**GAD65 autoantibody titres at diagnosis in Latent Autoimmune Diabetes in Adults (LADA) differ from Type 1 diabetes (T1D) and together with epitope specificity predict insulin requirement**

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**Background and aims:** Latent Autoimmune Diabetes in Adults (LADA) is a slowly-progressing form of autoimmune diabetes characterised by autoantibodies against glutamic acid decarboxylase (GAD65) in subjects with a clinical diagnosis of Type 2 diabetes (T2D). It is unclear whether there are differences in the autoimmune response to GAD65 between LADA and Type 1 diabetes (T1D). Our aims were: (i) To compare titres of GAD65 autoantibodies (GADA) in LADA patients from the UK Prospective Diabetes Study (UKPDS) cohort with those in T1D patients from the Bart's-Oxford (BOX) Study. (ii) To relate titre and epitope specificity of GADA in LADA to clinical phenotype.
**Materials and methods:** GADA titres at diagnosis (defined as 'Low', 'Medium' and 'High' according to titres in T1D) were determined by radioimmunoassay in 282 LADA subjects (median age 47yr [25-65]) and 689 GADA-positive children with T1D (median age 11yr [0.75-21]). Within the LADA cohort, GADA titre was related to clinical phenotype (age at onset, BMI, β-cell function and time to insulin requirement). GAD65/67 fusion proteins were used to determine immunoreactivity towards N-terminal (N), middle region (M) and C-terminal (C) epitopes of GAD65 in the LADA group.
**Results:** More patients with LADA than T1D had higher GADA titres; Low: 12% vs 33%, Medium: 29% vs 30%, High: 59% vs 37%, respectively (trend-test, $p<0.0001$). Among LADA patients, requirement for insulin therapy within 6 years of diagnosis correlated with GADA titre: lower third 62%, middle third 70% and upper third 78% (trend-test $p=0.039$). Higher GADA titres correlated also with immunoreactivity to multiple GAD65 epitopes at diagnosis. The proportion of patients immunoreactive to N : M : C epitopes by titre third were; lower third 21%:68%:53%, middle third 68%:92%:88%, upper third 89%:97%:96%, respectively (trend-tests $p<0.0001$). Reactivity to N-terminal epitopes in LADA was a significant predictor of insulin requirement by 6 yrs ($p=0.015$). Neither overall GAD65 antibody titre nor epitope positivity were associated with age at onset, BMI or %BHOMA.
**Conclusion:** Within the autoimmune diabetes spectrum, higher GADA titres associate with latent onset and a slowly-progressing disease process. However, within LADA, increasing GADA titre and N-terminal epitope reactivity at diagnosis increase the likelihood for future insulin requirement.