)[c]	515 (220)[c]	225 (139)

Frequency data are reported as *n* (%), otherwise mean (SD).
All post hoc analyses are referenced against Kraft I.
[a] $p < 0.001$ and Cohen $d \leqslant 0.2$.
[b] $p < 0.001$ and Cohen d 0.3–0.49.
[c] $p < 0.001$ and Cohen $d \geqslant 0.5$.
[d] $p < 0.01$ and Cohen d 0.3–0.49.

peak at 30 min. An insulin peak at two-hours equates with a Kraft pattern III. Future research should consider whether the addition of peak magnitude enhances the predictive nature of the insulin response patterns.

Although we have no long-term outcomes from this study, it is suggested that an increasing difference between glucose at 120 min and fasting glucose is associated with increased risk of cardiac events [29]. In this study, participants whose 2-h glucose did not return to baseline had a mean difference between glucose at 120 min and fasting levels of approximately 20 mg/dl. Our study shows that people with Kraft III and IV patterns both had a mean difference of $\geqslant$20 mg/dl.

Our study clearly shows that hyperinsulinaemia is associated with nearly every case of impaired glucose tolerance and type 2 diabetes. Therefore we contend that everyone with either impaired glucose tolerance or type 2 diabetes should be considered hyperinsulinaemic by default. Although a small proportion of people (2%) with either impaired glucose tolerance or type 2 diabetes also had a Kraft I pattern (normal insulin response) we believe this should be deemed a "pseudo-Kraft I" pattern as the glucose patterns suggest that the pancreas was unable to compensate for the glucose load [25].

We were surprised that there were small, and potentially non-clinically meaningful, differences in insulin response between people with impaired fasting glucose and those with normal glucose tolerance. This is believed to reflect the difference between insulin-mediated hepatic gluconeogenesis and peripheral glucose uptake which is hypothesised to drive the differences between impaired fasting glucose and impaired glucose tolerance [30]. The long-term clinical significance of this observation is unknown. However, as people with impaired fasting glucose comprised less than 2% of the complete sample ($n = 142$), the sample is too small from which to make generalisations and further research is recommended.

There is no current data on the test–retest repeatability of Kraft patterns. There are concerns about the repeatability of oral glucose tolerance tests, especially with respect to gastric emptying, but whether this has a significant effect on the overall insulin response pattern remains unknown [31]. Therefore it is unknown whether the patterns are repeatable with no change in clinical condition. Kraft patterning is based on a 100 g glucose load as this was standard practice in the USA when the data was collected. It is not yet known whether the patterns are repeatable with a 75 g load. These investigations should occur before further research using Kraft patterns are undertaken. However, due to a lack of long term outcome data, the benefits of using all five Kraft patterns remains uncertain, especially when the test is demanding in terms of time and resources. Further research should consider whether a dichotomy of normal/managed insulin response and hyperinsulinaemia can be developed using fewer blood samples, and then applied to long-term outcome data.

This study used data collected up to 40 years ago, therefore, it is uncertain if this represents a modern sample. Although the prevalence of people classified as overweight does not appear to have significantly changed since the

1980s, there has been a sharp increase in adults classified as either obese or extremely obese [32]. Additionally, from 1980 to 2011, the prevalence of diabetes has more than tripled [33]. It is highly plausible that should this study be repeated with a modern population that a much greater prevalence of hyperinsulinaemia would be detected. Additionally, due to the recruitment methods, there was an unspecified proportion of healthy volunteers to clinically referred participants. This means it is uncertain whether these proportions are representative of the population, with respect to both the prevalence of impaired glucose homeostasis in the total sample, but also with respect to the proportion of people with hyperinsulinaemia in the participants with normal glucose tolerance. Future studies should include concurrent data collection on ethnicity, family medical history, and other metabolic markers to determine if predictive factors for hyperinsulinaemia in the presence of normal glucose tolerance can be more simply obtained.

Current treatment of impaired glucose homeostasis, especially impaired glucose tolerance and type 2 diabetes mellitus focuses on glycaemic control. The impact of this focus on insulin homeostasis of these patients remains uncertain as many people only achieve glycaemic control through the administration of insulin secretagogues or exogenous insulin. Although glycaemic control must be maintained the question remains whether administering high doses of insulin aggravates cardiovascular disease, or increases the risk of developing cancer or dementia [2]. Research should explore alternatives to maintaining glycaemic control that minimises insulin requirements; both endogenous and exogenous. For example, carbohydrate-restricted diets provide greater improvements in glycaemic control, weight and other cardiovascular risk factors compared to high-carbohydrate diets, which are the current conventional dietary management of such conditions [34,35]. Although the use of insulin sensitisers, such as rosiglitazone, improve peripheral glucose uptake without increasing serum insulin levels [36], further research is needed to understand the impact of the increased glucose uptake leading to the increased formation of reactive oxidative species and advanced glycation end-products [37].

5. Conclusion

Globally, diseases associated with hyperinsulinaemia are increasing with associated morbidity and socioeconomic burden. In our study cohort, more than 75% of people with hyperinsulinaemia lacked other clinical symptoms, such as impaired glucose tolerance or obesity, therefore suggesting hyperinsulinaemia is a ‘silent disease’. Unlike measures of insulin resistance, insulin response patterns may be useful clinical tools to predict type 2 diabetes. Further prospective research in the benefits of insulin response patterns for disease risk prediction is urgently required to stem the global burden of chronic disease.

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Contribution statement

Catherine Crofts: Substantial contributions to manuscript concept, design, data analysis and interpretation. Drafted the article and performed data and statistical analysis.

Caryn Zinn: Substantial contributions to manuscript concept, design, data interpretation and critical revisions.

Mark Wheldon: Substantial contributions to manuscript design, data analysis and interpretation, and critical revisions.

Joseph R Kraft: Data collection, initial pattern development (1975), and contributions to manuscript drafting and data analysis.

Grant Schofield: Substantial contributions to manuscript concept, design, data interpretation and critical revisions.

All authors have approved the final version of the article.

Conflict of interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author.) Drs. Wheldon and Zinn declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work. Mrs. Crofts is supported by a grant from the Heart Foundation (NZ), and no other financial relationships with any organisations that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work. Dr. Kraft is the Chairman Emeritus of the Department of Clinical Pathology and Nuclear Medicine at St. Joseph Hospital, Chicago, Illinois U.S.A. Prof. Schofield reports personal fees from Vitality Works Ltd, and serves as a board member for Health Promotion Agency of New Zealand, a government agency (HPA).

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