Newcastle Mitochondrial Disease Guidelines

Diabetes Mellitus in Adult Mitochondrial Disease:
Screening and Initial Management

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Introduction
Diabetes mellitus is a common endocrine feature of patients with mitochondrial disease,\(^1\) predominantly due to its association with the m.3243A>G mutation,\(^2\) the most common heteroplasmic mitochondrial DNA (mtDNA) mutation causing human disease.\(^3\) The m.3243A>G mutation can give rise to several different syndromes: maternally inherited diabetes and deafness (MIDD); mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS); and chronic progressive external ophthalmoplegia (CPEO). However, there is often considerable overlap between phenotypes and diabetes can occur in all three of these syndromes.\(^4\) Diabetes also forms part of the established phenotype in a number of much rarer mtDNA mutations (eg m.14709T>C, single, large-scale mtDNA deletion).\(^5\)

Clinical presentation varies considerably, ranging from ketone positive, insulin dependent diabetes through to classical non-insulin dependent diabetes. There is an increased risk of gestational diabetes (GDM).\(^6\) In patients with the m.3243A>G mutation, diabetes usually develops in the early adult years peaking in the late 30s.\(^5\) It is most common for the clinical presentation to mimic type 2 diabetes, but patients are rarely obese and in fact usually have a low body mass index (BMI). Most patients progress rapidly to insulin dependency over a period of 2 to 4 years,\(^5\) as a result of pancreatic islet cell dysfunction.\(^2\) Autoimmune markers of type 1 diabetes (GAD and islet cell antibodies) are generally absent.

We recommend annual screening for the development of diabetes mellitus in any patient known to have mitochondrial disease, or in patients at risk of developing mitochondrial disease by virtue of pedigree analysis or known carrier status. Attendance at a specialist mitochondrial centre is recommended to oversee the management of multisystem disease and to provide guidance to the local diabetes services.

Patient-centred Care
This guideline offers expert consensus advice on the care of patients with mitochondrial disease. The care of these patients and their treatment should take into account patients’ needs and preferences. People with mitochondrial disease should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health guidelines –‘Reference guide to consent for examination or treatment’ (2001), available from [www.dh.gov.uk](http://www.dh.gov.uk). Healthcare professionals should also follow the code of practice accompanying the Mental Capacity Act (a summary of this code is available from [www.dca.gov.uk/menincap/bill-summary.htm](http://www.dca.gov.uk/menincap/bill-summary.htm)).

Good communication between healthcare professionals and patients is essential and should be supported by the best available information tailored to the patients’ needs. Treatment and care, as well as the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities and to people who do not speak or read English. If the patient agrees, families and carers should have the opportunity to be involved in decisions
about treatment and care. Families and carers should also be given the information and support they need.

**Key Priorities for Implementation**

In view of the diverse phenotypes of mitochondrial disease, we recommend that all patients diagnosed with mitochondrial disease should have annual screening for diabetes mellitus. This guidance also applies to those asymptomatic carriers deemed to be at significant risk of developing disease. Following diagnosis, all patients should be referred to the local diabetes service for diabetes education, support, and to start glucose monitoring. Attendance at a specialist mitochondrial centre is recommended to oversee the management of multisystem disease and to provide guidance to the local diabetes services. This document is intended for guidance only, and should not replace patient-specific management plans influenced by other factors such as patient preference and pragmatism.

1. Screening for Diabetes Mellitus in Patients with Mitochondrial Disease

1.1. **Asymptomatic patients**: HbA1c is recommended for patients as follows:
   
   1.1.1. All patients, at the time of diagnosis.
   
   1.1.2. All patients, at an interval of 12-months

1.2. **Symptomatic patients**: symptoms of polydipsia and/or polyuria should prompt a random glucose and HbA1c measurement.

1.3. **Pregnancy**: mitochondrial disease increases the risks of gestational diabetes (GDM).\(^6\)
   
   This is particularly true of genotypes associated with a diabetic phenotype (e.g. m.3243A>G mutation). Because of this increased risk we recommend an oral glucose tolerance test (OGTT) as follows:

   1.3.1. Previous GDM: in accordance with NICE guidelines we recommend OGTT at 16 weeks and again at 24-28 weeks if the 16 week OGTT was normal ([https://www.nice.org.uk/guidance/ng3/chapter/1-Recommendations#gestational-diabetes-2](https://www.nice.org.uk/guidance/ng3/chapter/1-Recommendations#gestational-diabetes-2)).

   1.3.2. High risk genotypes: women carrying mitochondrial mutations associated with a diabetic phenotype (e.g. m.3243A>G, m.14709T>C) should be screened by OGTT at 20 weeks gestation. This should also be offered to women who have a strong family history of diabetes associated with inherited mitochondrial disease.

   1.3.3. Other risk factors: women not falling into the two categories above should be offered OGTT at 24-28 weeks gestation if they have additional risk factors for GDM (e.g. BMI > 30kg/m\(^2\), ethnic background etc) as per NICE guidelines.

   1.3.4. Increasingly metformin is being used in gestational diabetes, however in patients with mitochondrial disease metformin risks worsening or precipitating lactic acidosis so is best avoided. We recommend the use of insulin therapy if required.
1.4. **Education**: patients/carers should be educated as to the risk of diabetes and warning symptoms that might require further investigation.

2. **Diagnosis of Diabetes Mellitus**
   2.1. **WHO recommendations**: diagnosis of diabetes is based on WHO recommendations and does not differ in mitochondrial disease ([https://www.who.int/publications-detail/who-ucn-ncd-20.1](https://www.who.int/publications-detail/who-ucn-ncd-20.1)).

   2.1.1. Asymptomatic patients: an HbA1c > 42 mmol/mol (6.0%) should prompt a confirmatory diagnostic test. This can be either a fasting plasma glucose or an oral glucose tolerance test (OGTT). A fasting plasma glucose ≥ 7 mmol/l and/or a 2 hour OGTT plasma glucose ≥11.1 mmol/l are diagnostic of diabetes. Impaired glucose tolerance (7.8mmol - 11.0 mmol) is monitored using annual HbA1c measurements.

   2.1.2. Symptomatic patients: for patients presenting with polydipsia and/or polyuria, a random plasma glucose ≥11.1 mmol/l is diagnostic of diabetes. A raised HbA1c should be investigated as in 2.1.1. above if the random glucose measurement is not diagnostic.

2.2. **Assessing insulin dependence**:
   2.2.1. Urinary and blood ketones: a positive ketone test points to insulin deficiency and the need for insulin therapy. Patients with mitochondrial diabetes have a high risk of insulin dependence. Recent vomiting/starvation can result in falsely raised ketones. Under these circumstances it is wise to stabilize the patient on insulin and check C-peptide later (see 2.2.2)

   2.2.2. C-peptide: a random C-peptide level helps to gauge pancreatic reserve.

   2.2.3. Anti-GAD antibody: a positive anti-GAD titre raises the possibility of coincidental autoimmune Type 1 diabetes.

3. **Glycaemic Management in Mitochondrial Diabetes**
   Following diagnosis, the patient needs to be referred to the local diabetes service for diabetes education, support, and to start glucose monitoring. The purpose of treatment is to relieve symptoms, ensure safety and prevent complications. The target HbA1c needs to be agreed
based upon personal circumstances, but as a general rule we aim for an HbA1c between 48 and 57 mmol/mol (6.5–7.5%).

We recommend the early introduction of blood glucose monitoring in view of the high risk of rapid progression to insulin therapy for a proportion of patients. As yet, there are no reliable clinical predictors of rapid glycaemic deterioration. Although patients with non-insulin dependent MIDD are generally non-obese,¹ they often have additional metabolic features such as fatty liver and partial lipodystrophy that complicate management.

3.1. **Insulin dependence**: features that point to insulin dependence include:

- Short history (weeks) of osmotic symptoms (polydipsia and/or polyuria) and weight loss
- Ketone positive
- C-peptide below the normal range

3.1.1 Insulin therapy: the presence of one or more of these features point to the need for immediate insulin therapy. The choice of insulin regimen should be guided by the patient’s capabilities and needs in relation to lifestyle, occupation and daily living.

3.1.2 Low BMI: patients with a low BMI generally need to start with lower dosages and titrate upwards.

3.1.3 It is recognized that patients with MIDD requiring insulin therapy often have fluctuating diurnal blood glucose levels. Under such circumstances, the patient may benefit from non-invasive flash monitoring such as the Libre system, and may be considered for other insulin delivery systems such as the insulin infusion pump.

3.2 **Non-insulin dependence**: features that point to non-insulin dependence include:

- Asymptomatic, only identified through screening
- Longer history (months) of osmotic symptoms with no clear weight loss
- Ketone negative
- C-peptide in the normal range or above
These patients can be treated using an adaptation of the Type 2 diabetes guidelines (https://www.nice.org.uk/guidance/ng28):

3.3 Therapeutic options:

3.3.1 Metformin

As a general rule, it is best to avoid metformin because of the enhanced risk of lactic acidosis.⁷ In most cases alternative agents are available (see below). Metformin may be used with caution under specialist supervision, but lactate levels should be monitored throughout treatment and patients (and GPs) educated as to scenarios where they should contact their specialist (or GP) to consider stopping the drug (eg acute infection).

3.3.2 Sulphonylureas

As most patients are not obese, sulphonylureas are an attractive therapeutic option. However, there is clinical evidence to suggest that patients with mitochondrial disease can show sulphonylurea sensitivity (unpublished clinical observation) with the associated increased risk of hypoglycaemia and fluctuating blood glucose levels. For this reason we recommend prescribing a sulphonylurea with a short half-life (eg tolbutamide, glipizide or gliclazide), starting at a low dose, titrating upwards and initiating home blood glucose monitoring.

3.3.3 Sodium Glucose Transport Protein 2 (SGLT2) Inhibitors (Glifozins)

These agents decrease glucose reabsorption by the kidneys leading to increased glycosuria. They are generally well tolerated, but currently should only be prescribed to patients with an eGFR > 60. There is an increased risk of thrush, and rare reports of ketoacidosis. In view of the increased risk of rapid progression to insulin deficiency in mitochondrial diabetes, it is important that patients are provided with urinary ketostix and told when and how to check for ketones. While there is no reported increase of hyponatraemia with SGLT2 inhibitor therapy, patients with mitochondrial disease are at increased risk of renal dysfunction and hyponatraemia. Regular checks of renal function are therefore recommended when SGLT2 inhibitors are prescribed. Finally, there is evidence that this class of agent lowers BP and improves cardiac function that may be of particular benefit to patients with mitochondrial diabetes.
3.3.4 Dipeptidyl peptidase 4 (DDP4) inhibitors (Gliptins)

The DDP4 inhibitors increase the insulin secretion and lower glucagon secretion by inhibiting DDP4. These are generally well tolerated, but should be avoided if there is a history of pancreatitis.

3.3.5 Glucagon-like peptide-1 (GLP-1) analogues

The GLP-1 analogues are particularly useful in patients with generalized obesity +/- fatty infiltration of the liver, and should be used according to current prescribing guidelines. In particular, they should not be used if there is a personal and/or family history of pancreatitis.

3.3.6 Pioglitazone

There is evidence that it may be beneficial in patients with fatty infiltration of the liver, but there is no evidence that it improves adipose tissue distribution in patients with partial lipodystrophy. However, in view of the risk of cardiac dysfunction in patients with mitochondrial disease, this agent needs to be used with care and avoided in combination with insulin.

3.3.7 Insulin therapy

This is a common therapeutic option not least because patients are invariably non-obese and because of the complexities of using the other agents listed above in patients with mitochondrial disease. We often start with a single injection of a basal insulin with or without the existing diabetes therapy and then move to a basal/bolus or pre-mixed insulin regime depending upon the patients preferences and needs.

3.3.8 Ubiquinone

Despite reports of benefit in mitochondrial diabetes there is currently insufficient evidence to recommend routine use in this context.
3.4 Therapeutic approach for management of Diabetes Mellitus in Mitochondrial Disease

Based on the benefits and risks of the individual classes of agents listed above, our approach is as follows:

- **1st line:** Start a DDP4 inhibitor
- **2nd line:** add either an SGLT2 inhibitor or Sulphonylurea. If fatty liver and/or obesity are factors, consider replacing the DDP4 inhibitor with a GLP-1 analogue or add pioglitazone
- **3rd line:** start insulin-either alone or in combination with existing agents if safe

4. Screening for Complications of Mitochondrial Diabetes

As the diabetes can present relatively early in the patient’s life and progress rapidly to insulin therapy, there is a need to offer standard systematic diabetes care and screening for complications. The prevalence of small vessel complications has been found to be increased in patients with MIDD compared with patients with type 1 and type 2 diabetes, suggesting an increased susceptibility to small vessel damage in MIDD. However, there is no clear relationship between mutation load and risk of complications. In line with standard diabetes care, annual screening should include:

4.1. Retinal screening for diabetic eye disease
4.2. Podiatry assessment (peripheral pulses and sensation) for diabetic foot disease
4.3. eGFR and urinary albumin creatinine ratio (ACR) for diabetic kidney disease
4.4. Blood lipid profile, blood pressure and LFTs (screening for raised ALT consistent with fatty liver).

5. Management of Cardiovascular Disease (CVD) Risk Factors

CVD risk factors need to be managed actively as in other diabetic patients. Cerebral, cardiac and renal function may be affected by mitochondrial diseases itself so it is important to keep additional vascular insults to a minimum.

5.1 Lipid lowering

Patients with a raised non-HDL cholesterol (>4mmol/l) need a lipid lowering agent. The 1st line agent should be a statin. As patients with mitochondrial disease have a
high likelihood of a pre-existing myopathy, a baseline creatine kinase (CK) is recommended before starting treatment and a low dose prescribed with a view to titrating up. Patients should have their CK repeated on treatment after 3 weeks and if patients report new weakness or myalgia. For those patients that cannot tolerate a statin, other possible treatments include ezetimibe and fibrates such as fenofibrate. However, these too carry the risk of low grade myopathy. In most cases we feel the benefits of lipid lowering agents (where indicated) outweigh the potential risks, with the possible exception of patients who have previously suffered episodes of rhabdomyolysis.

5.2 Blood pressure control
Blood pressure needs active management because of the high risk of renal disease and cardiac disease. The target BP is < 140/80 but should be lower (<130/70) in patients with evidence of renal/cardiac dysfunction. ACE inhibitors are the 1st line agents, but other agents can be added as required according to BP management guidance.

5.3 Smoking cessation
Patients should be advised to stop smoking.

6. Additional considerations

6.1. Additional support: Diabetes education and monitoring needs to be tailored to the individual. Some patients with mitochondrial disease may have learning difficulties or dementia. Others may be blind or deaf. In others, myoclonus or ataxia may necessitate help with blood glucose monitoring or insulin administration.

6.2. Feeding and nutrition: It is important to consider the effects of reduced oral intake in some patients, both in general but also during transient illness. Some patients may have a relatively low calorific intake or are obliged to eat small but frequent meals due to gastrointestinal dysmotility or dysphagia. Others may have PEG feeding. Occasionally paralytic ileus or encephalopathy may limit oral intake until the event has resolved.
6.3. **Kidney/pancreas transplant**: Progression to renal failure and dialysis is a real and challenging risk in mitochondrial diabetes. For those patients deemed suitable for kidney transplantation, consideration should be given to the possibility of simultaneous kidney/pancreas or pancreas after kidney transplantation. This is because the removal of the diabetes improves the survival of the kidney grafts, and also the grafts should survive longer than those given to patients with Type 1 diabetes who are at risk of graft damage due to the on-going autoimmune process.

6.4. **Multisystem disease**: Neuropathy, nephropathy and cardiomyopathy may occur due to mitochondrial disease alone, but it is important that this is not assumed to be the case and those treatable causes such as poor glycaemic control are addressed. Where possible it is helpful to try to ascertain the cause of end organ disease, whether diabetic, mitochondrial, or a combination of the two.

6.5. **Pregnancy**: Women with diabetes who are planning to become pregnant should be advised to take folic acid (5 mg/day) until 12 weeks of gestation to reduce the risk of having a baby with a neural tube defect. This is in accordance with NICE guidelines (https://www.nice.org.uk/guidance/ng3/chapter/1-Recommendations#gestational-diabetes-2).
7. Notes on the scope of this guidance
The guideline was developed by experts in mitochondrial disease and diabetes based at the Newcastle Mitochondrial Centre and the Newcastle upon Tyne Hospitals NHS Foundation Trust. This group specified which aspects of the screening, diagnosis and management of diabetes in patients with mitochondrial disease was to be included and excluded.

7.1 Audience
These guidelines are intended for use by the following people or organisations:
- all healthcare professionals
- people with mitochondrial disease and their carers
- patient support groups
- commissioning organisations
- service providers

7.2 Guideline Limitations
Limitations of these guidelines include:
- Lack of a firm evidence base for reference. Guidelines in mitochondrial disease are currently unable to adopt the evidence-based approach used by organisations such as NICE, and at present are predominantly based on consensus expert opinion.
- Overall, the evidence review identified no randomized controlled trials or high quality case-control or cohort studies.
- Further studies are needed (see research recommendations below).
- NHS Highly Specialised Services for Rare Mitochondrial Disorders are located in Newcastle, London, and Oxford. The development of these services represents an important advance in the care of patients with mitochondrial disease. 
  (https://mitochondrialdisease.nhs.uk/)
8. Implementation

Integral to this guideline is publication of the benefits of access to a specialist clinic with experience in mitochondrial disease.

- Specialist mitochondrial clinics are provided by selected centres with the support of the NHS Highly Specialised Services. The accumulation of experience within these centres, and access to focussed multi-disciplinary team input is designed to offer the best available care for patients with mitochondrial disease.

- Patient education is an important aspect of the initial consultation, but also as a vital component of future care. We aim to provide an understanding of the role of diabetic screening, and the potential impact of screening and early intervention on prognosis.

- Access to specialist clinics allows relevant genetic counselling and family tracing to facilitate the identification of those at risk of developing disease.

- Close liaison is required both with diabetic services at the specialist centre itself, but also local diabetic services who may be closely involved with future follow up and management of patients where frequent central review is impractical.
9. Research recommendations

9.1 Natural history studies
Many studies exist offering varying estimates of the prevalence of mitochondrial diabetes, or the proportion of diabetes attributable to mitochondrial DNA mutations. Further studies are required to clarify the progression, end organ involvement, response to treatment and overall morbidity/mortality attributable to mitochondrial diabetes.

9.2 Pancreatic/renal transplant outcomes
Pancreatic transplant is usually performed at the same time, or following renal transplant for end stage diabetic nephropathy. Pancreatic transplants in mitochondrial disease should in theory last longer than those in patients with autoimmune forms of type 1 diabetes where autoimmune damage to the graft may occur. Outcomes of pancreatic (and renal) transplants should be assessed.

10. Updating the guideline

The Newcastle Mitochondrial Guidelines are updated as needed so that recommendations take into account important new information. We check for new evidence every 2 years after publication, to decide whether all or part of the guideline should be updated. If important new evidence is published at other times, we may update the guidance prior to any scheduled changes.

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11. References


Appendix A: The Guideline Development Group

Dr Andrew M Schaefer
Consultant Neurologist
NHS Specialised Services for Rare Mitochondrial Disorders of Adults and Children
Directorate of Neurosciences
Royal Victoria Infirmary
Newcastle upon Tyne

Professor Mark Walker
Newcastle Diabetes Service
Campus for Ageing and Vitality

Dr Yi Shiau Ng
NIHR Clinical Lecturer in Neurology
NHS Specialised Services for Rare Mitochondrial Disorders of Adults and Children
Directorate of Neurosciences
Royal Victoria Infirmary
Newcastle upon Tyne

Professor Gráinne S Gorman
Honorary Consultant Neurologist
NHS Specialised Services for Rare Mitochondrial Disorders of Adults and Children
Directorate of Neurosciences
Royal Victoria Infirmary
Newcastle upon Tyne

Professor Robert McFarland
Professor of Paediatric Mitochondrial Medicine
NHS Specialised Services for Rare Mitochondrial Disorders of Adults and Children
Directorate of Neurosciences
Royal Victoria Infirmary
Newcastle upon Tyne

Professor Sir Douglass M Turnbull
Professor of Neurology
NHS Specialised Services for Rare Mitochondrial Disorders of Adults and Children
Directorate of Neurosciences
Royal Victoria Infirmary
Newcastle upon Tyne