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Pancreatic duct hyperplasia/dysplasia in type 1 diabetes and pancreatic weight in individuals with and without diabetes. Reply to Kobayashi T, Aida K, Fukui T et al [letter] and Saisho Y [letter]

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To the Editor

We thank the Editor for providing the opportunity to respond to comments made in a letter by Dr Kobayashi et al [1] regarding our recent short communication noting that relative pancreas weight ratios (ratio of pancreas weight to body weight) allows for comparison between children and adults with type 1 diabetes [2].

Kobayashi et al conclude from their own studies that patients with slowly progressive diabetes have reduced pancreas weight compared with those with the more acute onset form. Unfortunately, we were unable to document such a difference since there is great difficulty in distinguishing subtypes so many years post diagnosis. It is clear that there is marked heterogeneity in type 1 diabetes, with age, geographical, genetic and environmental factors likely representing important contributors [3, 4]. What ‘slowly progressive diabetes’ represents outside the Japanese population remains the subject of debate. This subgroup had been given various names including ‘type 1.5 diabetes’, ‘autoimmune diabetes in adults’ and ‘slow-onset diabetes in adults’ even before the latent autoimmune diabetes in adults (LADA)

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The authors declare that there is no duality of interest associated with this manuscript.

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acronym was coined to describe autoantibody-positive patients who were initially diagnosed with type 2 diabetes [5].

With this background of controversies and confusion with respect to diabetes classification terminologies, the natural question is one of how diabetes is defined in our investigational studies? In this work, patients are classified by a board-certified endocrinologist (D. Schatz) based on chart records, as well as standard clinical (ADA) criteria and evaluation of laboratory studies including islet autoantibodies, HLA and C-peptide levels prior to histopathological studies [6]. Consistent with the field, no unified criteria are reported for LADA, although three factors are commonly considered: positivity for GAD autoantibodies (GADA), age >35 years at onset and non-insulin therapy in the first 12 months after diagnosis [5].

Although Kobayashi et al reported that those identified as having LADA had significantly reduced pancreas weights compared with acute type 1 diabetes (29.8 ± 8.2 vs 42.1 ± 7.3 g, respectively) [1], it would be of interest if the authors had compared the relative pancreas weights of their two subgroups to those reported for Network for Pancreatic Organ donors with Diabetes (nPOD) organ donors. This might have allowed for better comparisons between the two studies. From our own examination, four donors exist in the nPOD biobank with Asian ethnicity of which three have pancreas weight data. Two were diagnosed as having type 2 diabetes and included in the type 2 diabetes donor set in our paper [2] while the third donor was pregnant at the time of death.

We believe it helpful to compare some reported clinical features between the two studies. Significant differences appear for age between the nPOD organ donors with type 1 diabetes and the patients reported in the Kobayashi et al letter (32.2 ± 16.2 years vs 60 ± 9 years, respectively) [1, 2]. In our recent *Diabetologia* paper [2], donors ranged from neonates to 59 years of age thus, making raw pancreas weights impossible to compare. Using raw pancreas weights from nPOD organ donors older than 18 years of age [7], we find significant overlap between donors with type 1 diabetes (any subtype) and those without diabetes in both studies (Table 1). This is critical to the argument by Kobayashi et al relating to the mixing of type 1 diabetes subgroups in our paper [2]. In a previous paper reporting ductular lesions studied by endoscopic retrograde pancreatography [8], the authors used different definitions: insulin-dependent diabetes mellitus (IDDM), islet cell antibody (ICA)-positive non-insulin-dependent diabetes mellitus (NIDDM), and ICA-negative NIDDM. The latter were unlikely to have clinical type 1 diabetes given their lack of insulin dependence.

Another comment by Kobayashi et al related to pancreases with reduced weights having lobular differences [9, 10]. It is unclear what issues are under dispute, according to these authors, as both referenced papers provided clear examples of lobular heterogeneity in CD8⁺ cell infiltration and HLA MHC Class I hyperexpression, respectively. Furthermore, lobular heterogeneity has been extensively reported in type 1 diabetes for residual beta cells and insulinitis (for example [11–13]).

The ductal epithelial hyperplasia/dysplasia (DEHD) lesion shown in Fig. 1 of the Kobayashi et al letter may be termed pancreatic intraepithelial neoplasia (PanIN) by others, with the

classification of the lesion as PanIN-1 [14]. As noted by the authors, such lesions are common in aged pancreases, particularly in those with obesity and fatty pancreatic infiltration; although, the actual incidences are dependent on the number of blocks and pancreas regions examined [15]. These lesions are also found in pancreases with pancreatic neuroendocrine adenomas, as previously published in a subset of the nPOD donor population with type 2 diabetes [16]; these type 2 diabetic donors were included in the paper on relative pancreas weights [2].

We would also take this opportunity to respond to a letter from Dr Saisho regarding our study [17]. We are thankful for his review as we are aware of his paper on pancreas weights and volumes [18]. Dr Saisho reports observing proportional increases in pancreas volume as determined by computerised tomography (CT) in both the pancreatic parenchyma and fat components during childhood but that the fat/parenchyma ratio increased in adulthood. Moreover, their study found that pancreas volume decreased after age ~60 years. The excellent and agreed-upon points are made that the volume of pancreas components may be different between childhood and adulthood and that our control donors did not include those over 60 years of age. We also agree that our study examined pancreas weight without division of fat and parenchyma compartments. While the weight of parenchyma, considered similar to muscle, would be expected to be the same as for fat, we would expect parenchyma to occupy a smaller volume compared with fat. Further studies would clearly be of interest to many. Finally, we would note that many patients with type 2 diabetes are insulin independent at diagnosis, and the final statement regarding individuals with type 2 diabetes references an article stating that those in the upper tertile of impaired glucose tolerance have lost >80% of their beta cell function [19].

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Abbreviations

LADA	Latent autoimmune diabetes in adults
nPOD	Network for Pancreatic Organ donors with Diabetes
PanIN	Pancreatic Intraepithelial Neoplasia

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Table 1

Raw pancreas weights for organ donors or patients over 18 years of age are comparable across two previously reported cohorts

Study	Group	n	Age (mean ± SD)	Diabetes duration (mean ± SD)	Duration range	Pancreas weight (mean ± SD)	Pancreas weight range
Campbell-Thompson et al [7]	T1D	20	31.5±9.6	18±10	7.0–14.0	44.9 ^a ±20.4 ^b	23.4–117.4
	Non-diabetic control	23	29.0± 8.9	–	–	81.4 ^a ±4.5 ^b	52.7–139.0
Kobayashi et al [1]	LADA	11	64±14	13±7	0.3–24.0	29.8±8.2	18.4–45.0
	AT1D	10	60±9	26±11	13.0–47.0	42.1±7.3	30.0–59.5
	Non-diabetic control	10	66±6	–	–	79.3±9.3	63.1–95.1

^aLeast squares means, as values were age- and BMI-adjusted

^bStandard error of the mean

(A)T1D, (Acute) type 1 diabetes