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C-peptide—an intriguing molecule: assays on the ADVIA Centaur and IMMULITE systems

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Answers for life.

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C-peptide measurements are used as aids in the diagnosis of diabetes mellitus, hypoglycemia and insulinoma.

Figure 2.
Sequence for human C-peptide.
The pentapeptide sequence is highlighted in blue.[3]

Introduction

C-peptide was initially thought to be just a by-product of insulin production and biologically inert; however, research findings indicate that it does have important biological activity, especially in relation to diabetes mellitus. Studies have linked low levels of C-peptide to diabetes mellitus complications, and evidence suggests that maintaining higher levels of C-peptide is especially beneficial for type 1 diabetics.[1] C-peptide measurements have also been used to classify diabetes mellitus and as a marker of pancreatic β-cell function. This report will provide a concise review of C-peptide production and physiology, explore its applications for diabetes mellitus, and briefly review its well-established roles in hypoglycemia and insulinoma.

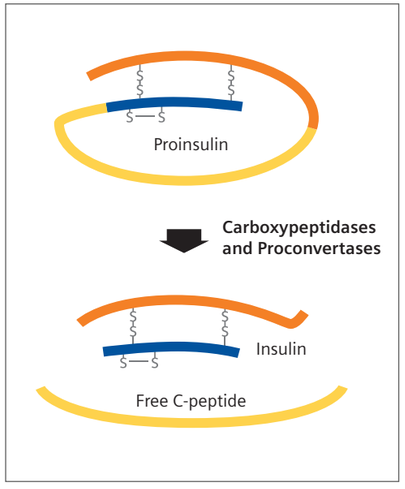

Figure 1.
Proinsulin is the precursor of insulin and C-peptide.

C-peptide production

C-peptide is produced by a series of enzymatic cleavages of the precursor molecules preproinsulin and proinsulin. Preproinsulin, a precursor of proinsulin, is produced in the endoplasmic reticulum of pancreatic β-cells in response to elevated blood glucose levels in healthy individuals; it is then cleaved by microsomal enzymes into proinsulin.[2] Proinsulin is the precursor of insulin and C-peptide. It consists of the α-chain and β-chain of insulin linked together by C-peptide (Figure 1). C-peptide is composed of 31 amino acids (Figure 2) and facilitates the correct folding of proinsulin to allow the cysteine disulfide bridges between the α-chain and the β-chain of insulin to form. Enzymatic cleavage of proinsulin by proconvertases and carboxypeptidases produces insulin and C-peptide, which are released in equimolar amounts from β-cells into the portal circulation (Figure 1). C-peptide is cleared by the kidney and has a half-life of about 20 to 30 minutes compared to insulin which is cleared through the liver and has a half-life of about 3 to 5 minutes.[2] The longer half-life, renal clearance and equimolar release of C-peptide make it an attractive proxy for estimating insulin secretion and β-cell function.

Mechanisms of action and biological activity

While the physiological functions of insulin are well established and understood, the functions of C-peptide are still being established and investigated. C-peptide has been shown to bind to specific cell surface receptors in cultured cells derived from human renal tubules, mesangium, skin fibroblasts and saphenous vein endothelium.[2] Data suggest that it acts through G-protein–coupled receptors to activate calcium-dependent signaling pathways via the C-terminal pentapeptide portion of the molecule.[3] C-peptide activation of calcium signaling is thought to increase the activity of Na+-K+-ATPase, which has been found to be reduced in patients with the advanced microvascular complications of diabetes mellitus (nephropathy and retinopathy). [2] The middle segment of the peptide has also been shown to activate Na+-K+-ATPase, but not as strongly as the full peptide or the pentapeptide sequence (Figure 2).[3] C-peptide's beneficial affects on the microvascular complications of diabetes mellitus are thought to be mediated through endothelial nitric oxide synthase.[2] In addition to receptor-mediated effects, C-peptide has been shown to produce non-receptor-mediated effects.[4]

Clinical research studies: C-peptide replacement in diabetes mellitus

In addition to the biological activity shown in the laboratory studies, clinical studies have found that replacement of C-peptide in type 1 diabetic patients improves many of the complications associated with this disease. Complications frequently associated with diabetes include retinopathy, nephropathy (characterized by glomerular hyperfiltration and albuminuria), neuropathy and cardiac disease. Johansson et al. have performed multiple studies evaluating the effects of the short-term replacement of C-peptide in type 1 diabetic patients. They investigated renal function and whole body glucose uptake in type 1 diabetic patients and found that low-dose C-peptide infusion as compared to sodium chloride infusion significantly increased whole body glucose utilization by 25 percent and decreased glomerular hyperfiltration by 6 percent.[5] In a follow-up study, they found that administration of C-peptide for 1 month in type 1 diabetics decreased HbA1c by 9 to 16 percent versus controls, which suggested that C-peptide improved glycemic control in these patients.[6] They also observed 40 percent and 55 percent decreases in albuminuria at 2 weeks and 4 weeks, respectively, indicating that C-peptide ameliorated the diabetic nephropathy.[6] In another follow-up study of type 1 diabetics, they compared the effects of subcutaneous injections of insulin and C-peptide or insulin and placebo for 3 months. During C-peptide treatment, albuminuria decreased, signs of autonomic neuropathy decreased as evidenced by increased respiratory heart rate variability, and sensory perception improved as evidenced by improved thermal thresholds. These changes were statistically significant as compared to the insulin plus placebo treatment period. [7] These studies consistently show that C-peptide replacement with or without insulin ameliorates several of the common complications experienced by diabetic patients.

Also supporting the role of C-peptide replacement for the amelioration of diabetic neuropathy are the results of a randomized double-blind placebo controlled study by Ekberg et al. This study found that in type 1 diabetic patients, administration of C-peptide for 3 months improved sensory nerve conduction and vibration perception.[8]

Diabetics are also at high risk for heart disease and often have diastolic dysfunction and myocardial perfusion abnormalities. The effect of C-peptide replacement on myocardial function was evaluated in a study by Hansen et al. This was a randomized double-blind crossover study which compared the effect of C-peptide infusion to saline infusion on myocardial function in type 1 diabetic patients. They used healthy volunteers as controls. Compared to age-matched controls, diabetic patients had reduced diastolic velocities and myocardial blood volume at baseline. During administration of C-peptide, however, the diastolic velocities and myocardial blood flow of the diabetics increased to the levels observed in the healthy controls. These findings suggest that C-peptide exerts a beneficial effect on myocardial function.[9]

C-peptide clearly has several important biological actions and more research is needed to fully delineate its functions and to characterize the effects and the role of long-term replacement therapy for diabetes mellitus.

Rationale for C-peptide measurement

Since C-peptide and insulin are released in equimolar amounts from the β-cells of the pancreas, the measurement of C-peptide has been used as a marker of β-cell function and an index of insulin secretion. Direct measurements of endogenous insulin by immunoassay are problematic in patients undergoing insulin therapy because assays can cross-react with the insulin analogs that the patient is taking. Moreover, these assays are affected by the presence of anti-insulin antibodies: [10,11] one study found that 36 percent of patients on human insulin developed autoantibodies after 12 months of treatment.[12] Thus, C-peptide measurements represent a better alternative index of insulin secretion and residual β-cell function. In addition, the extensive and variable hepatic extraction of insulin also makes it difficult to accurately estimate insulin secretion from peripheral insulin concentrations.[13] Monitoring residual β-cell function through the measurement of C-peptide is a strategy endorsed by the American Diabetes Association (ADA), and it recommends the use of C-peptide measurements as the outcome measure in clinical trials investigating methods to preserve β-cell function.[1,14]

Additionally, the use of C-peptide and insulin measurements together provides valuable information for the evaluation of hypoglycemia and the diagnosis of insulinoma and will be examined later in this report.

C-peptide and the classification of diabetes mellitus

The diagnosis of diabetes mellitus is based on the finding of glucose levels measured on two separate occasions exceeding the designated cutoff. Typically, patient history, age of onset, and physical characteristics like body mass index (BMI) are used to determine what type of diabetes a patient has; however, relying on these characteristics for accurate classification can be misleading. Type 1 accounts for 5 to 10 percent, and type 2 accounts for 90 to 95 percent of all diabetes. Misclassification of patients can lead to a delay in appropriate treatment and unnecessary patient morbidity: a type 1 diabetic not receiving insulin or a type 2 diabetic taking insulin unnecessarily.[15] Type 1 diabetes mellitus is characterized by β-cell destruction, which leads to very low or undetectable levels of C-peptide. In contrast, type 2 diabetes mellitus is associated with insulin resistance and typically initially has normal or elevated levels of C-peptide, which can decrease over the course of the disease.[16]

C-peptide levels are typically measured in serum or plasma and can also be measured in urine. Urine measurements generally require a 24-hour collection and are not as convenient as serum or plasma measurements. The testing protocols used for serum or plasma C-peptide measurements include fasting, random and stimulated protocols. In the stimulation protocols, the stimulant mimics the rise in glucose induced by meals and gives an estimate of the β-cell function. C-peptide can be stimulated by a glucose load, mixed meal, or glucagon. In type 1 diabetics, little or no increase would be expected above baseline in a C-peptide stimulation test, but type 2 diabetics would be expected to show an increase in levels over baseline. Agreement between C-peptide immunoassay methods is poor, so measurements for comparison should be done with a single method at a single institution.[17]

The inaccuracy of clinical diagnosis and the usefulness of C-peptide in the classification of diabetes mellitus are illustrated in a study by Wright-Pascoe et al. on a small series of diabetic patients treated with insulin. Patients were classified on the basis of the criteria of the National Diabetes Data Group and the World Health Organization that relies on glucose levels and patient history. This study found that using fasting C-peptide measurements, only 5 of 13 patients (38 percent) initially classified as having type 1 diabetes mellitus actually had the disease.[18] In a similar study also using C-peptide measurements, 31 percent of type 2 diabetics (diagnosed by ADA and WHO criteria) were determined to be misclassified as type 1 diabetics.[19] Shiraj et al. found that 84 percent of type 1 diabetics, 7 percent of type 2 diabetics and 4 percent of healthy controls had basal C-peptide levels below a cutoff of 0.6 ng/mL (0.2 nmol/L), indicating that C-peptide can discriminate between these populations. Similar percentages were obtained for glucagon-stimulated C-peptide below a cutoff of (0.32 nmol/L): 86 percent of type 1 diabetics, 8 percent of type 2 diabetics and 0 percent of healthy controls had levels below the cutoff.[20]

Other clinical studies have also shown that C-peptide measurements can be used to aid in the classification of diabetes mellitus.[21–23] Berger et al. compared classification of diabetes by random, fasting and glucagon-stimulated C-peptide measurement to classification by a prior diagnosis of type 1 or type 2 diabetes mellitus made without C-peptide measurements. Patients diagnosed with type 1 diabetes mellitus had to be on insulin for at least 3 years after diagnosis and patients with type 2 diabetes mellitus had to have been managed without insulin for 3 or more years after initial diagnosis. In this study, 1093 patients and 1449 samples were analyzed. Using ROC curve analysis, all three methods were able to distinguish between type 1 and type 2 diabetics (Table 1).[21] Random C-peptide also correlated well with both fasting and glucagon-stimulated C-peptide, with r values of 0.78 and 0.77, respectively. These data show that a random C-peptide was slightly but not significantly better than fasting and glucagon stimulated C-peptide for the classification of diabetes mellitus.
The optimum cutoffs identified in this study were 1.5 ng/mL (0.5 nmol/L) for random C-peptide, 1.27 ng/mL (0.42 nmol/L) for fasting C-peptide, and 1.81 ng/mL (0.6 nmol/L) for glucagon-stimulated C-peptide.[21]

Consistent with the Berger et al. study, Bakhtadze et al., in another diabetes classification study, found that patients diagnosed with type 1 diabetes mellitus had significantly lower ($p < 0.0001$) median fasting plasma C-peptide than patients with type 2 diabetes mellitus or diabetes mellitus that was unclassified. The median values were 0.73 ng/mL (0.24 nmol/L) for type 1 diabetes mellitus, 2.24 ng/mL (0.74 nmol/L) for type 2 diabetes mellitus and 1.45 ng/mL (0.48 nmol/L) for unclassified diabetes mellitus. In this study they also tested for the presence of islet cell antibodies and HLA-DRQB1 genotypes, both of which are associated with type 1 diabetes. Type 1 diabetic patients were 3.6 times more likely to have islet cell antibodies (autoantibodies) than were type 2 diabetics. Moreover, patients with islet cell antibodies had markedly lower mean fasting plasma C-peptide levels than those without islet cell antibodies (0.73 ng/mL [0.24 nmol/L] versus 2.1 ng/mL [0.69 nmol/L], $P < 0.0001$). The patients with HLA-DRQB1 genotypes that are associated with a risk for type 1 diabetes mellitus and negative islet cell antibodies also had lower median levels of C-peptide than those without the risk-associated genotypes (1.54 ng/mL [0.51 nmol/L] versus 2.24 ng/mL [0.74 nmol/L]). The authors propose that low C-peptide levels and the presence of a HLA-DRQ1 genotype may be used to differentiate idiopathic type 1 diabetes mellitus (negative for autoantibodies) from type 2 diabetes mellitus, which would not have the HLA-DRQ1 genotype and would have normal or high levels of C-peptide.[22]

Clearly, although there is some overlap, C-peptide levels can be used to discriminate between type 1 and type 2 diabetes mellitus.

C-peptide and subclassification of type 1 diabetes

C-peptide levels may also be able to subclassify type 1 diabetes. C-peptide levels were found by Tanaka et al. to distinguish a subtype of type 1 diabetes mellitus called fulminant type 1 diabetes mellitus. This condition is characterized by an abrupt onset of symptoms, marked hyperglycemia, severe diabetic ketoacidotic coma, normal or near normal HbA1c levels, absence of autoantibodies and involvement of the exocrine pancreas with elevated levels of serum pancreatic enzymes. They recruited 125 patients who met the criteria for type 1 diabetes mellitus as defined by the American Diabetic Association (ADA).
A subset of these patients (n = 25) who were negative for autoantibodies against pancreatic antigens and had HbA1c levels of less than 8.3 percent were diagnosed as having fulminant type 1 diabetes mellitus. The remaining patients were labeled as type 1 diabetes mellitus. They found that the integrated C-peptide levels (∑C-peptide taken at 0, 30, 60, 90 and 120 minutes during an oral glucose tolerance test) were lower in patients with fulminant type 1 diabetes mellitus at onset and at 1 and 2 years after onset than in patients with type 1 diabetes mellitus. Consistent with these results, fasting C-peptide levels at onset for fulminant type 1 diabetics were also lower than fasting C-peptide levels for type 1 diabetes mellitus. ROC curve analysis found an AUC for integrated C-peptide of 0.974 and fasting C-peptide of 0.973 for distinguishing between these two types of diabetes mellitus. The optimum cutoff for integrated C-peptide was less than or equal to 1.63 ng/mL (0.540 nmol/L) and for fasting C-peptide was less than or equal to 0.1 ng/mL (0.033 nmol/L).[23]

Several studies present consistent evidence that supports the use of C-peptide as an aid in the classification of diabetes mellitus and suggests that it might be a useful tool in the management of this disease.

Table 1.
ROC curve analysis results of random, fasting and glucagon-stimulated C-peptide tests.[21]

C-peptide protocol	ROC curve (AUC)	Confidence interval (95%)
Random	0.98	0.97 to 0.99
Fasting	0.91	0.89 to 0.93
Glucagon-stimulated	0.92	0.87 to 0.96

C-peptide used as indicator of glycemic control and declining β-cell function

The Diabetes Control and Complications Trial (DCCT) found that C-peptide levels correlate with overall glycemic control. They analyzed patients on the basis of a mixed meal–stimulated C-peptide levels. Patients with stimulated C-peptide greater than 0.6 ng/mL (0.2 nmol/L) had significantly lower HbA1c levels and were treated with less insulin, indicating better overall glycemic control, as compared to those with levels less than 0.6 ng/mL (0.2 nmol/L) (Table 2). The DCCT found that there was less retinopathy and nephropathy with preserved β-cell function.[1] Thus, in addition to good glycemic control, the preservation of β-cell function is now a therapeutic goal for type 1 diabetes mellitus, and monitoring β-cell function in these patients via C-peptide levels is a rational approach because insulin measurements would be complicated by the presence of exogenous insulin.

While type 1 diabetes mellitus is associated with markedly decreased β-cell function, following β-cell function in type 2 diabetics may also be important since it can decline over the course of the disease. Kim et al. found that type 2 diabetic patients positive for glutamic acid decarboxylase antibodies (GADA) experienced a decline in C-peptide values over 2 years, indicating a decrease in β-cell function. Fasting C-peptide levels

Characteristic	C-peptide ≥0.6–1.51 ng/mL (≥0.2–0.5 nmol/L)	C-peptide <0.6 ng/mL (< 0.2 nmol/L)	*P*
n	138	274	
Age (years)	28.2 ± 6.7	26.1 ± 7.4	<0.007
HbA1c	8.3 ± 1.6	9.2 ± 1.6	<0.001
Insulin (U/kg/day)	0.49 ± 0.20	0.69 ± 0.24	<0.001

Table 2.
A comparison of type 1 diabetics in the DCCT intensive treatment group on the basis of levels of stimulated C-peptide.[1]

decreased from 1.24 ng/mL (0.41 nmol/L) to 0.95 ng/mL (0.31 nmol/L) and stimulated C-peptide from 1.99 ng/mL (0.66 nmol/L) to 1.61 ng/mL (0.53 nmol/L). In patients without GADA, there was no decrease in C-peptide, indicating no decrease in β-cell function.[16] This suggests that a GADA screen in combination with C-peptide measurements can be used to identify a subset of type 2 patients whose disease is progressing and who may need to be treated more aggressively.

Lower C-peptide levels in type 2 diabetics are also associated with insulin treatment. Siraj et al. found lower basal and glucagon-stimulated C-peptide levels in type 2 diabetic patients treated with insulin than in type 2 diabetics not treated with insulin.[20] These data suggest that C-peptide levels might be able to identify type 2 diabetic patients that would be managed better with insulin.

C-peptide and transplant failure

In severe cases of diabetes that have not been managed successfully with insulin, transplantation may be warranted (pancreas or β-cell transplant). After transplantation, monitoring graft function by monitoring β-cell function has been used to detect transplant failure. Transplant failure is typically monitored with measurements of insulin, glucose and C-peptide, and in some protocols graft failure has been defined by a specific level of C-peptide.[24,25]

C-peptide levels are predictive of autoantibodies

Törn et al. have found that C-peptide levels can predict the presence of autoantibodies (defined as the presence of at least one of the following: islet cell antibodies, glutamic acid decarboxylase antibodies or tyrosine phosphatase antibodies). They determined that a random C-peptide value of below 0.91 ng/mL (0.3 nmol/L) had a 94 percent positive predictive value for patients with autoantibodies and a value above 2.42 ng/mL (0.8 nmol/L) had a 72 percent positive predictive value for patients without autoantibodies.[26]

Hypoglycemia

Hypoglycemia is a symptom associated with a wide range of conditions, and a careful history in addition to the appropriate laboratory tests are necessary for its evaluation (Table 3). The population most at risk for hypoglycemia is diabetics, particularly type 1 diabetics. It has been estimated that 10 to 30 percent of these patients have one episode of hypoglycemia requiring third-party assistance per treatment year.[27] In these patients, the cause of hypoglycemia is usually due to insulin overdose, and C-peptide levels would be low in comparison to insulin levels. Thus, C-peptide measurements can be used to confirm the diagnosis. In the evaluation of a nondiabetic patient with hypoglycemia, C-peptide can be a useful aid in narrowing the differential diagnosis.

C-peptide measurements in the evaluation of hypoglycemia are performed in the context of the 72-hour (prolonged) fast, the gold standard procedure. The prolonged fast, generally an inpatient procedure involves repeated measurements of insulin, C-peptide, and glucose (every 6 hours) until glucose levels fall to 40 to 45 mg/dL or symptoms of hypoglycemia develop or until 72 hours have elapsed.[28–30] Elevated C-peptide and insulin levels at the end of the fast point to an insulinoma or sulfonylurea ingestion as the cause for the hypoglycemia, whereas low C-peptide levels and high insulin levels point to exogenous insulin administration as the cause; low glucose with low insulin and C-peptide levels indicate a non-insulin-mediated hypoglycemia. Sulfonylurea drug use can be determined by measurement of the drug in plasma or urine.

Type	Examples
Organ related	Insulinoma, nesidioblastosis, multiple endocrine neoplasia, noninsulinoma pancreatogenic hypoglycemia, severe liver disease, end-stage kidney disease, dialysis, congestive heart failure, acute respiratory failure
Endocrine disorders	Generalized hypopituitarism and hypothalamic deficiency, adrenal failure, hypothyroidism, after removal of pheochromocytoma
Inborn errors of metabolism	Glycogen storage disease, hereditary fructose intolerance, galactosemia, carnitine deficiency, disorders of gluconeogenesis, disorders of mitochondrial β oxidation
Nonislet tumor	Insulin-like growth factor–secreting tumor (mesenchymal tumors, hemangiopericytomas), lymphoma, myeloma, leukemias
Miscellaneous	Sepsis, starvation, total parenteral nutrition, severe excessive exercise
Drug-induced and dietary toxins	Insulin, sulfonylurea, repaglinide, salicylates, paracetamol, quinine, beta-blockers, alcohol, mushrooms, unripe ackee fruit
Reactive hypoglycemia	Post–gastric surgery, alcohol induced

Table 3.
Causes of adult hypoglycemia modified from reference 31.

Insulinoma

An insulinoma is a tumor of the β-cells of the pancreas and it is the most common cause of hypoglycemia due to endogenous hyperinsulinism. Age of onset is generally 40 to 60 years, but insulinomas may present as early as 6 weeks and as late as 70 years. These tumors are typically solitary adenomas and are rarely metastatic. Most are small with 90 percent less than 2 cm in diameter, but they can be as large as 15 cm. Endoscopic ultrasound, transabdominal ultrasound and intraoperative ultrasound are the preferred imaging modalities, but CT, MRI and in some cases PET imaging have also been used. These tumors are hard to localize because of their small size and anatomic location and are typically treated by surgical resection.[32]

Patients present with symptoms of hypoglycemia at irregular intervals and of varying duration. Symptoms include but are not limited to light-headedness, altered mental status and abnormal behavior and commonly occur in the morning after overnight fast, after skipping a meal or after exercise; however, symptoms can occur at other times as well, and patient presentations are variable. Diagnosis of insulinoma typically involves the 72-hour fast.

The C-peptide suppression test can also be used to confirm the diagnosis since elevated insulin during the test is suggestive of insulinoma.[27,28] This test involves the infusion of insulin and the measurement of glucose and C-peptide during the infusion. The basis of the test is the administration of exogenous insulin to suppress endogenous insulin and C-peptide production. Lack of suppression (percent below baseline) is suggestive of endogenous hyperinsulinism likely due to an insulinoma.[27]

Summary

C-peptide is an important, biologically active molecule. Short-term replacement of C-peptide improves some of the complications associated with diabetes mellitus. In addition, type 1 patients who are able to maintain C-peptide levels have fewer complications and better glycemic control. C-peptide measurements play a key role in the evaluation of hypoglycemia and insulinoma, are a useful aid in the classification of diabetes mellitus, and may play a larger role in its management in the future.

Features of C-peptide assays on Siemens immunodiagnostic systems

The C-peptide assay on the IMMULITE® family of platforms has been improved by replacing a competitive rabbit polyclonal format with a murine monoclonal sandwich format. The assay has better specificity with decreased cross-reactivity to proinsulin (10.3 percent versus 15.7 percent). The working range of the assay has been extended from 0.5–7 ng/mL (0.17–2.32 nmol/L) to 0.1–15 ng/mL (0.033–4.97 nmol/L), and the sensitivity is sixfold lower at 0.05 ng/mL (0.017 nmol/L) (Table 4).

Other improvements include a threefold decrease in the sample volume and a 50 percent decrease in incubation time. Time-to-first-result is 42 minutes on the IMMULITE® and IMMULITE® 1000, and 35 minutes on the IMMULITE® 2000 and IMMULITE® 2500. The assay has been developed for use on the entire IMMULITE family of platforms, which makes it accessible to laboratories of all sizes. Performance across all platforms indicates a maximum total CV of 5.5 percent, within-run CV of 3.3 percent, and linearity ranging from 79 percent to 103 percent (Table 5).

Along with the improved C-peptide assay on the IMMULITE family of systems, Siemens offers an 18 minute C-peptide assay on the ADVIA Centaur® platform in a two-site chemiluminescence sandwich format (Table 4 and 5).

Table 4.
A comparison of the ADVIA Centaur C-peptide assay and the old and new C-peptide assays on the IMMULITE platforms.

Key Features	ADVIA Centaur CP and XP Assays	New IMMULITE Assay	Old IMMULITE Assay
Assay code	CpS	PEP	CPE
Sample size	50 µL	25 µL	75 µL
Assay format	Two-site direct chemiluminescence sandwich	Two-site murine monoclonal sandwich	Rabbit polyclonal competitive
Incubation cycles	1 x 7.5 minutes (XP) 1 x 9.66 minutes (CP)	1 x 30 minutes	2 x 30 minutes
Working range	0.05–30 ng/mL	0.1–20 ng/mL	0.5–7 ng/mL
Cross-reactivity with			
Proinsulin 10 ng/mL	See Table 5	10.2%[a]	15.7%[a]
Insulin 200 µLU/mL	See Table 5	ND	ND
Glucagon 15,000 ng/mL	See Table 5	ND	ND

[a]Average across all IMMULITE platforms.
ND = Not detectable

Table 5.
A comparison of C-peptide assays on the IMMULITE and ADVIA Centaur systems. The assays on the IMMULITE family of systems are equivalent enough that the working range in serum is expected to be similar.

System	ADVIA Centaur CP and XP	IMMULITE/ IMMULITE 1000	IMMULITE 2000	IMMULITE 2500
Expected range (95% CI)				
Serum Urine	0.81 - 3.85 ng/mL <156.46 µg/day	Not determined 2.5 – 249 µg/day	0.9–7.1 ng/ml 3.6 – 253 µg/day	Not determined 2.5 –232 µg/day
Linearity	84.1%–119.9%	79%–103%	85%–100%	81%–100%
Within-run CV	3.7% - 4.7% (XP) 3.6% - 7.2% (CP)	1.9%–3.3%	1.7%–2.3%	1.9%–3.2%
Total CV	5.1% - 9.5% (XP) 5.3% - 7.4% (CP)	3.8%–5.5%	3.3%–4.8%	2.9%–5.4%
Sensitivity	0.05 ng/mL (analytical)	0.09 ng/mL (functional)	0.08 ng/mL (functional)	0.08 ng/mL (functional)
High dose hook effect	None up to 200 ng/mL (XP) None up to 140 ng/mL (CP)	None up to 3560 mg/mL		
Hemolysis	None up to 250 mg/dL	None up to 500 mg/mL		
Lipemia	None up to 1000 mg/dL	None up to 3000 mg/mL		
Bilirubin	None up to 20 mg/dL	Unconjugated and conjugated bilirubin up to 200 mg/L may cause a depression in values		
Cross-reactivity with	Recovery (%)	Cross-reactivity (%)	Cross-reactivity (%)	Cross-reactivity (%)
Proinsulin				
IMMULITE 10 ng/mL		10.5	10	10
Centaur 1.25 ng/mL	103.4			
Insulin				
IMMULITE 200 µIU/mL		Not detectable	Not detectable	Not detectable
Centaur 375 µIU/mL	95.8			
Glucagon				
IMMULITE 15,000 ng/mL		Not detectable	Not detectable	Not detectable
Centaur 2.5 ng/mL	96.4			

Method Comparison
The ADVIA Centaur CP method was compared to the Centaur XP method on 346 serum samples and 363 urine samples across the assay range. The relationships are described by the equations below:

Serum Centaur CP = 0.99*Centaur – 0.27 ng/mL, r= 0.98
Urine Centaur CP = 0.98*Centaur + 0.37 ng/mL, r= 0.98

The new C-peptide assay was compared to the old C-peptide assay on the IMMULITE 2000 using 89 serum samples ranging in concentration from 1.2 to 6.9 ng/mL, and using 87 urine samples ranging in concentration from 0.6 to 6.9 ng/mL. The relationships are described by the equations below:

Serum IMMULITE 2000 new assay = 0.94 (Serum IMMULITE 2000 old assay) - 0.30 ng/mL, r = 0.923
Urine IMMULITE 2000 new assay = 1.01 (Urine IMMULITE 2000 old assay) - 0.33 ng/mL, r = 0.969

Type 1 diabetes patients who are able to maintain C-peptide levels have fewer complications and better glycemic control.

Conclusions

- C-peptide measurements have been shown to be a useful aid in the classification of diabetes mellitus, an application that warrants further investigation.
- Short-term C-peptide replacement alleviates the microvascular complications of diabetes mellitus.
- C-peptide measurements play key roles in the laboratory assessment of hypoglycemia and insulinoma.
- The reformulated C-peptide assay for the IMMULITE family of platforms has improved performance characteristics.
- The ADVIA Centaur CP C-peptide method demonstrates excellent agreement with the ADVIA Centaur XP method.

Immunoassay Systems

IMMULITE® 1000 Immunoassay Systems
IMMULITE® 2000 Immunoassay Systems
IMMULITE® 2500 Immunoassay Systems

ADVIA Centaur® XP Systems
ADVIA Centaur® CP Systems
ADVIA Centaur® Classic Systems

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