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IMx (Abbott) Immunoassay of Insulin: A Practical Alternative to RIA Hyperinsulinemia Identification in Idiopathic Neurootology and Other Hyperinsulin Metabolic Disorders

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Abstract: Hyperinsulinemia identification as defined by glucose/insulin tolerance has been established as the prime etiological factor in idiopathic neurootological disorders. Insulin assays by radioimmunoassay (RIA) and the IMx (Abbott) immunoassay yielded in 558 of 595 glucose/insulin tolerance a concurrence of 93.7%. The latter measures insulin without cross-reaction with proinsulin. The RIA methodology includes proinsulin. The IMx (Abbott), a microparticle enzyme immunoassay (MEIA), gave lower values due to its nondetection of proinsulin.

Based upon defined insulin values, the dynamic patterns of euinsulinemia, hyperinsulinemia with elevated fasting insulin levels and hyperinsulinemia with impaired and/or hyperglycemia glucose tolerance were concurred 100% by MEIA. All of the nonconcurrences were with normal glucose tolerances when the second and/or third hour insulin values were borderline. The limited utilization of RIA technology and the potential availability of enzymatic immunoassay which requires less technical skills presents MEIA as a practical and precise alternative to RIA hyperinsulinemia identification.

The increasing world-wide significance of the clinical pathology of hyperinsulinemia becoming manifest in all disciplines of medicine, warrants the identification and/or exclusion of hyperinsulinemia by cost-effective technology.

Key words: Hyperinsulinemia; IMx; glucose-insulin tolerance; MEIA; euinsulin

INTRODUCTION

Hyperinsulinemia identification whether by radioimmunoassay (RIA) or by enzymatic immunoassay has world-wide significance. By the year 2000, hyperinsulinemia identification and/or exclusion will be a major cost-effective player in clinical medicine. Public awareness of the clinical pathology of hyperinsulinemia will mandate diagnostic and prospective application of hyperinsulinemia identification.

The clinical pathology of hyperinsulinemia especially that associated with euglycemia glucose tolerances has been identified as an etiological factor in essential hypertension, [1] atherosclerosis mainly coronary artery disease, [2] primordial follicle dysfunction, [3] gestational diabetes, [4] idiopathic peripheral neuropathy in addition to the pioneer identification of idiopathic disorders in the discipline of clinical neurootology [5].

BACKGROUND

The first major impact of hyperinsulinemia in the clinical arena was in the discipline of neurootology. Updegraff in 1977 identified idiopathic Meniere's disease with hyperinsulinemia [6]. The hyperinsulinemia identified by glucose-insulin tolerance was irrespective of the glycemia status. The cases were an intermix of normal, impaired, and/or diabetic (NIDDM) glucose toler-

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ances. All who maintained nutritional management compliance sustained clinical response. Updegraff's studies based on hyperinsulinemia identification by glucose/insulin tolerance were subsequently substantiated by others.

Mangabeira-Albernaz [7], Fukuda [8], and Proctor [9] independently identified hyperinsulinemia as the major diagnostic factor in up to 84 to 92% of their cases of idiopathic dizziness and tinnitus. Their cases included classic Meniere's disease. Updegraff further reported a correlation of hyperinsulinemia and migraine [10]. The relationship of hyperinsulinemia and Subjective Idiopathic Tinnitus (SIT) was specifically addressed by Proctor [9].

Independently, all investigators achieved and reported dramatic relief and sustained therapeutic response to their medical nutritional therapy. Sustained compliance yielded sustained response unequaled by other modalities [11].

It is of historical interest that Bornstein in 1951 [12], using a bioassay for insulin, demonstrated increased insulin in the noninsulin-dependent diabetic (NIDDM). In 1960 Yallow's refinement of a radioimmunoassay for insulin demonstrated in known diabetics increased insulin (hyperinsulinemia) following a 100 g. Glucose load [13]. A Nobel Prize was awarded to Yallow for this procedural development which became the cornerstone of radioimmunoassay as an analytic clinical chemistry tool.

In 1972 our laboratories applied the insulin radioimmunoassay (RIA) to the standard 3 and/or 4 hour glucose tolerance. The procedure was identified as glucose/insulin tolerance [14]. The glucose and insulin response to an optimum glucose load demonstrated a dynamic process. The insulin patterns were repetitive and associated with normal, impaired, and hyperglycemic glucose tolerances. The insulin assays with diabetic glucose tolerances not only concurred with Yallow's findings of increased insulin but further identified and classified specific hyperinsulinemia patterns of the noninsulin dependent diabetic state.

Specific dynamic patterns of euinsulinemia and hypoinsulinemia also were established. Hypoinsulinemia when associated with diabetic glucose tolerances designated the low insulin response of Diabetes Mellitus, insulin deficient diabetes mellitus, Type I potential. Our data base of 15,000 glucose/insulin tolerances has statistically confirmed and reaffirmed the gold-standards for euinsulinemia, hypoinsulinemia, and hyperinsulinemia [15] (Table 1).

Fasting insulin levels greater than 30 uU/ml. (180 pml/L) or the sum of the second and third hour levels greater than 60 uU/ml. (360 pml/L) define hyperinsulinemia. Ten percent of patients with hyperinsulinemia can be identified by the fasting levels [16]. A screening procedure has been proposed. Following a 100 g. Glucose load, the second hour insulin level of greater than 40 uU/ml yields a sensitivity and specificity of 89% for hyperinsulinemia [17]. This would be equally applicable to the MEIA IMx of insulin.

Table 1. Insulin Pattern Comparison

Pattern I:	Normal fasting (<30 Micro units) 1/2-1 hr peak above fasting 2 + 3 hr sum (<60 Micro units)
Pattern II:	Normal fasting/peaking 2 + 3 hr sum >60 Micro units
Pattern III:	Insulin peaking above fasting at 2 or 3 hr +
Pattern IV:	Fasting insulin >30 Micro units
Pattern V:	All values within fasting range

I = euinsulin
II III IV = hyperinsulin
V = hypoinsulin

METHODS AND RESULTS

In March 1996 a study of insulin assay comparison was initiated. In 381 patients the glucose/insulin tolerances with two insulin determinations by two different techniques were compared (Table 2). Our standard glucose/insulin tolerance determined insulin levels by the Coat-A-Count Insulin procedure (Diagnostic Products Corp., Los Angeles, CA). This is a solid-phase $_{125}$I radioimmunoassay which includes a cross-activity with proinsulin. The IMx insulin assay is based on the Micro

Table 2. Glucose/Insulin Tolerance (n = 381)

	0 (213)	**1/2 (62)**	**1 (51)**	**1 1/2 (19)**	**2 (22)**	**3 (14) = 381**
I	38	3	1	—	—	—
II	110 (−28)*	17	10	3	1	—
III	52 (−2)*	36	32	15	17	4
IV	13	6	8	1	4	5
V	—	—	—	—	—	5

glucose tolerance = Wilkerson point system (18)
Fasting >130 mg/dl one (1) point
1 hour >195 mg/dl 1/2 point
2 hour >140 mg/dl 1/2 point
3 hour >130 mg/dl one (1) point
two points or more are judged diagnostic of Diabetes (18)
0 points = normal tolerance
1/2-1 1/2 points = impaired tolerance
2-3 points = hyperglycemia tolerance
* 28 hyperinsulin patterns II and 2 hyperinsulin patterns III by RIA gave slightly lower values by the MEIA at the second and/or third hour assays thereby designating a pattern I by the MEIA.

Table 3. Glucose/Insulin Tolerances (n = 595)

	(381)	(214)		
I	42	32	=	74
		(+1)*		
II	141	72	=	213
	(−28)*	(−6)*		(34)*
III	156	102	=	258
	(−2)*			(2)*
IV	37	8	=	45
V	5	—	=	5
	381	214		595

*34 hyperinsulin patterns II and 2 hyperinsulin patterns III by RIA gave slightly lower values by the MEIA at the second and/or third hour assays thereby designating a pattern I. There was one pattern I by RIA which became a pattern II by the MEIA.

particle Enzyme Immunoassay (MEIA) technology and shows no cross-activity with proinsulin.

Insulin, a polypeptide hormone (MW 6000), is composed of two nonidentical chains, A and B, that are joined by two disulfide bonds. Insulin is formed from a precursor, proinsulin (MW 9000) in the beta cells of the pancreas. In proinsulin, the A and B chains are joined by a connecting peptide, referred to as the C-peptide. All are stored in the secretory granules of the islet cells of the pancreas. **Clinical relevance of proinsulin per se has not been definitely established.**

In Table 2 the 381 glucose/insulin tolerances are arranged according to their glucose tolerance status and their insulin patterns (Table 1). The glucose tolerances are classified by the Wilkerson point system [18]. In all tolerances judged impaired or diabetic (1/2 thru 3 Wilkerson point), the insulin patterns were concurred 100% by the MEIA procedure. The euinsulin patterns I and the hypoinsulin patterns V were also 100% concurred (Table 1).

Frozen glucose/insulin tolerance specimen from 1988 to 1993 provided an additional 214 examinations for comparison. This extended our study to 595 examinations (Table 3) with a concurrence of 93.7%. All of the nonconcurrence were with normal glucose tolerances when the second and/or third hour insulin values were borderline reflecting the nondection of proinsulin by the MEIA (see Table 3).

CONCLUSION

It has been statistically affirmed that hyperinsulinemia precedes hyperglycemia [19,20]. The earliest identification of the hyperinsulinemia state occurs with normal glucose tolerance. In 1974 this was identified as Diabetes Mellitus in situ (occult diabetes) [21,22]. Clinical relevance of this finding first noted in the idiopathic neurootology of Meniere's disease, tinnitus, migraine and S.I.T. has now been affirmed in the entire spectrum of the clinical pathology of hyperinsulinemia.

Irrespective of the glucose status, hyperinsulinemia thereby has potential impact into every discipline of medicine with world-wide clinical application.

By the year 2000, hyperinsulinemia identification and/or exclusion will be a major cost-effective player in clinical medicine. **This unprecedented prospective application into the entire clinical pathology spectrum of hyperinsulinemia becomes a major paradigm in clinical medicine.**

The limited utilization of RIA insulin technology and the potential availability of enzymatic immunoassay for insulin which requires lesser technical skills, strongly favors the latter to be the instrumentation of choice to meet this world-wide need.

Our study presents the IMx (MEIA) as a practical and precise alternative to RIA insulin determination.

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