Journal of Diabetes Mellitus, 2015, 5, 21-27
Published Online February 2015 in SciRes. http://www.scirp.org/journal/jdm
http://dx.doi.org/10.4236/jdm.2015.51003

Progressive β Cell Failure in Type 2 Diabetes Mellitus: Microvascular Pancreatic Isletopathy?*

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Received 11 November 2014; revised 13 December 2014; accepted 22 December 2014

Academic Editor: Sharma S. Prabhakar, Texas Tech University Health Sciences Center, USA

Abstract

Background: UKPDS suggested relentless deterioration of β cell function as a part of natural course of type 2 diabetes mellitus. However, the course was apparently not universal since many patients maintained glycemic goal (HbA1c < 7.0%) at 9 years while receiving conventional life style programs consisting of diet and exercise or/and oral agents. Moreover, β cell failure occurred around the same time as the time of onset of microvascular complications. Finally, the exact mechanism of progressive β cell failure remains to be defined. It is plausible that β cell failure may be due to fibrosis of pancreatic islets secondary to microangiopathy since no organ or tissue is exempt from this complication. Objective: To assess epidemiologic correlation between presence of β cell failure and microvascular complications by determining the prevalence of β cell failure in subjects with type 2 diabetes with increasing number of known microvascular complications. Methods: 650 Subjects with ages 40 - 75 years and duration of DM 4 - 23 years were divided into 4 groups according to number of microvascular complications, e.g. retinopathy, nephropathy, and neuropathy. β cell failure (β − ve) is defined as HbA1c > 7.0% with any therapy or HbA1c ≤ 7.0% with insulin, either monotherapy or in combination with oral agents. β cell function is deemed "preserved" (β + ve) with HbA1c < 7.0% with treatment consisting of life style program or/and oral drugs. Results: Prevalence of β cell failure progressively rose with increasing number of microvascular complications from 0 to 2 with no further significant rise with 3 complications whereas subjects with preserved β cell function declined with increasing number of microvascular

*The study was presented in part at International Diabetes Federation Meeting in Dubai, UAE in December 2011.
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How to cite this paper: Kabadi, U.M., Kabadi, M.U., Weber, S., Bubolz, A. and Finnerty, E. (2015) Progressive β Cell Failure in Type 2 Diabetes Mellitus: Microvascular Pancreatic Isletopathy? *Journal of Diabetes Mellitus*, **5**, 21-27.
http://dx.doi.org/10.4236/jdm.2015.51003

complications ($p < 0.01$ for both groups). Significant relationships were also noted between the age and the duration of diabetes and prevalence of β cell failure ($p < 0.01$). The relative risks rose progressively for β cell failure/β cell preserved with increasing number of microvascular complications as well as the greater duration of Diabetes. However, a significantly ($p < 0.01$) higher relative risk for β cell failure persisted for rising number of microvascular complications even after eliminating the influence of age and duration of diabetes. Conclusion: β cell failure may be a manifestation of microvascular pancreatic isletopathy similar to other microvascular complications.

Keywords

Type 2 Diabetes, Beta Cell Failure, Pancreatic Isletopathy

1. Introduction

UKPDS suggested relentless deterioration of β cell function as a part of natural course of type 2 diabetes mellitus [1]-[3]. However, beta cell function rose promptly from 50% at diagnosis to 80% following treatment with sulfonylureas indicating induction of reversal in early duration in the course of the disease [4]. Several early studies have also demonstrated that sulfonylurea drugs improve insulin secretion and thus beta cell function in subjects with type 2 diabetes in the initial stage of the disorder [5] [6]. And more recently, other newer secretogogues; e.g., DPP4 Inhibitors and GLP1 analogs are also well documented to improve insulin secretion [7]-[13]. Thus, the decline in beta cell function noted at the time of diagnosis is apparently reversible. Moreover, several recent studies have documented apparent reversal of beta cell failure by reduction in the daily dose or even elimination of the requirement of insulin and/or oral antihyperglycemic drugs while attaining and maintaining desirable glycemic control following bariatric surgery in morbidly obese subjects with type 2 diabetes [14]-[16]. Similarly, reinitiation of oral agents and implementation of life style intervention including an appropriate diet and exercise with induction of weight loss also lowers the daily dose of insulin or eliminates the need for insulin in morbidly obese subjects with type 2 diabetes [17]-[22]. Therefore, these studies indicate that beta cell failure may not be irreversible even after prolonged duration of the disorder as emphasized in UKPDS but may actually be reversible. Finally, progressive beta cell failure suggested in UKPDS may be apparent rather than real because the gradual increase in the daily dosage of oral agents and insulin or need for use of multiple drug combinations required to maintain desirable glycemic control with increasing duration of diabetes may be actually secondary to rising insulin resistance due to weight gain [2] [3]. A similar observation was also noted in another "Adopt" clinical trial [23]. Finally, maintenance of desirable glycemic control (HbA1c $\leq$ 7%) at 9 years in 25% of patients treated with SUs, 13% in metformin group and 11% managed with conventional program with life style intervention alone suggest that progressive beta cell failure may not be universal [24]. Therefore, progressive β cell failure is neither universal, nor total, nor permanent and actually may be reversible. However, the exact mechanism of progressive β cell failure remains to be defined. It is plausible that β cell failure may be secondary to microangiopathy of the islets resulting in reduction in the number of β cells as well as deranged function of the remnant since no organ or tissue is exempt from this complication. Moreover, in UKPDS, β cell failure as reflected by rising HBA1c > 7.0 on oral agents occurred around the same time as the time of onset of microvascular complications [1] [2]. Therefore, we examined epidemiologic correlation between presence of β cell failure and well established microvascular complications.

2. Subjects and Methods

A retrospective study was conducted with a review of records of 650 subjects, 400 men and 250 women with a diagnosis of type 2 diabetes attending a diabetes clinic at Veterans Affairs Medical Center, Phoenix, Arizona between January and June 1996 as well as at Endocrinology clinic at University of Iowa Hospitals and Clinics, Iowa City, Iowa between October 1998 and June 1999. The study protocol was approved by research and development committees as well as institutional review boards at both institutions. We recorded the age, the duration of type 2 diabetes, HbA1c levels, treatment regimen consisting of life style modification consisting of diet and exercise or/and oral hypoglycemic agents (OHA) or/and insulin, as well as the presence of diabetes related microvascular complications: Neuropathy Retinopathy and Nephropathy.

The subjects were divided into 4 groups according to the number of microvascular complications: 0) no complication; 1) one complication; 2) 2 complications and 3) 3 complications. Furthermore, the subjects were also divided into 2 further sub groups according to their β cell function: 1) β cell failure (β − ve) defined as HbA1c > 7.0% with any therapy or HbA1c ≤ 7.0% with insulin, either monotherapy or in combination with oral agents and 2) β cell function "preserved" (β + ve) with HbA1c ≤ 7.0% while receiving treatment consisting of lifestyle intervention including diet and exercise or/and oral drugs. Statistical methods used were continuous data analysis by parametric procedures including Student's t-test, ANOVA and as assessment of relative risks. Frequency distributions were analyzed by Chi Square procedures. Univariate and multivariate analyses were conducted for determining relative risks between two and multiple variable factors respectively. Statistical significance was defined as $p < 0.05$.

3. Results

The mean age of the subjects was 61 ± 12 years with the subjects with beta cell failure being significantly ($p < 0.01$) older, 70 ± 8 years in comparison to subjects with preserved beta cell function, 52 ± 5 years. However, no significant correlation was observed between age and beta cell failure The average duration of type 2 diabetes for the entire cohort was 12.2 ± 8.7 years (range 5 - 45 years).However, the average duration of diabetes was significantly longer ($p < 0.001$) in patients with beta-cell failure when compared with subjects in whom beta cell function was preserved (**Figure 1**). Moreover, although no significant correlation was evident between the duration of diabetes on one aspect and number of subjects with beta cell failure on the other, beyond the duration of nine years, number of subjects with beta cell failure were significantly higher than the number of subjects with preserved beta cell function (**Table 1**). Finally, a distinct relationship was evident between the integrity of beta cell function and presence of microvascular complications (**Table 2**). The majority of subjects with no known microvascular complications manifested preserved beta cell function and the number of these subjects declined with increasing number of microvascular complications (**Table 2**). On the other hand, the number of subjects with beta cell failure progressively rose with increasing number of microvascular complications from 0 to 2 with no further significant rise with 3 complications (**Table 2**). Furthermore, the number of subjects with beta cell failure were significantly greater than number of subjects with preserved beat cell function even in presence of a single microcrovascular complication (**Table 3**). Finally, the relative risks progressively rose for the ratio, β cell failure/β cell preserved with increasing number of microvascular complications as well as the duration of diabetes (**Table 2**). However, the relative risks remained significantly higher for β cell failure with increasing number of complications even after eliminating the influence of age of the subjects and the duration of diabetes; RR ± CI vs 0 complication; 2.1 ± 0.2 for 1 complication; 3.1 ± 0.4 for 2 complications; 3.0 ± 0.3 for 3 complications ($p < 0.01$ for all correlations).

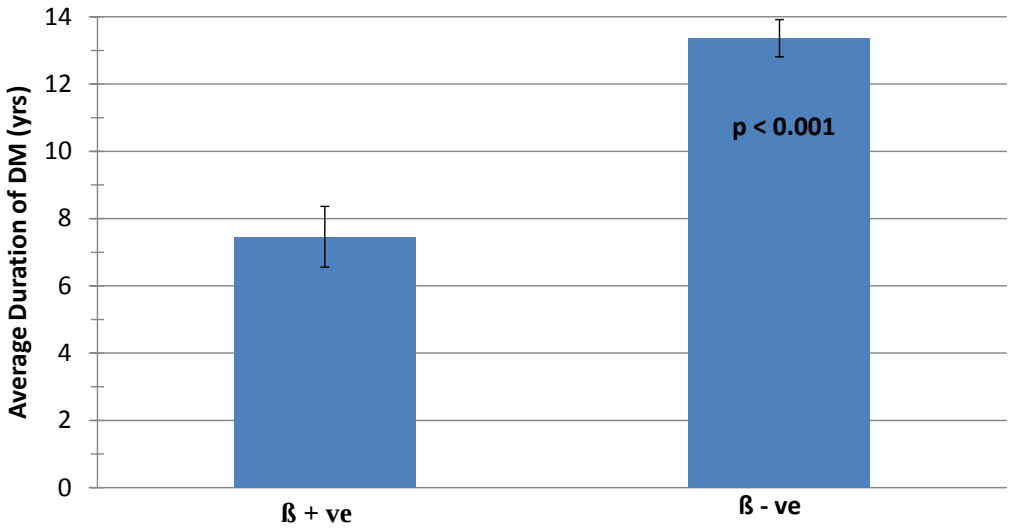

Figure 1. Duration of diabetes in subjects with preserved beta cell function (β + ve) and with Beta cell Failure (β − ve).

Table 1. Number of subjects (%) with preserved beta cell function (β + ve) and beta cell failure (β − ve) as well as proportion of β – ve/β + ve in groups divided according the duration (years) of type 2 Diabetes.

Beta cell function	0 - 9	10 - 19	20 - 29	>29
β + ve	72	18	6	2.0
β − ve	40	32	22	6.0
β − ve/β + ve	0.55	1.8*	3.6†	3.0†
RR ± CI‡		3.3 ± 0.39†	6.5 ± 0.84†	5.7 ± 0.68†

*p < 0.01 vs. group 0; †p < 0.001 vs. group 0; ‡RR (relative risk) ± CI (confidence interval) for β − ve/β + ve.

Table 2. Number of subjects with preserved beta cell function (β + ve) and beta cell failure (β − ve) as well as proportion of β − ve/ β + ve in groups divided according to number of microvascular complications (MC). % of patients are shown in parentheses.

No. of MC	0	1	2	3
β + ve	193 (65)	67 (34)*	12 (13)†	9 (14)†
β − ve	105 (35)	127 (66)*	83 (87)†	54 (86)†
Total	298 (100)	194 (100)	95 (100)	63 (100)
β − ve/β + ve	0.65	1.9*	6.7	6.2
RR ± CI‡		3.0 ± 0.22*	10.3 ± 0.77†	9.5 ± 0.65†

*p < 0.01 vs. group 0; †p < 0.001 vs. group 0; ‡RR (relative risk) ± CI (confidence interval) for β – ve/β + ve.

Table 3. Prevalence of individual microvascular complication (neuropathy, retinopathy, nephropathy) in subjects with type 2 diabetes divided according to beta cell function*.

Beta cell function	Neuropathy	retinopathy	Nephropathy
Beta cell preserved	23%	12%	15%
Beta cell failure	49%†	33%†	27%†

*Some patients manifested more than one microvascular complication. (**Table 1**) †p < 0.01.

4. Discussion

Progressive beta cell failure has been proposed to be the natural course of the disorder of type 2 diabetes [1]-[3]. However, the pathophysiologic mechanism of the progressive beta cell failure remains to be elucidated. A recent publication focused on several hypotheses regarding possible mechanisms and recommended a direction for future research [25]. Another recent study proposed oxidative stress to play a major role in induction of decline of beta cell mass via several mechanisms [26]. The average duration of diabetes in this study [26] in subjects with beta cell failure of almost 10 years is similar to the duration of diabetes over 9 years in the majority of subjects with beta cell failure in our study which demonstrated that beta cell failure may be related to the duration of diabetes as well. However, the prevalence of microvascular complications in this study [26] is not documented. We believe that the relationship between aging and duration of diabetes on one hand and beta cell failure on the other is similar to relationships between these 2 factors on one aspect and onset and progression of microvascular complications on the other [27]-[29]. Moreover, the progressive rise in number of subjects with beta cell failure and a gradual decline in number of subjects with preserved beta cell function with increasing number of microvascular complications noted in this study may indicate a distinct epidemiological relationship between beta cell failure and microvascular complications. Therefore, it is plausible that progressive beta cell failure may also be a microvascular complication involving beta cells themselves or pancreatic islets. We believe that onset and progression of beta cell failure may be secondary to by fibrosis of beta cells or pancreatic islets caused by a disruption of blood supply due to occlusion or narrowing of microvasculture of the islets as documented in an autopsy study [30]. The same mechanism may be responsible for oxidative stress in islets described in another

study [26].

Pathogenesis of microvascular complications in diabetes is attributed to deposition of advanced glycated products [31]-[33]. Deposition of Amylin, an Amyloid, a glycoprotein in pancreatic islets documented in type 2 DM [34] [35] may be similar to deposition of advanced glycated products causing microvascular involvement in other tissues and therefore may also be a causative factor in inducing fibrosis of pancreatic islets (isletopathy) with consequential reduction in beta cell mass and therefore insulin secretion.

Prevention or delay in onset of micrvascular complications by attaining and maintaining desirable glycemic control in both type 1 and type 2 diabetes is well established [36]-[42]. Therefore, achieving and preserving desirable glycemic control may also prevent and delay occurrence of beta cell failure "microvascular pancreatic isletopathy" as documented recently in subjects with type 2 diabetes treated with oral agents or insulin glargine over a 6 year period [36]-[42]. This hypothesis is also consistent with the documentation of a significantly longer period of preserved beta cell function (Honey moon Period) in subjects with type 1 diabetes in DCCT [43]. Moreover, persistent preserved beta cell function in many subjects with type 2 diabetes for upto 9 years noted in UKPDS adds credence to our hypothesis of "pancreatic isletopathy" [24]. Finally, a documentation of islet cell fibrosis in post mortem examination in subjects with type 2 diabetes [30] may be a further evidence of "macrovascular pancreatic isletopathy".

Therefore we propose that the onset and progression of beta cell failure in type 2 DM may be attributed to microvascular disease of the Pancreatic Islets (Isletopathy), similar to other microvascular complications and therefore may be influenced by glycemic control.

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