We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

The Pancreas Secreting Insulin for Decades after Onset of Type I Diabetes — Implications for Care and Management

Denise L. Faustman and Miriam Davis

Additional information is available at the end of the chapter

Abstract

Up until recently, the prevailing dogma was that insulin secretion ceased within a couple of years after the diagnosis of type I diabetes, a clinical time period called the honeymoon. But a series of recent studies have established that release of C-peptide, which is the best measure of endogenous insulin production, can commonly persist for decades after disease onset. The release of C-peptide, even at low levels, is shown to have functional and clinical significance. For example, C-peptide levels >10 pmol/l are associated with fewer diabetes complications, i.e., nephropathy, neuropathy, foot ulcers, and retinopathy. The diabetic population may also be heterogeneous in risk for fall in C-peptide, with early age of diabetes onset a risk factor for more rapid C-peptide decline. The persistence of insulin release for decades and its functional and clinical significance suggest that assays for C-peptide should be a regular part of diabetes management. Furthermore, patients with established diabetes should be eligible to participate in clinical trials of immune therapies since preservation of these low levels appears clinically important to prevent complications.

Keywords: Type 1 diabetes, C-peptide, insulin secretion, complications

1. Introduction

1.1. Background

The reigning view of the type I diabetes field had been until recently that the pancreas commonly stops secreting insulin within a number of years of diagnosis. The so-called honeymoon period post disease onset has been explained to patients since the seminal publication in 1986 by George Eisenbarth on the natural history of diabetes [1]. After the

honeymoon period, patients were cautioned to expect that their pancreas was functionally inactive as it related to insulin secretion and could no longer be saved. An iconic image depicting the rapid demise of islet function as measured by C-peptide, which is cosecreted with insulin, has been a staple for teaching medical students and in continuing education courses for physicians. And the consequence of the honeymoon period has been that patients with established disease are routinely excluded from immune intervention trials. Most, if not all, immunotherapy trials conducted over the past 20 years have excluded all but new-onset cases of type 1 diabetes under the assumption that the pancreas was not salvageable if the disease was past the honeymoon period and all insulin secretion has ceased. Indeed, the current definition of type 1 diabetes by the American Diabetes Association (ADA) is a disease leading to "absolute insulin deficiency" [2].

Despite this dogma, there were clues questioning the view that the pancreas of type 1 diabetics ceases function within a short number of years after diagnosis. There had been histological indications that the islets were not uniformly dead dating back as early as 1902. The pathologist M.B. Schmidt documented the rare existence of intact islet-like structures in an autopsy of a child with type I diabetes [3]. Decades later, several other studies from 1959 to 1985 also documented histologically the existence of occasional intact islet cells among patients at all stages of disease [3-8]. More recent confirmation of histologically intact islet cells comes from several studies [9-12]. Nevertheless, these studies did not prompt questioning of the short honeymoon period because the evidence was only histologic and not accompanied by functional studies. It was thought by the majority that if the insulin-secreting structures could be found they lacked functional insulin secretion since it could not be detected.

An early indication of long-term persistence of insulin release was present in 2008 with an immune interventional trial that compared long-term diabetic serum samples in the traditional C-peptide assays compared to newer more sensitive C-peptide assays. C-peptide assays are the best measures of endogenous insulin secretion. C-peptide is cosecreted with insulin in equimolar amounts by the pancreatic beta-islet cells upon enzymatic cleavage of the prohormone precursor proinsulin. C-peptide is more advantageous to measure than insulin because it is unaffected by exogenous insulin treatment, and because the liver metabolizes much of the insulin secreted into the portal vein, but negligibly metabolizes C-peptide. Insulin's high metabolism by the liver means that peripheral insulin levels may not best reflect portal insulin secretion. C-peptide is also advantageous because its half-life is longer than that of insulin, circulating systemically at concentrations about five times higher. Low C-peptide can be used to distinguish type 1 from type 2 diabetes, the latter marked by high levels of C-peptide early in disease [13].

The immune interventional trial of Bovine Calmette Guerin (BCG) in diabetic patients with established disease (a mean of 15 years) [14] studied fasting and stimulated C-peptides over a 2-year period. A condition of enrollment in the trial was that there was no fasting or stimulated C-peptide as measured by traditional C-peptide assay whose lower limit of detection is about 50 pmol/l. To the surprise of all, at the end of the trial all serum was restudied for C-peptide, this time using ultrasensitive C-peptide assay. All long-term recipients of the immunotherapy,

as well as placebo patients, had low yet detectable levels of C-peptide at baseline both as fasting and stimulated and throughout the course of the trial.

2. Persistence and functional significance of C-peptide

This unexpected finding motivated a systematic study of C-peptide levels in 182 diabetic patients using the ultrasensitive assay. Glycemic levels were also evaluated in a subset of patients—with normoglycemia at <150 mg/dl and hyperglycemia at >150 mg/dl. Samples from hyperglycemic patients had significantly higher C-peptide levels than those with normoglycemia [15]. The study found a linear relationship between glycemic levels and C-peptide, indicating intact islet-cell functioning because higher glycemic levels stimulate release of insulin. Islet-cell function was intact at C-peptide levels as meager as 2.8 pmol/l. These analyses revealed that despite low levels of C-peptide, some islet-cell function remains decades after diagnosis. The release of C-peptide was analyzed according to 5-year disease duration intervals. C-peptide was found above limits of detection in patients with up to 40 years of disease duration (Figure 1). As duration increased, C-peptide levels tended to gradually decline over decades. In order of increasing duration, C-peptide was higher than the detection limit at rates of 78.9% (0-5 years duration), 59.5% (6-10 years duration), 39.5% (11-20 years duration), 39.1% (21-30 years duration), 10% (31-40 years duration), and 0% (>40 years duration). Thus, longer disease duration is related to lower levels of C-peptide production. The long-term persistence of C-peptide release contradicts the traditional model that C-peptide disappears 1-2 years or a short time after diagnosis and contradicts the ADA definition of type 1 diabetes as an absolute deficiency of insulin. Also, it was reported that type 1 diabetics with early age of onset had a faster decay of C-peptide; type 1 diabetics with later onset of diabetes had slower declines in C-peptide. This suggested that there was age-of-onset variability in the diabetic population as related to total loss of pancreas function.

A study by Oram and colleagues [16] soon followed and confirmed the long-term persistence of C-peptide secretion as measured by stimulated urine studies. Studying 74 volunteers, they found that 73% of patients with type I diabetes of more than 5 years duration (median 29 years) had detectable C-peptide as measured by electrochemiluminescence assay (detection limit 3.3 pmol/l). To study function, the investigators conducted a mixed-meal tolerance test. C-peptide levels either rose (n=43) or remained the same (n=11) in response to a meal in all patients with detectable serum C-peptide in urine. The study concluded that most diabetics with long-term disease continue to produce low levels of insulin and that a small number of islet cells are still functional, suggesting that these cells are escaping immune attack or are regenerating. This study was also of note since the measurement of remaining C-peptide was performed using a different C-peptide assay from Wang and colleagues, thus decreasing the chance that these early reports of persistent C-peptide secretion were an artifact of the improved C-peptide monitoring techniques and assays.

Three other investigative teams, reporting in abstract form, uncovered evidence of the long-term persistence of C-peptide production in early 2014. Two of the studies also found increased
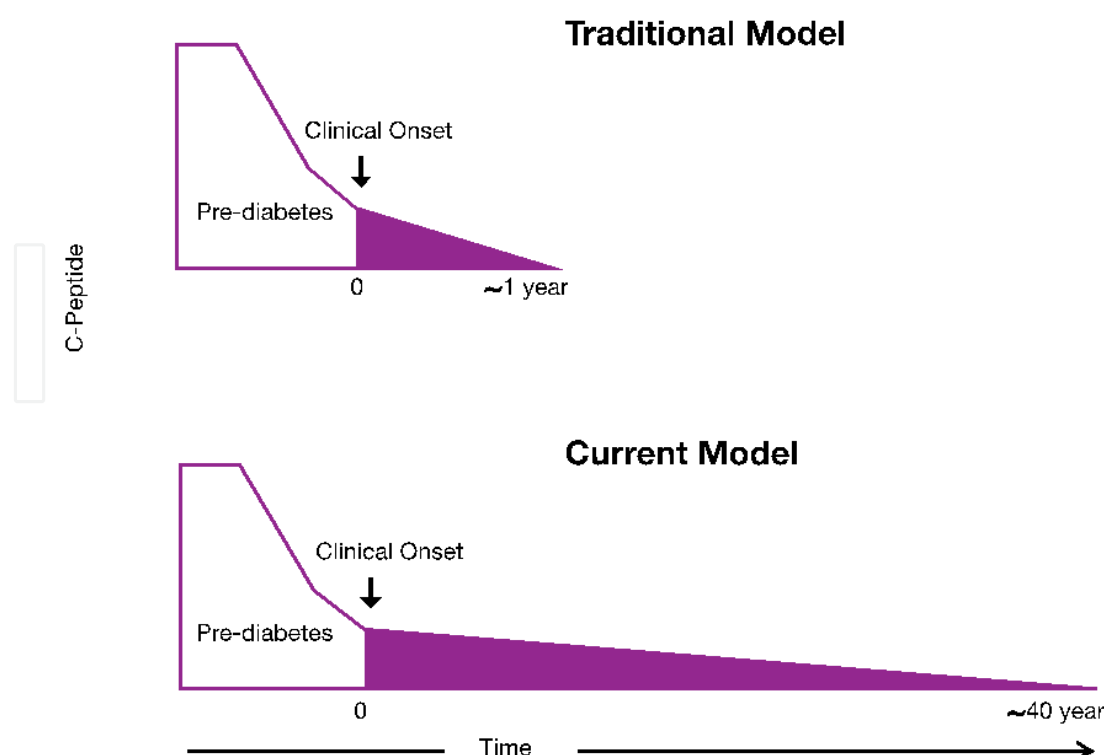
Figure 1. The traditional model of type 1 diabetes predicts the pancreas will stop producing C-peptide within a short time after disease onset, typically 1-3 years. New data now show that a typical course of type 1 diabetes is the long-term persistence of C-peptide for decades in many type 1 diabetic subjects.

output of C-peptide after a mixed-meal tolerance test [17, 18]. The third study was large: it recruited 944 patients in a population-based study design, finding insulin secretion in long-duration type 1 diabetics, but the study did not examine islet-cell function [19].

More recently, in late 2014, the rapidly expanding literature confirmed the frequent and long-term persistence of C-peptide for decades after the onset of type 1 diabetes. McGee and colleagues evaluated whether clinically relevant concentrations of stimulated C-peptide can be detected after 30 years in the Diabetes Control and Complications Trial (DCCT) cohorts. Studying 58 participants, 17% of the enrolled subjects had a definitive response with stimulated C-peptide greater than 30 pmol/L [20]. Using nonfasting random C-peptides, Davis and colleagues detected 29% of 919 individuals with remaining C-peptide with a lower limit of sensitivity of 20 pmol/L in a C-peptide assay [21].

What protects or places at risk type 1 diabetic subjects for improved preservation of C-peptide? In 1978, Madsbad and colleagues reported on the prevalence of residual beta cell function in insulin-dependent diabetics in relation to age of onset and duration (21). In 1987, two research groups found similar associations of early age of onset associated with faster decay of C-peptide immediately after diabetes onset [22, 23]. Wang and colleagues, using C-peptide assays with lower limits of detection to 2.5 pmol/L combined with a decades-long evaluation of the full disease course, confirmed that age of onset was related to long-term preservation for up to 40 years after diagnosis [15]. Ludvigsson and colleagues studied the decline of C-peptide

during the first year after diagnosis of type 1 children and adolescents and reported a faster decline of C-peptide in younger subjects [24]. Barker and colleagues, in a large 3,668 subject study for 5 years after diagnosis, more recently demonstrated age at diagnosis of type 1 diabetes was a strong correlate of a more rapid decline of C-peptide function, with young children again losing pancreas insulin secretion at more rapid rates [25]. Therefore, a very clear protective factor for a slow C-peptide decay is older age of onset, and a very clear risk factor for rapid decline in C-peptide is younger age of onset. The only exception to this reproducible trend is with age of onset of diabetes greater than 40 years of age: C-peptide again starts to decay faster and these subjects are also notable for the majority having long-standing hypothyroidism prior to diabetes onset [15].

Should it have been known earlier that the ADA definition of "absolute insulin deficiency" of type 1 diabetes was wrong, especially as it relates to residual C-peptide over decades, not just variable fall in C-peptide close to onset? It was known from the Joslin 50-year Medalist Study that some fortunate type 1 diabetics that lived for at least 50 years with this disease were also blessed with random C-peptide levels greater than 30 pmol/L [12]. Still it was viewed that these very fortunate type 1 diabetics were the exception. These data reinforced early the concept that residual C-peptide was associated with better HbA1c and longevity. Again, using less sensitive assays with cutoff values of 40-50 pmol/L it was known from the DCCT that only 11% of patients screened by stimulated C-peptide measurements had any C-peptide at 2 years after diagnosis [26]. As mentioned earlier, for nearly 100 years histologic studies had uncovered islet-like structures consistent with the insulin-secreting cells of the pancreas, but without accompanying functional data of insulin secretion it was difficult to interpret the findings.

3. Do low levels of C-peptide have clinical significance?

Low levels of C-peptide may be produced but do they have any clinical significance? The answer to the question is a resounding yes, according to recently study that was published [27]. First, the 8-year study replicated—in a much larger sample (n = 1273) than an earlier study—the findings that the pancreas continued to produce C-peptide for decades after diagnosis was confirmed. The study also found that fasting C-peptide output, above as low as 10 pmol/L, is associated with fewer diabetes-related complications (e.g., nephropathy, neuropathy, and cardiovascular disease). Low levels of C-peptide were also associated with poorer metabolic control, as captured by HbA1c. The study found that the lowest levels of C-peptide were associated with severe hypoglycemia. Finally, all levels of measurable C-peptide were responsive to fluctuations in blood glucose levels as assessed by 1,5-Anhydroglucitol, a marker responsive to glucose fluctuations. This study complements the work of Lachin and colleagues that restudied the DCCT subjects, albeit with older C-peptide assays with less sensitivity and lower limits of sensitivity to 40-50 pmol/L [28]. Regardless, both fasting and stimulated C-peptide remaining levels were associated in a linear manner to prevention of complications. This resulted in a conclusion that preservations of stimulated C-peptide greater than 200 pmol/L has clinical benefit. The Kuhtreiber study suggests that preservation of fasting C-peptide to the new lower limits of detection of 2.5 pmol/L is even clinically significant.

The studies finding the long-term persistence of C-peptide help to interpret two puzzling scientific observations published more than 15 years ago. The first observation was in identical twins who were discordant for type I diabetes for greater than 20 years who received a hemi-pancreas transplant from the identical twin [29]. Within several weeks, the half-pancreas transplant from the healthy twin to the diabetic twin failed. This was unexpected, because transplants normally are rejected after years, not weeks. The fact that the diabetic twin mounted an aggressive autoimmune response decades after disease onset and after the pancreas was thought to be dead indicates functional islet cells still capable of provoking an autoimmune response. The second observation related to B-lymphocytes: 67% of patients with disease duration of 10 years were positive for at least one diabetes-associated autoantibody and 42% of patients tested positive for 2 to 3 autoantibodies [30]. This finding can now be explained by a primed immune cell attack against residual islet-cell regeneration or long-term survival.

4. Conclusions

The weight of the evidence from several recent studies now points to viable and functional islet cells in long-term type 1 diabetes and should refute therapeutic nihilism that, after a short time after diagnosis, most type 1 diabetics have a pancreas that can no longer produce any insulin. Instead, low-level insulin release can commonly persist for decades after disease onset and has functional and clinical significance. Insulin release is best measured by C-peptide, which is cosecreted with insulin by the beta cells in the islets. C-peptide is preferable to studying remaining insulin secretion because it is unaffected by exogenous insulin treatment and now more sensitive assays allow better limits of detection. Maintenance of even low levels of C-peptide is associated with fewer diabetic complications, better metabolic control (as captured by HbA1c), and is associated with less severe hypoglycemia. The functional and clinical significance of even low levels of C-peptide release suggests that patients should be monitored routinely for C-peptide output combined with other clinical monitors of residual insulin production. The evidence of viable and functional islet cells decades after diagnosis of type 1 diabetes and their protection against diabetic complications also suggest that patients with long-standing disease should not be excluded from immunotherapy clinical trials.

Author details

Denise L. Faustman[1,2]* and Miriam Davis[1]

*Address all correspondence to: faustman@helix.mgh.harvard.edu

1 Immunobiology Laboratory, Massachusetts General Hospital, Boston, MA, USA

2 Harvard Medical School, Boston, MA, USA

References

[1] Eisenbarth GS (1986) Type I diabetes mellitus: a chronic autoimmune disease. *New Engl J Med*. 314: 1360-1368.

[2] American Diabetes A (2014) Standards of medical care in diabetes–2014. *Diabetes Care* 37 Suppl 1: S14-S80.

[3] Schmidt MB (1902) Uber die Beziehung der Langerhans' schen Inseln des Pankreas zum Diabetes Mellitus. *Munch med Wochenschr* 49: 51-54.

[4] Maclean N and Ogilvie RF (1959) Observations on the pancreatic islet tissue of young diabetic subjects. *Diabetes* 8: 83-91.

[5] Gepts W (1965) Pathologic anatomy of the pancreas in juvenile diabetes mellitus. *Diabetes* 14: 619-33.

[6] Doniach I and Morgan AG (1973) Islets of Langerhans in juvenile diabetes mellitus. *Clin Endocrinol* (*Oxf*) 2: 233-48.

[7] Junker K, Egeberg J, Kromann H and Nerup J (1977) An autopsy study of the islets of Langerhans in acute-onset juvenile diabetes mellitus. *Acta Pathol Microbiol Scand A* 85: 699-706.

[8] Foulis A (1985) Autumn Books: Bernard on le pancreas. *Br Med J* (*Clin Res Ed*) 291: 1182.

[9] Meier JJ, Bhushan A, Butler AE, Rizza RA and Butler PC (2005) Sustained beta cell apoptosis in patients with long-standing type 1 diabetes: indirect evidence for islet regeneration? *Diabetologia* 48: 2221-8.

[10] Willcox A, Richardson SJ, Bone AJ, Foulis AK and Morgan NG (2009) Analysis of islet inflammation in human type 1 diabetes. *Clin Exp Immunol* 155: 173-81.

[11] Atkinson MA and Gianani R (2009) The pancreas in human type 1 diabetes: providing new answers to age-old questions. *Curr Opin Endocrinol Diabetes Obes* 16: 279-85.

[12] Keenan HA, Sun JK, Levine J, Doria A, Aiello LP, Eisenbarth G, Bonner-Weir S and King GL (2010) Residual insulin production and pancreatic ss-cell turnover after 50 years of diabetes: Joslin Medalist Study. *Diabetes* 59: 2846-53.

[13] Jones AG and Hattersley AT (2013) The clinical utility of C-peptide measurement in the care of patients with diabetes. *Diabet Med* 30: 803-17.

[14] Faustman DL, Wang L, Okubo Y, Burger D, Ban L, Man G, Zheng H, Schoenfeld D, Pompei R, Avruch J and Nathan DM (2012) Proof-of-concept, randomized, controlled clinical trial of Bacillus-Calmette-Guerin for treatment of long-term type 1 diabetes. *PLoS One* 7: e41756.

[15] Wang L, Lovejoy NF and Faustman DL (2012) Persistence of prolonged C-peptide production in type 1 diabetes as measured with an ultrasensitive C-peptide assay. *Diabetes Care* 35: 465-70.

[16] Oram RA, Jones AG, Besser RE, Knight BA, Shields BM, Brown RJ, Hattersley AT and McDonald TJ (2014) The majority of patients with long-duration type 1 diabetes are insulin microsecretors and have functioning beta cells. *Diabetologia* 57: 187-91.

[17] Bingley PJ, Aitken RJ, Wilson IV, Long AE, Williams AJK, McDonald TJ, Wong S, Hattersley AT and Gillespie KM (2014) Residual beta cell function in long-standing childhood onset type 1 diabetes. *Diabetologia* 57: S189-S190.

[18] Tamer G, Dogan B, Ocakoglu I, Kostek O, Kartal I, Sagun G, Adas M, Tamer I, Mutlu HH and Orhun A (2014) Functioning beta cells in type 1 diabetes may not be as low as it is presumed. *Diabetologia* 57: S189.

[19] McDonald TJ, Oram R, Shields B, Pearson E and Hattersley A (2014) Most people with long duration of type 1 diabetes are insulin microsecretors and produce their own endogenous insulin. *Diabetologia* S510:

[20] McGee P, Steffes M, Nowicki M, Bayless M, Gubitosi-Klug R, Cleary P, Lachin J, Palmer J and Group DER (2014) Insulin secretion measured by stimulated C-peptide in long-established Type 1 diabetes in the Diabetes Control and Complications Trial (DCCT)/ Epidemiology of Diabetes Interventions and Complications (EDIC) cohort: a pilot study. *Diabet Med* 31: 1264-8.

[21] Davis AK, DuBose SN, Haller MJ, Miller KM, DiMeglio LA, Bethin KE, Goland RS, Greenberg EM, Liljenquist DR, Ahmann AJ, Marcovina SM, Peters AL, Beck RW, Greenbaum CJ and for the TDECN (2015) Prevalence of detectable C-peptide according to age at diagnosis and duration of Type 1 diabetes. *Diabetes Care* 38:476-81

[22] DCCT (1987) Effects of age, duration and treatment of insulin-dependent diabetes mellitus on residual beta-cell function: observations during eligibility testing for the Diabetes Control and Complications Trial (DCCT). *J Clin Endocrinol Metab* 65: 30-6.

[23] Giordano C, Galluzzo A, Panto F, Caruso C and Bompiani G (1987) Prevalence of residual B-cell function related to age at onet and genetic profile in newly diagnosed type 1 diabetics. *Acta Diabetol* 24: 317-323.

[24] Ludvigsson J, Carlsson A, Deli A, Forsander G, Ivarsson SA, Kockum I, Lindblad B, Marcus C, Lernmark A and Samuelsson U (2013) Decline of C-peptide during the first year after diagnosis of Type 1 diabetes in children and adolescents. *Diabetes Res Clin Pract* 100: 203-9.

[25] Barker A, Lauria A, Schloot N, Hosszufalusi N, Ludvigsson J, Mathieu C, Mauricio D, Nordwall M, Van der Schueren B, Mandrup-Poulsen T, Scherbaum WA, Weets I, Gorus FK, Wareham N, Leslie RD and Pozzilli P (2014) Age-dependent decline of be-

ta-cell function in type 1 diabetes after diagnosis: a multi-centre longitudinal study. *Diabetes Obes Metab* 16: 262-7.

[26] Steffes MW, Sibley S, Jackson M and Thomas W (2003) Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. *Diabetes Care* 26: 832-6.

[27] Faustman DL, Kuhtreiber WM, Washer SLL, Hsu E, Zhao M, Reinhold PE, Burger DE and Zheng H., Faustman DL (2015) Low levels of C-peptide production protect from complications and improve HbA1c control in long-standing type 1 diabetes. Diabetic Medicine DOI: 10.1111/dme.12850.

[28] Lachin JM, McGee P, Palmer JP and Group DER (2014) Impact of C-peptide preservation on metabolic and clinical outcomes in the Diabetes Control and Complications Trial. *Diabetes* 63: 739-48.

[29] Sutherland DE, Sibley R, Xu XZ, Micheal A, Srikanta AM, Taub F, Najarian J and Goetz FC (1984) Twin-to-twin pancreas transplantation: reversal and reenactment of the pathogenesis of type I diabetes. *Trans Assoc Am Phys* 97: 80-87.

[30] Savola K, Sabbah E, Kulmala P, Vahasalo P, Ilonen J and Knip M (1998) Autoantibodies associated with Type I diabetes mellitus persist after diagnosis in children. Diabetologia 41: 1293-7.