East Kent Hospitals University NHS Foundation Trust

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DIABETES AUTOANTIBODY REQUESTING GUIDELINES

Version:	2.0
Ratified by:	Clinical Biochemistry Senior Staff and Clinical Services Care Group
Date ratified:	October 2022
Name of originator/author:	Dr Joanna Sheldon / Lorna Miller (Chief Biomedical Scientist)
Director responsible for implementation:	Dr Edmund Lamb (Clinical Director)
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Target audience:	Clinical staff (medical, nursing and scientific), Trust wide and primary care

Version Control

Version	Date	Author	Status	Comment
1.0	6th June 2017	Mrs Lorna Miller	archived	
2.0	August 2022	Ellen Bealing/S Stock		Changed to new format, additional section clarifying when not to request

Consultation Schedule

Name & Job Title of Individual / Meeting name	Date consulted
Dr Joanna Sheldon, Consultant Clinical Scientist (Immunology)	18 August 2022
Dr Stonny Joseph, Consultant Endocrinologist	17 March 2022
Dr Chris McGettigan, Consultant Endocrinologist	22 July 2022

Ratification Schedule

Name of Meeting / Committee	Date approved / authorised
Clinical Biochemistry Senior staff	August 2022 (see Q-Pulse)
Pathology Management and Governance Committee (PMGC)	September 2022
Clinical Support Services governance meeting	October 2022

Contents

1. Introduction, Background and Purpose

Type I diabetes represents between 10 and 15% of all diabetes. Approximately 70% of the beta- cells in the islets of Langerhans make insulin with the other cells making glucagon, somatostatin and pancreatic polypeptide. At the diagnosis of type I diabetes, the histology of the islets show a mixture of patterns. Early in the disease process, the islets will appear normal with few infiltrating cells. Gradually the intact beta-cells become surrounded by activated T and B lymphocytes and antigen presenting cells and finally the beta cells will be destroyed and the tissue shows no inflammatory cells. The pathogenic process is T cell driven but during the cellular destruction, antigens are released and the immune system can make autoantibodies to these previously "hidden" antigens and to insulin. Antibodies to these antigens are summarised in Table 1; they are not pathogenic and are only seen "associated" with type I diabetes rather than causing type I diabetes: this limits their diagnostic utility.

Table 1 – the antigens associated with autoantibodies in Type I diabetes.

Antigen/ autoantibody	**Islet specificity**	**Function**	**% of patients positive at diagnosis**
Glutamic Acid Decarboxylase (GAD)	No – present in other islet cells and CNS	Catalyses synthesis of ɣ amino butyric acid (neurotransmitter) – likely regulates insulin release	65 -75%, more in adults - (also a target in stiff person syndrome)
Islet Tyrosine Phosphatase (IA-2)	No – present in other islet cells and CNS	Unknown	50-60%, more in children
Zinc transporter 8 (ZnT8)	β cell specific	Zinc transport	50-60%

1. Definitions

GAD - Glutamic Acid Decarboxylase antibody

IA-2 – islet antigen 2 antibody

ZnT8 – zinc transporter 8 antibody

LADA – latent autoimmune diabetes in adults

MODY – maturity onset diabetes of the young

CNS – central nervous system

2. Scope

This document gives guidance that is consistent with guidance developed by NICE (NG17 and 18)

3. Guidance

1. Diagnosis of Type 1 Diabetes

Diagnosis of type I diabetes is based on the WHO criteria and includes the concentrations of blood glucose and HbA1c. Neither the presence of autoantibodies nor the concentration of the autoantibodies is part of the diagnostic criteria.

C-peptide is commonly requested to distinguish between type 1 and other types of diabetes. C-peptide should not be measured at initial presentation and has better discriminative value the longer the test is done after diagnosis (NICE NG17 and NG18).

2. The role of autoantibodies in the investigation and management of patients with diabetes

The measurement of these antibodies in patients with diabetes is part of many research projects and it is clear that the presence of these antibodies does confer an increased risk of developing type I diabetes. Positivity of at least 2 of the autoantibodies (GAD, IA-2, ZnT8) gives a patient a 10% per year risk of developing type I diabetes and over a 20-year period, the majority of these patients (>95%) will have developed type I diabetes.

Patients with atypical presentations e.g. adults thought to have type 2 diabetes but with increasing insulin requirements (LADA) may benefit from antibody testing to better classify their diabetes. The prevalence of all 3 autoantibodies is < 1% in MODY and testing for these close to diagnosis can be used to discriminate type 1 diabetes from MODY.

An alternate atypical presentation is in pregnancy, when there is the need to have a low threshold to perform diabetes autoantibody estimation. This is the most likely time for patients with undiagnosed type 1 diabetes to present for the first time.

3. Analytical and technical considerations

There is no certified reference preparation or EQA programme for antibodies to any of the antigens associated with type 1 diabetes.

The timing of samples with respect to the time of diagnosis of type I diabetes is important. There is a narrow and variable window of antibody positivity around the time of diagnosis and the false negative rate increases as the time from diagnosis increases (NICE NG 17).

4. When should the antibodies be used?

- Consider measurement of diabetes autoantibodies in adults if classification is uncertain and confirming type 1 diabetes would have implications for therapy (NICE NG17)
- Consider measurement of diabetes autoantibodies in adults if type 1 diabetes is suspected, but the clinical presentation is atypical (NICE NG17)

5. What autoantibodies should be requested?

Samples will be sent to the Royal Devon and Exeter laboratory for their panel of 3 autoantibodies (GAD, IA-2 and ZnT8).

6. When should autoantibodies not be used?

Diabetes autoantibodies should not be measured routinely to confirm type 1 diabetes in adults, children or young people (NICE NG 17 and 18). Such requests will not be processed.

4. Consultation and Approval

East Kent Hospitals University NHS Foundation Trust is the key stakeholder for this guideline. This document was prepared in consultation with diabetes and endocrine consultants.

5. Review and Revision Arrangements

Two years from implementation date, by author.

6. Training

Dissemination to relevant staff within Pathology via Q Pulse. Dissemination to users of the service via documentation hosted in the healthcare professional zone of Trustnet. Information may also be contained within the Pathology MicroGuide

7. Document Control including Archiving Arrangements

Archive of this document will be through Q Pulse with the current version held on Trustnet.

8. Monitoring

Within the Trust, compliance with this policy must rest with the requesting Care Groups with vetting of requests in Clinical Biochemistry. Compliance will also be subject to occasional audit within Clinical Biochemistry and immunology.

9. References and Associated Documents

Diabetes (type 1 and type 2) in children and young people: diagnosis and management
NICE guideline (NG18): August 2015
https://www.nice.org.uk/guidance/ng18

Type 1 diabetes in adults: diagnosis and management
NICE guideline (NG17): August 2015
https://www.nice.org.uk/guidance/ng17

Bingley P 2010 Clinical applications of diabetes antibody testing. J Clin Endocrinol Metab 95(1):25-53

Brooking H, Ananieva-Jordanova R, Arnold C, Amoroso M, Powell M, Betterle C, Zanchetta R, Furmaniak J, Smith BR. A sensitive non-isotopic assay for GAD65 autoantibodies. Clin Chim Acta. 2003 May; 331(1-2):55-9.

Nilson E, Ekholm B, Rees Smith B, Törn C, Hillman M. Calcium addition to EDTA plasma eliminates falsely positive results in the RSR GADAb ELISA. Clin Chim Acta. 2008 Feb; 388(1-2):130-4.

A comparison of serum and EDTA plasma in the measurement of glutamic acid decarboxylase autoantibodies (GADA) and autoantibodies to islet antigen-2 (IA-2A) using the RSR radioimmunoassay (RIA) and enzyme linked immunosorbent assay (ELISA) kits. Rahmati K, Lernmark A, Becker C, Foltyn-Zadura A, Larsson K, Ivarsson SA, Törn C. Clin Lab. 2008; 54(7-8):227-35.

McDonald TJ, Colclough K, Brown R, Shields B, Shepherd M, Bingley P, Williams A, Hattersley AT, Ellard S. 2011. Islet autoantibodies can discriminate maturity-onset diabetes of the young (MODY) from Type 1 diabetes. Diabet Med 28:1028-1033.