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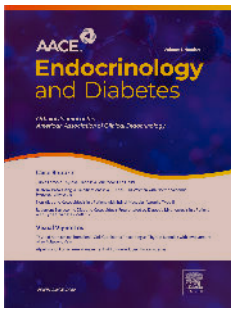


Diagnosis and management of type 3c diabetes– a consensus statement by Endocrine Society of Bengal

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# Title page

**Title:** Diagnosis and management of type 3c diabetes– a consensus statement by Endocrine Society of Bengal

**Running title:** Diagnosis and management of type 3c diabetes

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AD,AK, SN and SP. Upon receiving the inputs from all the members of consensus committee, the draft was complied, revised and edited by SM, SC, SoG and RB. This was further reviewed and edited by all the coauthors. All authors met the ICMJE criteria of authorship. Each author believes that the manuscript represents honest work. All the authors were agreed upon the final version of the manuscript before submission.

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**Highlights**

- T3cDM is a common cause for young onset diabetes especially in tropical countries.
- Multiple controversies exist from its nomenclature, diagnosis and management.
- No comprehensive guidelines exist till date.
- This consensus on T3cDM gives holistic, updated evidence-based statements.

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**Title : Diagnosis and management of type 3c diabetes– a consensus statement by Endocrine Society of Bengal**

**Abstract**

**Background:** Type 3c diabetes (T3cD), or diabetes secondary to exocrine pancreatic disease, remains underdiagnosed and frequently misclassified, particularly in regions with high prevalence of chronic pancreatitis and fibrocalculous pancreatic diabetes (FCPD).

**Objective :** This consensus statement by the Endocrine Society of Bengal aims to provide standardized recommendations for the nomenclature, classification, diagnosis, and management of T3cD to improve recognition and optimize patient outcomes.

**Methods:** A multidisciplinary consensus development group comprising of 49 experts conducted a structured literature review using PubMed (up to June 2025). A two-round modified Delphi process was undertaken to formulate and refine consensus statements. Agreement ≥70% was predefined as consensus. Statements addressed nomenclature, etiological classification, diagnostic criteria, imaging, genetic evaluation, nutritional therapy, pharmacological management, pancreatic enzyme replacement therapy (PERT), pain management, and complication monitoring.

**Results:** The panel endorsed "T3cD" as the preferred umbrella terminology for diabetes secondary to exocrine pancreatic disorders. Etiological classification should specify the underlying pancreatic pathology, including chronic pancreatitis, pancreatic neoplasms, post-pancreatectomy states, and FCPD as a distinct subtype. Diagnosis requires standard diabetes

criteria, evidence of pancreatic structural abnormality, and reasonable attribution to primary pancreatic disease process. Fecal elastase (FE) is recommended as the first-line test for pancreatic exocrine insufficiency. Imaging should begin with ultrasonography followed by Computed Tomography (CT) or magnetic resonance imaging/cholangiopancreatography MRI/MRCP as indicated. Metformin is recommended as first-line therapy in mild hyperglycemia, while most patients eventually require insulin. Use of incretin-based therapies is not advised. PERT, multidisciplinary care, and vigilant hypoglycemia monitoring are emphasized.

**Conclusions:** This consensus provides pragmatic, context-specific guidance for the diagnosis and comprehensive management of T3cD, addressing a critical gap in clinical practice and aiming to improve recognition, therapeutic precision, and long-term outcomes.

**Keywords** : Pancreatic diabetes, FCPD, T3cD, Type 3c Diabetes, fecal elastase

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## I. Introduction:

Few topics in endocrinology are more shrouded in controversy than pancreatic diabetes or type 3c diabetes (T3cD). Multiple nomenclatures exist for this entity, which logically should include any form of diabetes that is caused by structural and/or functional loss of insulin secretion in the context of exocrine pancreatic dysfunction, and includes a multitude of inflammatory, congenital, surgical as well as benign and malignant conditions affecting the exocrine pancreas. A survey reported T3cD to account for as high as 9.2% of all forms of diabetes, of which chronic pancreatitis (CP) accounted for 79% of the cases.(1) Fibrocalcific pancreatic diabetes (FCPD) is a unique type of CP and diabetes, occurring commonly in India and other tropical countries. (2) Patients with T3cD have damage to the islet of Langerhans affecting the β, α, and γ cells leading to a combination of low insulin, glucagon, and pancreatic polypeptide (PP). This leads to a form of "brittle diabetes" with rapid fluctuations in blood glucose, high risk for hypoglycemia but lower risk of diabetic ketoacidosis.(3) The natural history of those with T3cD is also different from other forms of diabetes, with patients more likely to require early insulin initiation and a different profile of macro- and microvascular complications than other forms of diabetes, while having a high risk for pancreatic malignancies. (3) Several challenges exist

in its management due to the absent standardized criteria for diagnosis, frequent misclassification, limited evidence regarding treatment protocol and the absence of tailored guidelines. Indian endocrinologists and physicians encounter and manage a large number of these cases, and in the absence of a proper guideline, the recommendations for type-2 diabetes (T2D) are extrapolated to these patients. All these made it imperative to have an expert consensus on the diagnosis and management and optimize outcomes in this unique form of diabetes.

## II. Methodology:

A Consensus Development group (CDG) was set up by assembling a multidisciplinary team comprising 49 board certified endocrinologists, one gastroenterologist, one gastro-surgeon, a nutritionist. The CDG had two sub-groups– a steering committee of 10 members (all endocrinologists) and an expert panel of the remaining forty. The steering committee defined the scope of the consensus, formulated the key questions, and developed an initial list of statements addressing key aspects of T3cD, including definition, classification, diagnosis, monitoring and management based on evidence-based summary of the literature relating to each particular question.

Because the evidence base on this topic was limited and heterogeneous, the initial items for rating were generated from expert input and a targeted review of relevant literature rather than a formal systematic review. Evidences were retrieved using the PubMed database using the search strategy "Pancreatic Diabetes" [Title/Abstract] OR "Pancreatogenous Diabetes" [Title/Abstract] OR "Type 3c Diabetes" [Title/Abstract] OR "Type 3c D*" [Title/Abstract] OR

"T3cD*" [Title/Abstract] OR "Diabetes of the exocrine pancreas" [Title/Abstract] OR "PPDM*"[Title/Abstract] OR "Post-pancreatitis Diabetes Mellitus"[Title/Abstract] OR "Fibrocalculous pancreatic diabetes" [Title/Abstract] OR "FCPD" [Title/Abstract] OR "Tropical calcific pancreatitis" [Title/Abstract]. PubMed advanced search was used to retrieve all randomized clinical trials, observational studies, systematic reviews and meta-analyses, guidelines, retrospective studies, narrative reviews, consensus statements and case series/reports published in English language on humans published till 30th June 2025. **(Fig 1)** Though we included them under the purview of T3cD, the management considerations for cystic fibrosis related diabetes ; post-pancreatectomy and post-traumatic T3cD have been excluded from the current consensus to avoid heterogeneity in management issues and to keep the focus mostly on chronic pancreatitis associated T3cD, mainly FCPD, which is a condition commonly seen by the consensus experts. Since the consensus comprises mostly endocrinologists, we have excluded the surgical aspects of managing the disease including endoscopic interventions, stones, chronic pain and stricture management for which separate guidelines have been laid by global gastroenterology societies for medical and surgical gastroenterologists. Similarly, while the guidelines include criteria for suspicion and screening biochemical tests and imaging for pancreatic adenocarcinoma, the further evaluation and management of pancreatic malignancies have been excluded from the scope of this consensus. We also excluded chronic pancreatitis without diabetes or other forms of diabetes with PEI. (Fig 1)

A consensus meeting was convened on 6$^{th}$ June 2025 at Nilratan Sircar Medical College, Kolkata for a two-round modified Delphi process under the aegis of Endocrine Society of Bengal. Conflicts of interest (COI) were declared upfront. In the first Delphi round, panellists independently rated each statement using a structured agreement scale. Voting was conducted

anonymously to minimize the influence of dominant individuals and to encourage unbiased expression of opinion. Panellists were also invited to provide written comments and suggest modifications or additional statements. Responses from the first round were aggregated, and the level of agreement for each statement was calculated. Consensus was predefined as agreement by a specified proportion of panellists (≥70% agreement). (4) Statements not meeting the predefined consensus threshold were revised based on quantitative results and qualitative feedback from the panel. In the second Delphi round, revised statements were redistributed to panel members for repeat anonymous voting. Panellists re-evaluated each statement after reviewing the group feedback. Statements achieving the consensus threshold were finally accepted, while those failing to reach consensus were either further refined or excluded.

Since a structured systematic review and meta-analysis couldn't be done, we used modified evidence-grading framework adapted from established guideline grading system for the recommendations. Level of evidence (LOE) was graded using a predefined five-level hierarchy, and strength of recommendation (SOR) was assigned A or B according to the consistency and clinical relevance of the available evidence and the percentage of consensus agreement (consensus). (Table 1A and 1B).

## III. Consensus statements

### Chapter 1. Nomenclature

**1.1. Diabetes occurring secondary to diseases affecting the exocrine pancreas should be clubbed under the nomenclature of T3cD.** (LOE: 3, Consensus : 98%, SOR: B)

**1.2. Alternative terminologies like "pancreatic diabetes" or "pancreatogenous diabetes" or "diabetes of the exocrine pancreas" may be used to denote the same entity.** (LOE: 3, Consensus : 95 %, SOR: B)

**1.3. Terms like 'New onset diabetes after pancreatitis', post-pancreatectomy diabetes or FCPD may be used to denote specific subtypes of T3cD, but not as alternative nomenclature.** (LOE : 5, Consensus: 89%, SOR: C)

Historically, the term 'pancreatic diabetes' was coined in 1892, several decades before the discovery of insulin. The term was introduced to denote the development of diabetes in animals after removal of the pancreas. (5) It was followed by the term 'pancreatogenic diabetes' in the early 1970s, the golden era of pancreaticoduodenectomy. (6) Resurgence of interest in this area occurred in early 21st century by Dr Andersen and Dr Chari in the USA, Dr Ewald in Germany, and COSMOS group in New Zealand. (7)(8) In 2014 American Diabetes Association (ADA) introduced a table where "diseases of exocrine pancreas" (subtype C) had been named under "other specific types" of diabetes (type III).(9) Since then, the term "type IIIC diabetes" or "type IIIc diabetes" or "type 3C diabetes" or "type 3c diabetes" had become popular in literature. However, to ameliorate the ambiguity, experts had recommended usage of "type 3c diabetes" to address all diabetes secondary to exocrine pancreatic pathology.(10) The terminology type "3c" is preferred over type "IIIC" as it is more consistent with the names type 1 and type 2 diabetes. Another terminology "Diabetes of the exocrine pancreas (DEP)" has been recognized later.(11) The WHO in 2019 had included "Diabetes due to diseases of the exocrine pancreas" in their classification system for diabetes. (12) It is now an established fact

that any type of diabetes is ‘pancreatic’ or ‘pancreatogenic’ to some extent. Patients with long-standing T1D and T2D can have exocrine pancreatic insufficiency of different degrees, and are also prone to single or recurrent episodes of acute pancreatitis (AP) and/ or CP. (13,14) Furthermore, patients with previous episodes of pancreatitis may also develop T1D and T2D independent of their exocrine pancreatic disease.(11) Some health professionals use terms like ‘diabetes following pancreatic disease’, ‘diabetes secondary to pancreatic disease', or ‘diabetes due to disease of the exocrine pancreas’. (8) While these may be understood to denote the same entity, we recommend against using them to maintain brevity in the nomenclature. The terms ‘New onset diabetes after pancreatitis’ (NODAP) and ‘Post-pancreatitis diabetes mellitus’ (PPDM) have both been used to describe diabetes in the context of AP or CP (11,15). As NODAP reasonably excludes those with other types of pre-existing diabetes who presented with pancreatitis, it may be a more appropriate term to use. We recommend NODAP to be considered as a subtype of T3cD rather than as a separate nomenclature. We recommend against using the terms ‘Pancreoprivic” or ‘Apancreatic diabetes mellitus’, since the degree of structural loss of the pancreatic parenchyma in T3cD is variable. Similarly, terminologies like ‘post-resection diabetes mellitus” after pancreato-duodenectomy may be considered as subtypes in the classification of T3cD instead of as a separate nomenclature for this entity. It is important to understand that though the FCPD variant of T3cD has many similarities with malnutrition related diabetes (MRDM), they are not synonymous. (16) Both the conditions occur predominantly in the tropical countries, involve non-autoimmune beta-cell dysfunction, present in young, non-obese and/or undernourished individuals and are not associated with ketosis. A detailed clinical history, nutritional assessment, and pancreatic imaging are essential in distinguishing between these two forms of secondary diabetes. Another word of caution in this context is that “type 3 diabetes” is not synonymous with T3cD. The former is sometimes

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used interchangeably with Alzheimer's disease to denote insulin resistance as the crucial pathophysiological underpinning.(17)

Overall, we suggest using T3cD as the preferred umbrella terminology to denote a myriad of etiologies of pancreatic pathologies leading to structural and/or functional impairment of β-cells.

## Chapter 2. Classification

**2.1. In the absence of an accepted classification system of T3cD, it is prudent to specify the etiology causing T3cD knowing that each etiology has unique management principles.** (LOE: 5, Consensus agreement : 95%, SOR: B)

**2.2 The term "New onset diabetes after pancreatitis' (NODAP) should be used in preference to post-pancreatitis diabetes mellitus (PPDM) as a subtype of T3cD, since NODAP excludes pre-existing other types of diabetes who presented with pancreatitis.** (LOE: 5, Consensus: 98% , SOR: B)

**2.3 Fibrocalculous pancreatic diabetes (FCPD) should be regarded as a separate entity and is not synonymous with diabetes due to other causes of CP.** (LOE: 3, Consensus: 100%, SOR: B)

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T3cD is classified according to the underlying etiologies (Table 2). The Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC) suggested subclassification of T3cD according to the underlying pathophysiological mechanisms into four different categories -- a. Paraneoplastic due to pancreatic ductal adenocarcinoma (PDAC); b. Transient hyperglycemia of AP; c. Congenital or acquired complete absence of islets, where both pancreatic agenesis and total pancreatectomy have been included; d. Acquired partial absence of functional islets which includes CP, partial pancreatectomy, severe AP, cystic fibrosis, and hemochromatosis (18). However, this classification system seems to have limited practical implications. Among the pancreatic neoplasms only PDAC has been mentioned in CPDPC panel, although association (relatively weaker than PDAC) of diabetes has been described with other types of pancreatic neoplasms including intraductal papillary mucinous neoplasms , pancreatic metastasis from other primary neoplasm , non-functioning pancreatic neuroendocrine tumor.(19–21) There is also a concern regarding the term “paraneoplastic” in the classification, as pathophysiological basis of PDAC-associated diabetes is not just restricted to paraneoplastic mechanisms alone.(18) The entity of new-onset diabetes in pre-symptomatic PDAC (NOD-PDAC) is also worth mentioning here.(15) It is now established that antecedent diabetes is an early and reliable marker of PDAC in its presymptomatic stage, when pancreatic imaging may be normal.(22,23) Whether NOD-PDAC could be included under the diagnostic umbrella of T3cD needs further contemplation.

Both AP and CP increase the risk of diabetes by several folds. A separate nomenclature PPDM has been suggested to specify this group.(11) This has further been subdivided into PPDM-A (PPDM after AP) and PPDM-C (PPDM after CP). While insulin resistance from inflammatory milieu is the chief driving force for development of PPDM-A, β-cell failure from pancreatic volume loss is the pathophysiological basis of PPDM-C. However, it might be difficult to

differentiate recurrent AP from early CP. It is, thus, best recognized as the two ends of a continuous spectrum rather than two distinct categorical states.(15) NODAP is another terminology used in the same context. However, we believe the term NODAP is more appropriate to truly denote a subclass of T3cD, as in its original conceptual framework, previously unrecognized diabetes and NODAP were collectively included into the PPDM group. NODAP is defined as patients with PPDM with documented normal glucose homeostasis at baseline.(11) It excludes patients with unrecognized diabetes, before the event of pancreatitis, and up to 3 months post discharge. New-onset prediabetes after pancreatitis (NOPAP) is also a recognized entity diagnosed based on usual ADA criteria for diagnosis of prediabetes.(15) The CPDPC panel mentions “transient hyperglycemia of AP” as “other” subclass of T3cD.(18) To denote this type of dysglycemia, the term “stress hyperglycemia” was mentioned by Petrov, and not included in PPDM spectrum. This had been defined as “any elevated level of blood glucose during the course of pancreatitis and/or within 3 months after hospital admission in patients without previous diagnosis of diabetes”.(11) Thus, the consensus body recommends that it is important to identify transient or stress hyperglycemia following pancreatitis and it is not justified to include this in subclassification of T3cD. In its classification of T3cD, CPDPC panel included only “severe” AP , although it is quite evident that the risk of NODAP even after a single attack of mild AP is comparable to recurrent severe pancreatitis.(24,25)

Major international stakeholders have included FCPD within the same bracket of diabetes from CP group. (15,18) The ADA mentions it separately in its list of etiologies of T3cD.(9) However, FCPD is different in various aspects from the prototype variety of diabetes secondary to CP [such as chronic calcific pancreatitis (CCP) from alcoholic pancreatitis] (Table 3).(26–29) Thus, we recommend that FCPD be regarded as distinct taxon from other causes of CCP.

The term FCPD seems to be more rational than “tropical” chronic pancreatic diabetes as the disorder is being reported from non-tropical countries too.(30)

Although cystic fibrosis is a well-established cause for CP or recurrent AP and diabetes, cystic-fibrosis-related diabetes (CFRD) is a unique entity with distinct pathophysiology and management issues. Though it may be classified as T3cD, its management is beyond the scope of the current consensus. Authors Petrov and Basina excluded hereditary hemochromatosis from DEP, probably due to its non-specific nature of organ involvement and bidirectional relationship between pancreatic exocrine dysfunction and iron metabolism.(15)(31) However, based on the available evidence and following other major international guidelines, we recommend that both primary and secondary hemochromatosis are to be included in the etiological classification. Similarly, it has been argued that inclusion of post-pancreatectomy diabetes may cause pseudo-inflation of the incidence of DEP, as the most common indications of pancreatic surgery are pancreatitis and pancreatic cancer (core disease entities in their DEP classification criteria). Pancreatic trauma as a cause of DEP was also not included in the aforementioned classification system.(32) However, there are several reports of development of T3cD after both operative and non-operative pancreatic injury, establishing a causal relationship.(33) A systematic review published in 2020 catering 36 articles with 5636 patients undergoing pancreaticoduodenectomy, 3922 patients with distal pancreatectomy and 315 cases with central pancreatectomy had revealed that the risk of development of new onset T3cD was associated with type of pancreatic resection (distal pancreatectomy- 21%, pancreaticoduodenectomy 16%, and central pancreatectomy 6%), lower remnant pancreatic volume, and higher preoperative glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG).(34) In this regard, development of T3cD after total pancreatectomy deserves special attention due to its unique pathophysiological basis (deficient amylin, exocrine insufficiency

and post-surgical alterations of gastrointestinal anatomy) with greater brittleness in glycemic status. Thus, researchers have ascribed a new nomenclature "post-total pancreatectomy diabetes mellitus" (PTPDM) to specifically designate this subtype of T3cD.(35) Therefore, considering the overall evidences available till date, we recommend post-pancreatic resection diabetes to be included in the classification of T3cD. Diabetes due to congenital structural defects in pancreas (such as pancreatic agenesis) and rare cases of pancreatic tuberculosis leading to diabetes are also included in the classification. (36,37) However, since diabetes due to congenital structural defects in pancreas (such as pancreatic agenesis) due to transcription factor defects (IPF-1/PDX) are included classically in MODY or neonatal diabetes classification, we suggest not including them under the umbrella term T3cD. (38,39)

## Chapter 3. Diagnosis

### Recommendation 3.1 - When to suspect pancreatic diabetes

**3.1.1 T3cD should be suspected in persons with diabetes having one or multiple known diseases affecting the pancreas and/or biochemical and imaging findings suggestive of diseases affecting the pancreas.** (LOE: 3 , Consensus: 98%, SOR: B)

**3.1.2. T3cD should be suspected in all persons with diabetes who are non-obese, and/or have diabetes diagnosed at young age, and/or have risk factors for pancreatitis like chronic alcoholism, residence in tropical countries, and/or have symptoms suggestive of pancreatic exocrine insufficiency (PEI), and/or do not have characteristic manifestations**

**of T1D or other secondary causes for diabetes or clinical markers of insulin resistance.** (LOE: 4, Consensus: 92%, SOR: B)

**3.1.3. All patients with AP should be screened for diabetes within 3 to 6 months following the episode and annually thereafter. All patients with CP should be screened for diabetes annually.** (LOE: 3, Consensus: 100%, SOR: B)

Pancreatic diabetes must be suspected in those with diabetes who have one or more manifestations and/or risk factors for pancreatitis. These include clinical features of exocrine insufficiency like pain abdomen, steatorrhea, known structural diseases of pancreas like CP, PDAC, congenital abnormalities or history of pancreatic surgery (40). Often, symptoms of exocrine insufficiency like steatorrhea may not manifest overtly due to less fat percentage in diet.(3) In subjects with risk factors for pancreatitis like chronic alcoholism and resident of tropical country/endemic regions, T3cD should be suspected in all persons with diabetes. Young age, lower body mass index (BMI) and absence of T1D-specific antibodies further strengthen the cause to look for possible T3cD.(40)

Screening for diabetes is of primordial importance in individuals with pancreatitis. A 2014 meta-analysis by the COSMOS group statistically aggregated follow-up data from 24 clinical studies of individuals after the first attack of AP. (41) The study found that 23% of people after the first attack of AP developed PPDM-A. Similarly, another metanalysis revealed about 30% incidence of diabetes in subjects with CP.(42) The 2020 LACERTA study by the COSMOS group was the first prospective longitudinal cohort study which looked at the trend in glycaemia at regular intervals in unselected AP patients.(43) They followed up subjects with AP over a period of time and found out that the cumulative incidence of NODAP was 3.3% at 6 months, 7.2% at 12 months, 9.2% at 18 months, and 11.2% at 24 months follow-up. Based on these

observations it is recommended that screening for diabetes should be done at 3-6 months following an episode of AP, following which, annual screening is necessary. Similarly, in individuals with CP, diabetes screening should be done yearly.(44)

**Recommendation 3.2- Diagnostic tests**

**3.2.1. Diagnosis of T3cD should be made in the presence of diabetes according to standard criteria, presence of pancreatic disease [including pancreatic exocrine insufficiency (PEI)] along with consistent pancreatic abnormality on imaging, and when the diabetes is reasonably ascertained to be secondary to the pancreatic disease. (**LOE 3, Consensus : 98%, SOR : B)

**3.2.2. Diabetes diagnosed according to standard criteria with FPG, 2 hours post-prandial plasma glucose (PPPG) and HbA1c.** (LOE 1, Consensus : 100%, SOR: A)

**3.2.3. To differentiate T3cD from T1D in young individuals requiring insulin, islet cell antibodies should be tested.** (LOE 4, Consensus : 95%, SOR : B)

**3.2.4 Measurement of serum C-peptide levels in fasting, post-prandial or following stimulation tests can be done to predict T3cD with severe pancreatic endocrine disruption, but no specific cut-off can be used for diagnosing T3cD or differentiating it from T1D. (**LOE 4, Consensus : 88 %, SOR : C)

**3.2.5 Measurement of Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), glucagon, incretins or pancreatic polypeptide (PP) may be used in research settings for supportive evidence but should not be used routinely for the diagnosis of T3cD.** (LOE 4, Consensus : 90 %, SOR : B )

**3.2.6. In the absence of PEI, T3cD can be diagnosed if there is high likelihood of diabetes linked to pancreatic disorder i.e. diabetes developing after AP in a previously known non-diabetic or diabetes post ductal adenocarcinoma (PDAC)**. (LOE 5, Consensus : 94 % agreement, SOR : B)

Diabetes in T3cD should be diagnosed as per the criteria laid down by the ADA to diagnose diabetes in general. This includes any one of the following: FPG ≥126 mg/dL (7.0 mmol/L) (fasting is defined as no caloric intake for at least 8 hours), or, 2 hours PPPG ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT), using a glucose load containing the equivalent of 75 gm anhydrous glucose dissolved in water, or HbA1c ≥6.5% [should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardised to Diabetes Control and Complications Trial (DCCT) assay], or in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).(44) For all criteria, the diagnosis requires confirmation unless there is unequivocal hyperglycemia.

It is important to consider the possibility of T3D in all cases where a secondary cause is suspected especially in those with onset of diabetes is below 35 years of age. While C-peptide (preferably stimulated C-peptide post a mixed meal after glycemic control), forms an important step for diagnosing secretory defect, results of C-peptide levels in T3cD have been variable and no specific cut-off could be recognised.(45,46) While the absence of islet autoantibodies (GAD65, IA-2, ZnT8, or IAA) reasonably rules out T1D , it is important to note that rarely,

pancreatic antibodies have been reported in T3cD. (27,47,48) Patients of T3cD are mostly non-obese and lack features of insulin resistance but these lack specificity. Family history may be present in T3cD, though usually not as strong as for Maturity Onset Diabetes in Young (MODY) or T2D.(49) Given the costs involved in the myriads of tests to diagnose most other forms of diabetes, we suggest that an imaging of the pancreas should be done as a relatively inexpensive test to rule in the diagnosis of T3cD and must be done in all cases of diabetes, prioritising those with young age of onset and the non-obese.

There are no universally recommended criteria for diagnosing T3cD. In the only published criteria for T3cD, Ewald and Bretzel proposed the following major criteria, all of which must be present- PEI, consistent pancreatic abnormalities on imaging, and absence of related autoimmune markers of T1D.(8) Minor criteria included impaired β-cell function (as measured by homoeostatic model assessment for β-cell function, or C-peptide or glucose concentrations), absence of insulin resistance (as defined by HOMA-IR), impaired incretin secretion (glucagon-like peptide-1 [GLP-1] or PP, or both), and low serum concentrations of lipid soluble vitamins (A, D, E, and K).(50) While all the major criteria must be present, the minor criteria are considered supportive but not essential for diagnosis.

The major criteria have certain limitations. PEI may be present in long standing T1D (26-74%) and T2D (28-36%) due to a multitude of reasons.(50–54) Insulin has a trophic effect on acinar cells and insulinopenia in long standing diabetes leads to pancreatic atrophy and loss of exocrine function. (55) Autonomic dysfunction due to diabetic neuropathy may also play a role in exocrine dysfunction.(56) There may be simultaneous endocrine and exocrine dysfunction arising out of a common pathogenic mechanism involving either an autoimmune process or genetic defects leading to destruction of both islet and acinar cells.(57)(58)(59) Additionally, PEI is not universal in T3cD, specially in T3cD developing as a sequela to AP or due to PDAC in the initial stages.(18)

Testing for the minor criteria including markers of β cell function, insulin resistance , incretins or PP are mostly non-specific, costly, not easily available and may be reserved for use only in research settings. There is lack of high-quality studies that have looked at the glucose homeostasis in pancreatic diabetes.(18) It is now an established fact that in addition to insulin deficiency and β-cell dysfunction, insulin resistance also plays a significant role in pathogenesis of pancreatic diabetes. (60)(61)62)

Results of studies investigating C-peptide levels in T3cD have been variable. Majority reported lower fasting and stimulated C-peptide concentration in T3cD than T2D but higher than in T1D, suggesting partially preserved β-cell reserve.(45)(63,64) though some suggested similar serum or urinary C-peptide levels as T1D. (65,66). One study suggested similar C-peptide levels in T3cD as in T1D at the time of diagnosis, which improved following insulin therapy and improvement in metabolic status.(67) In another study, variable C-peptide levels were seen in T3cD, with the highest levels in those who responded to oral anti-diabetics, intermediate in those requiring insulin, and lowest in a subgroup of ketosis proneT3cD.(68) Impaired beta-cell function is enlisted as a minor criterion to define T3cD by Ewald et al. However, based on current overall evidences , it is apparent that C-peptide levels in T3cD can be variable and the cut-offs usually employed for the diagnosis of insulin-dependent or T1D may not be applicable to diagnose all cases of T3cD. C-peptide levels in serum/plasma can be measured in the fasting state or post appropriate stimulation tests with glucagon, mixed meal tolerance or OGTT. While the former method is simple, quick and less affected by confounders, fasting samples may be insufficient to detect subtle rises in C-peptide levels while the stimulated methods are more sensitive, reproducible and found in studies to correlate well with diagnosis. A random non-fasting sample collected within 5 hours of a meal has been also found to correlate well with the diagnosis provided the patient was not hypoglycemic at that time. A fasting serum C-peptide of <= 80 pmol/l or a stimulated / random C-peptide < = 200 pmol/l may indicate either T1D or T3cD with severe pancreatic endocrine disruption. (69)Conversely, a C- peptide >600 pmol/l (fasting/simulated/ random) would suggest a diagnosis of T2D. (70)

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Data pertaining to incretin response in pancreatic diabetes is conflicting. Studies have demonstrated that in T3cD, secretion and sensitivity to GLP-1 seems to be intact, while levels

682 of glucose-dependent insulinotropic polypeptide (GIP) and the late-phase insulin secretion
683 response to GIP is reduced, similar to that seen in T2D.(71–73) However, in a study by Ghosh
684 et al it was seen that in FCPD, there is resistance to GLP-1. (46)
685 Glucagon levels in T3cD have been found to vary based on reports from different studies.
686 While advanced forms of T3cD are expected to have low glucagon levels, there have been
687 reports of preserved or even exaggerated post prandial glucagon secretion after glucose
688 challenge in chronic pancreatitis with IGT or diabetes. (74,75) Other studies have reported an
689 exaggerated glucagon response at baseline and in response to oral glucose though a suppressed
690 glucagon response was noted following an intravenous glucose tolerance test in T3cD,
691 implicating the possible role of incretins. (76) Apart from alpha cell destruction, alpha cell
692 dysfunction has also been implicated in the pathogenesis of T3cD. There is preferential
693 destruction of beta-cell mass over alpha cells resulting in differential hyperglucagonemia at
694 least in the earlier stages of the disease while gross destruction of overall islet cell mass occurs
695 relatively later in advanced phases of the disease. Studies have shown that alpha cell numbers
696 are not significantly decreased in T3cD, or even might be increased. (77) An extra-pancreatic
697 source of glucagon has also been suggested. (78) Though changes in insulin and glucagon
698 levels can influence hypoglycemia and glycemic variability (GV) in such patients, there is also
699 the modulatory role of multiple glucoregulatory peptides namely glucagon like peptide -1
700 (GLP-1), gastric inhibitory peptide-1 (GIP 1). (79) One postulated mechanism had been a shift
701 in the L-cells of the intestine towards secretion of more glucagon (mediated by prohormone
702 convertase 2 enzyme) due to lack of pancreatic alpha cells. A stimulus for L-cells could be an
703 altered delivery of nutrients including glucose. A recent study found that although C-peptide
704 levels may be higher, the levels of PP were specifically lower in T3cD than T1D, even if the
705 latter had associated presence of PEI. (80) Similarly, fasting as well as meal-stimulated PP
706 values were found to be reduced in new-onset T3cD associated with PDAC or CP in

comparison to T2D.(81) Assays for incretins like GIP, GLP-1, PP or glucagon are not standardised and do not have established cut-offs. Due to rapid degradation, accurate measurement of GIP and GLP-1 requires very strict sample handling and specific inhibitor protocols. Many of the immunoassay kits have cross-reactivity with precursor peptides or metabolites and are unable to distinguish intact hormone from total GLP-1 forms including inactive cleavage products such as GLP-1(9-36). HOMA-IR is now known to be only a surrogate marker of insulin resistance and while it is of use in epidemiologic studies, it should not be used as a stand-alone diagnostic test for an individual patient. Its major limitation is lack of a universal cut-off and the proposed thresholds vary widely by ethnicity, age, sex, BMI, and study method (82). No cut-off has been established for GIP, GLP-1, PP, glucagon or HOMA-IR for the diagnosis of T3cD and need further studies. Thus, till further data are available, we recommend these tests to be reserved only in research settings rather than using them routinely in the diagnosis of T3cD. For practical purposes, the diagnosis of T3cD should include the establishment of a diagnosis of diabetes according to standard criteria, the presence of structural pancreatic abnormality and when diabetes is reasonably ascertained secondary to pancreatic disease.

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**Recommendations 3.3 Assessment of PEI**

**3.3.1 Measurement of fecal elastase (FE) in freshly passed non-watery stool specimens should be considered the first line test to diagnose PEI, with values < 200 µg/gm of stool indicative of PEI.** (LOE : 2, Consensus : 100%, SOR : A)

**3.3.2 In cases with high suspicion of pancreatic insufficiency but normal faecal elastase, other tests like stool quantitative fat estimation and direct secretory function tests may be performed but are cumbersome and usually reserved for research settings. (**LOE : 3; Consensus : 97 %, SOR : Grade B)

**3.3.3 In the absence or inability to do any tests, clinical symptoms suggestive of PEI in the presence of structural abnormalities of the pancreas may be suggestive.** (LOE : 3 , Consensus : 90 %, SOR : B)

**3.3.4 Diagnosis of PEI should not be established on the basis of the treatment response to pancreatic enzyme replacement therapy (PERT).** (LOE : 5 , Consensus : 90%, SOR : C)

PEI is associated with clinical symptoms like diarrhoea, steatorrhea, bloating, abdominal cramps, and flatulence. There is also associated nutritional deficiency in form of vitamin deficiency especially the fat-soluble vitamins along with micronutrients and protein deficiency. The symptoms of pancreatic exocrine insufficiency are somewhat non-specific and pancreatic function testing should be performed to confirm pancreatic exocrine insufficiency. In certain cases where there is structural pancreatic changes like pancreatic resection, FCPD with intraductal calculi, pancreatic carcinoma with symptoms suggestive of pancreatic insufficiency it may not be required to perform pancreatic function testing.(83)(84)

The FE-1 test is the most commonly used test to assess pancreatic function. It's a non- invasive test and less cumbersome to perform as it requires small amount of stool sample. Values less than 200 mcg/gm of stool suggest pancreatic insufficiency and values less than 100 mcg/gm suggest severe pancreatic insufficiency.(85–87) The lower the value of FE-1, the higher the chance of exocrine insufficiency. It is important to understand the limitations of FE-1 test. It

should be performed on semi-solid or solid stool sample. FE-1 values greater than 200 mcg/gm in a subject with low pretest probability has false negative rate of 1.1 %, indicating value as an accurate screening test.(88) In subjects with high pre- test probability with negative FE-1, the test can be either repeated or a separate test can be done. Other tests include quantification of the coefficient of fat absorption (CFA) after a 72-h stool collection with the patient on a standardized 100 g fat diet and the 13C-mixed triglyceride (MTG) breath test.(88,89) Coefficient of fat absorption is considered to be gold standard however it is cumbersome and difficult to perform. The test demands consumption of high fat diet which may lead to severe dyspepsia. Alternatively, MTG breath test can be performed. Direct tests that assess pancreatic secretion and enzyme quantification in the duodenal fluid after intravenous administration of secretin and CCK are rarely performed due to their invasive nature and are reserved for research settings only.(84)

Limited evidence suggests that serum levels of fat-soluble vitamins, trace elements such as magnesium, selenium and zinc, and plasma proteins, including retinol binding protein, albumin, and pre- albumin, may have diagnostic utility in PEI. (84,88,90–98)

PEI should not be diagnosed on entirely on basis of response to PERT therapy as because other conditions like irritable bowel syndrome can have partial response to the same.(84,85) However response to PERT in a subject with structural pancreatic disease is an important pointer towards PEI.(84)

**3.4 FCPD should be diagnosed in people with diabetes (as per standard diagnostic criteria for diabetes) residing in a tropical country and having evidence of CP - either in the form of pancreatic calculi visualized in X-ray abdomen or any three of - abnormal pancreatic morphology with ductal dilatation detected by imaging, abnormal exocrine**

**pancreatic function tests, chronic recurrent pain since childhood or steatorrhea, provided alternative etiologies like chronic alcoholism have been excluded.** (LOE : 4, Consensus : 100% , SOR: B)

FCPD is a unique form of T3cD reported from tropical countries. The most accepted diagnostic criteria of FCPD was proposed by Mohan et al and remains relevant till today.(2) FCPD is unique in many aspects from other forms of T3cD related to CP. Additionally, subjects with FCPD are more prone to develop PDAC than other forms of T3cD.(99) Generally, FCPD presents at a young age, the classical presentation being pain abdomen in childhood with subsequent PEI and overt diabetes developing at last. Affected subjects are underweight and emaciated. However, FCPD is now diagnosed in older individuals and low BMI may not be universally present. Many individuals may not experience pain or steatorrhea at the time of presentation with diabetes. The classical presentation of pain abdomen, steatorrhea and diabetes in present in only 15% of all FCPD subjects.(100) Apart from a few isolated case reports, FCPD has not been seen outside tropical countries.(30)

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## Chapter 4. Imaging

**4.1 The initial imaging for the diagnosis and delineation of pancreatic pathology in T3cD should be an ultrasonography (USG) of the abdomen followed by non-contrast computed tomography (NCCT) scan of abdomen if ultrasonography is inconclusive or negative.** (LOE : 3, Consensus : 96 %, SOR: B)

**4.2 In cases where both USG and computed tomography (CT) scan fail to identify the pancreatic pathology, magnetic resonance imaging (MRI) or magnetic resonance cholangiopancreatogram (MRCP) should be done.** (LOE : 3, Consensus : 98.5 %, SOR: B)

**4.3 Invasive tests including endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS) may be done on an individualised basis, especially if a endoscopy-based therapeutic intervention or histopathological investigation is planned.** (LOE : 3, Consensus : 97 %, SOR: B)

**4.4 In resource limited settings, straight X-ray of the abdomen can be done. Calcifications along and around the pancreatic ducts and contour are considered indicative of advanced stages of PPDM-C. (**LOE : 5 , Consensus : 90%, SOR: C)

**4.5 The pattern and size of calculi/calcifications and the degree of ductal dilatation can be used to differentiate FCPD from PPDM-C of other etiologies.** (LOE : 5 , Consensus : 85.5 %, SOR Grade : C)

Transabdominal ultrasonography is recommended as the initial imaging method due to its accessibility and non-invasiveness, with a sensitivity of 67% and specificity of 98%. (101) Typical findings include irregular pancreatic contours, hyperechoic foci (fibrosis), ductal dilatation, and calcifications. (102) Mass forming CP is better differentiated from PDAC by using contrast-enhanced ultrasonography (CEUS) in which PDAC typically appears hypoechoic during the arterial phase, whereas focal CP demonstrates contrast enhancement.(103)

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Contrast-enhanced computed tomography (CECT) is considered the gold standard for evaluating both CP and PDAC, due to its capacity for detailed visualization of pancreatic parenchyma, ductal systems, and peripancreatic tissues. Meta-analyses indicate that CECT achieves a sensitivity of 75% and a specificity of 91% for differentiating CP and pancreatic neoplasms.(104) Characteristic findings on CECT include pancreatic duct dilatation, atrophy of the pancreatic parenchyma, pseudocyst formation, pancreatic calcifications, and hypo-enhancing pancreatic masses suggestive of malignancy. (105) In cases where subtle or very small calcifications are suspected, a NCCT may be necessary, as it provides improved sensitivity for identifying fine or punctate calcific foci that might be obscured by contrast.

MRI including MRCP offers superior soft-tissue contrast compared to CT and is particularly valuable for identifying subtle parenchymal changes in early-stage pancreatic disease. A meta-analysis of 14 studies reported a sensitivity of 78% and a specificity of 96% for MRI/MRCP in diagnosing CP.(104) MRCP enables non-invasive evaluation of the pancreatic ductal system, effectively detecting features such as ductal narrowing, dilation, and intraductal filling defects with moderate to high diagnostic accuracy. However, a normal MRI or MRCP cannot reliably exclude mild or early CP, limiting its sensitivity in such cases. Secretin-enhanced MRCP (S-MRCP) may further improve the visualization of small ductal abnormalities in early CP. Exocrine function assessed by S-MRCP has been shown to correlate with FE-1 levels,. (106)

Endoscopic ultrasound (EUS) is among the most sensitive modalities for detecting CP, particularly in its early or minimal-change stages and may improve detection in cases of suspected T3cD with negative CT and MRI results. The Rosemont criteria, a structured scoring system categorizing parenchymal and ductal features provides enhanced reproducibility and improved diagnostic performance, yielding a specificity range of 82–95% and sensitivity of

70-89% to detect CP. (103,104) EUS also facilitates fine needle aspiration cytology (FNAC) or biopsy (FNB), allowing for cytological or histological evaluation to differentiate CP from pancreatic neoplasms or autoimmune pancreatitis.

In resource-limited settings, a plain abdominal X-ray can serve as the initial diagnostic tool for detecting pancreatic calcifications, which are highly specific for CP including FCPD. Although it has low sensitivity (30-70%), it is widely available, inexpensive, and capable of identifying moderate to coarse intrapancreatic calcifications in advanced disease. (107)

Apart from diagnosis, imaging is also important to differentiate the different etiologies of T3cD (Table 4). Overall, the choice of imaging should be tailored not only by the diagnostic accuracy but also invasiveness, availability, operator experience and cost-effectiveness.

## Chapter 5. Role of genetic tests

**5.1 Genetic testing using clinical/whole exome sequencing may be offered to patients with T3cD with a positive family history, those aged less than 20 years and to patients without any other identified aetiology of the pancreatic disease. The panel of genes tested should include *PRSS1, SPINK1, CTRC* and *CFTR*.** (LOE : 4 , Consensus : 92% , SOR : B)

Genetic screening cannot be recommended for every patient with T3cD since upto 60% of adult cases might be secondary to alcoholic CP, there are other identifiable etiologies, and the genetic results do not alter the medical treatment , but genetic results might help understand the disease course better and aid in family planning and pre-conceptional counselling. In line with the HaPanEU

Guidelines for CP, we suggest that focussed genetic testing, through clinical genetic panels or whole exome sequencing, may be considered in patients with T3cD who have a documented positive family history of pancreatic disorders or early-onset disease and also to patients without any other identified aetiology of the pancreatic disease (108). When performing genetic testing, the selected panel of genes should ideally include *PRSS1* (cationic trypsinogen gene), *SPINK1* (serine protease inhibitor Kazal type 1), *CTRC* (chymotrypsin C), and *CFTR* (cystic fibrosis transmembrane conductance regulator) as pathogenic variants in these genes are well-established contributors to hereditary pancreatitis and related conditions.(109) Studies from Indian subcontinent suggest that the N34S variant of *SPINK1* is a susceptibility gene for FCPD.(110,111) However, in a recent study isolated *SPINK1* (N34S) mutation was detected in 5.88% of patients with FCPD, 6% of patients with T2D, and 2% of healthy controls with in silico analyses showing conflicting evidence regarding pathogenicity.(112) Thus, this mutation is considered unlikely to be clinically relevant in this context. In this study *PRSS1* and *CTRC* (exons 2–3) mutations were present in approximately 7.8% and 2% of FCPD patients, respectively.

The results of genetic testing should be interpreted with caution in conjunction with clinical findings, family history, and other diagnostic data, ideally in consultation with a geneticist or genetic counsellor. It is worth to mention here that these investigations are especially valuable in research settings, where genetic profiling can contribute to a better understanding of disease mechanisms, genotype–phenotype correlations, and the identification of novel pathogenic variants. However, clinical utility of genetic testing among FCPD patients is yet to be established in day-to-day practice.

## Chapter 6. Management

**6.1 Management of T3cD should be by a multidisciplinary team involving endocrinologists, gastroenterologists, radiologists, gastro-surgeons, nutritionists and diabetes educators.** (LOE : 5 , Consensus: 100% , SOR : B)

**6.2 Medical nutrition therapy in T3cD**

**6.2.1 Dietary management of pancreatic diabetes should follow the same principles as other forms of diabetes, except that a more liberal calorie and protein intake may be advised.** (LOE : 3 , Consensus : 92 % , SOR: B)

**6.2.2 Patients with PEI should be advised to consume smaller portions and eat more frequently throughout the day, with limitations of fat intake. If PEI symptoms persist despite adequate PERT, restriction of dietary fiber intake may be advised.** (LOE : 3 , Consensus: 85 % , SOR : C)

**6.2.3 Physical activity recommendations should follow the same principles as for T2D with emphasis on daily aerobic exercise for a minimum of 30 minutes at least 5 times in a week. Muscle strengthening exercises should be encouraged to improve muscle health.** (LOE : 5 , Consensus : 98 % , SOR: B)

**6.2.4 Abstaining from alcohol and smoking cessation are strongly recommended to reduce pancreatic inflammation and vascular complications.** (LOE : 3 , Consensus : 95 % , SOR: B)

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In contrast to T2D where major goal of diabetes management is optimising glycemic control, in T3cD dietary therapy also aims to prevent malnutrition, reduce symptoms of steatorrhea and prevent deficiency of fat-soluble vitamins.(108) A more liberal calorie intake may be necessary as most patients have low body mass index and protein intake should be adequate. Fat restriction is suggested if steatorrhea is present, but it is not required when patient is receiving adequate PERT therapy. Dietary fibre restriction is recommended for those suffering from steatorrhea despite being on PERT. Fat soluble vitamins (A, D, E, K) and Vit $B_{12}$ and minerals (Ca, Zn, Mg and chromium) are common and should be replaced only in presence of clinical manifestations of deficiency. Routine testing or supplement of these vitamins are not recommended.(10) The differences in dietary management between T1D, T2D and T3cD are summarised in Supplementary Table 1.

In peri-operative situations, patients with T3cD may require enteral nutrition (EN) and total parenteral nutrition (TPN). EN (with nasogastric or naso-jejunal tubes or via feeding jejunostomy) is usually preferred over TPN as the former is associated with fewer infectious and metabolic complications. PERT is to be continued along with enteral feeding. TPN is reserved for patients who cannot receive enteral nutrition and requires intensive glucose monitoring due to a high risk of GV.(113)

In the absence of evidence, no specific exercise recommendations can be made for patients with T3cD. So, we recommend them to follow the exercise recommendations outlined by the ADA for T2D. (114) Daily aerobic exercise of 30 minutes at least 5 days a week has been shown to improve glucose control and reduce comorbidities. In view of low muscle mass and young age, we recommend incorporating muscle strengthening exercise in their regular exercise programmes. Abstinence from alcohol and smoking cessation are strongly recommended to reduce pancreatic inflammation and vascular complications.(115)(116)

954

955 **Recommendation 6.3 Pharmacological therapy in T3cD**

956

957 **6.3.1. Oral anti-diabetic agents (OADs) can be used as the initial pharmacotherapy for**
958 **glycemic management in T3cD cases with mild hyperglycemia (HbA1c <8%).** (LOE : 3 ,
959 Consensus : 82 % , SOR: C)

960

961 **6.3.2. Metformin can be considered as first line oral agent for glycaemic management as**
962 **it has been associated with a reduced risk of pancreatic cancer.** (LOE : 3 , Consensus : 95
963 % , SOR : B)

964

965

966 **6.3.3 Although low incretins have been demonstrated in T3cD, there is controversy**
967 **regarding the use of incretin-based therapy due to their higher risk of pancreatitis and**
968 **their use should be avoided at present time until their safety is confirmed.** (LOE : 5 ,
969 Consensus : 100 % , SOR: B)

970

971 **6.3.4 Other agents like sulfonylureas, pioglitazones and SGLT2 inhibitors can be used for**
972 **glycemic control, knowing that the presence of PEI might increase their discontinuation**
973 **rates and reduce the effectiveness of sulfonylureas and metformin.** (LOE : 3 , Consensus:
974 85 % , SOR : C)

975

976 **6.3.5 Majority of patients will need insulin for control of diabetes. (**LOE : 5 , Consensus :
977 95 % , SOR : B)

978

Journal Pre-proof

**6.3.6 Insulin therapy should be initiated at doses similar to that used in T1D.** (LOE : 3 , Consensus : 95 % , SOR : B)

**6.3.7 Multiple daily subcutaneous injections of insulin should be the preferred regimen and insulin pumps should be considered in motivated patients if they experience a brittle form of T3cD.** (LOE : 5 , Consensus: 80 % , SOR : C)

In spite of the primary pathology being in the pancreas, many patients with T3cD can have better preserved beta cell function as assessed by C-peptide levels as compared to T1D but worse than T2D, and therefore may respond well to OADs. (117) A UK database study, including 7084 pancreatic diabetes and 97227 T2D patients, evaluated the use of metformin, sulphonylureas, SGLT2-inhibitors and thiazolidinediones and concluded oral therapies were effective in T3cD, with substantial HbA1c reductions.(118) An existing guideline recommends initiation of OADs for mild hyperglycemia (HbA1c <8%). (10) As in T2D, metformin should be considered as the first line agent for glycemic management. Gastrointestinal intolerance including nausea, abdominal discomfort, diarrhoea may be common and patients need to be counselled regarding this. (119) Although considered weight-neutral, metformin might also lead to weight loss in some. In a recent meta-analysis comprising 10 cohort studies and 3 case control studies, metformin has been shown to be associated with a significant lower risk of pancreatic cancer [RR 0.63, 95% confidence internal (CI) 0.46–0.86, p = 0.003], which makes it an attractive choice as first line agent in management of T3cD.(120)

Most studies have suggested low incretin levels in T3cD, although others have shown that fasting and stimulated GLP-1, but not GIP, increases 1.5 to 2 times in FCPD as compared with T2D and controls although there were no differences seen in dipeptidyl peptidase type-IV

(DPP-IV), indicating incretin resistance. (46,99) In both the scenarios, incretin-based therapies would have been an attractive choice for the management of diabetes. However, there is a concern about increased risks of pancreatitis with incretin-based therapies, though some studies and meta-analysis refute this. (46,121,122) Additionally, animal model studies have shown that GLP-1 analogues can increase *PDX1* expression leading to the transformation of PDAC to a malignant phenotype.(123) Therefore, we recommend against the routine use of incretin-based therapies in T3cD until their safety is confirmed.

A recent population-based cohort study has shed light on the efficacy, safety and discontinuation rates of different OADs in T3cD. While all the agents led to glycemic reduction, it was seen that those with PEI had lower HbA1c reductions (9.4 mmol/mol vs. 12.2 mmol/mol in non-PEI) and higher odds of discontinuation (OR 2.03 vs. 1.08 for non-PEI) due to side effects.(124) Metformin and sulphonylureas showed reduced effectiveness in patients with PEI, while SGLT2-inhibitors and thiazolidinediones maintained effectiveness across groups. Thus, OADs can be an important component of glycaemic management in T3cD, but PEI patients may require closer monitoring due to reduced tolerability and effectiveness. Data with alpha glucosidase is scarce, however, may be used to control post-prandial glycemic surge, with caution due to risk of compounding gastrointestinal symptoms.

Pancreatic diabetes is associated with progressive pancreatic damage, ultimately leading to poor beta cell reserve, which in due time necessitates insulin therapy. Majority of individuals with T3cD are likely to require early initiation of insulin therapy. It is important to educate patients regarding the signs and symptoms of decompensated hyperglycemia, as well as the probable necessity for insulin treatment in future at the outset. Insulin therapy should be initiated using dosing calculations comparable to those used for patients with T1D, given that many individuals with T3cD retain peripheral insulin sensitivity and have an increased risk of hypoglycemia along with residual insulin secretion and compromised glucagon.(125)

However, some data from eastern India shows slightly higher insulin requirement for FCPD patients as compared to T1D (1.16 U/kg vs 1.01 U/kg).(117)

With ongoing pancreatic destruction, the mass of insulin-secreting beta cells diminishes, resulting in the need for multiple daily doses of insulin in a basal-bolus insulin regimen. If glycaemic control remains unstable, the use of insulin pumps may be considered for appropriately motivated individuals. In addition, patient education should emphasize the importance of regular glucose monitoring and recognition of early signs of both hypoglycemia and hyperglycemia, particularly given the variable insulin requirements and susceptibility to metabolic fluctuations in T3cD. Recent studies have shown that insulin therapy may lead to an increased risk of PDAC (OR = 2.2, 95% CI = 1.6–3.7) and must be used with caution in T3cD patients with existing inflammatory pancreas pathology.(126) However, the risk was restricted to those on insulin for ≤3 years (OR = 2.4) only while insulin use of >10 years was associated with a reduced risk of pancreatic cancer (OR = 0.5, 95% CI = 0.3–0.9; $p < 0.0001$). Further research is required to reach a definitive conclusion regarding the association between insulin use and the risk of pancreatic cancer.

In T3cD due to chronic pancreatitis or pancreatectomy, islet auto-transplantation after total pancreatectomy seems to be an interesting strategy to preserve endogenous β-cell function, reduce glycaemic variability, and in a subset of patients possibly to achieve prolonged insulin independence. The best opportunity to preserve endogenous insulin secretion is before or at the time of total pancreatectomy, termed as total pancreatectomy with islet auto transplantation (TPIAT) where the patient's own islets are infused into portal vein. TPIAT is indicated in cases- i) CP with intractable pain unresponsive to medical or endoscopic therapy, ii) recurrent AP due to irreversible cause, iii) undergoing high-risk pancreatic surgery, iv) some selected neoplasms, v) extensive traumatic pancreatic injury. (127,128). Unfortunately, there is little scope for autologous islet transplantation for patients with already established T3cD due to expected poor

yield of healthy islets. However, recent reports have shown that having T3cD should not automatically exclude patients from autologous islet transplantation as these patients also had encouraging results in terms of pain scores, although they remain insulin dependent. (129) Allogenic islet transplant is practically not possible in T3cD, while stem cell derived immune evasive islet replacement is still not indicated outside research settings.(130)

**Recommendation 6.4 Pancreatic enzyme replacement**

**6.4.1 PERT should be given in the form of pancreatin supplementation preferably in the form of small enteric-coated tablets containing at least 40,000 to 50,000 units of lipase with meals and 20,000 to 25,000 units with snacks. For children the recommended dose can be calculated according to body weight (500-2500 units units/kg/meal), or according to the daily fat intake (500-4000 units of lipase/gm of fat/day).** (LOE : 3 , Consensus: 98 % , SOR : B)

**6.4.2 Patients on higher doses of PERT without adequate resolution of symptoms should be advised concomitant administration of Proton Pump Inhibitor (PPI) and restriction of dietary fibres.** (LOE : 4 , Consensus : 92%, SOR : B)

**6.4.3 Patients requiring very high dose of PERT without adequate resolution of symptoms should be screened for the presence of malabsorptive diseases including celiac disease, bacterial overgrowth syndrome, giardiasis etc.** (LOE : 4 , Consensus : 88 %, SOR : C)

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**6.4.4 The long-term use of very high dose of PERT (>10,000 units of lipase/kg/day) should be avoided keeping in mind the rare serious adverse effect of fibrosing colonopathy.** (LOE : 5, Consensus: 90% agreement, SOR : C)

The dosage for PERT in T3cD depends on the lipase activity. The initial dose of lipase into the duodenum should be approximately 10% of the physiologically secreted dose.(108) Administration of a minimum dose of 40,000–50,000 units of lipase with main meals and half of that dose (20,000–25,000 units) with snacks has been shown to be effective in adult patients.(83) A lower dose of 25000 units/meal can be initiated for milder symptoms but severe PEI will require doses exceeding 40,000-50,000 units/meal. Doses should be increased gradually till steatorrhea resolves or the maximum dose is reached. For children, weight-based dosing may be appropriate. Requirement of doses exceeding 2500-3000 units/kg of body weight is unusual and compliance should be ensured in them.(131,132) Restriction of dietary fibres to < 25 grams/day and the concomitant use of PPI to reduce gastric acid secretion and enhance absorption can lead to improved response. (133,134) After ensuring compliance higher PERT dose should arise the suspicion for malabsorptive conditions like bacterial overgrowth syndrome, celiac disease, bile acid malabsorption and intestinal infections like giardiasis.(135,136)

PERT is associated with improved outcomes in terms of mortality and morbidity in subjects with T3cD. Meta-analyses have shown that PERT can significantly improve fat malabsorption and fat fecal fat excretion in cases with chronic pancreatitis.(137) PEI-related malnutrition, maldigestion and abdominal symptoms like excessive bloating and steatorrhea can affect the QoL of patients. Short term studies have reported a positive impact of PERT on QoL, with improvement across several domains on gastrointestinal related QoL.(138,139) Apart from improving exocrine function, PERT recipients have also been reported to have improved

glycemic control and reduced GV in diabetes with PEI . (28,137,140,141) However, effect on hypoglycemia is controversial however. The effect of PERT might be more prominent in those with later stages of the disease with more severe pancreatic exocrine dysfunction. It is safe and well tolerated however certain adverse effect can occur with long term use and higher doses. Adverse effects have been mostly mild gastrointestinal symptoms. Higher doses can cause gastrointestinal symptoms like nausea, vomiting, constipation and diarrhoea. (83) Other symptoms like pruritus, rash and myalgia can occur.(142) (143) Fibrosing colonopathy can occur with prolonged use of high dose of PERT and has been reported in subjects with cystic fibrosis. (144) (28,137,140,141)Thus, subjects receiving higher doses for longer period should be monitored for potential complications.

The management of acute or chronic pain related to pancreatitis, endoscopic or surgical interventions for ductal strictures and management of pancreatic malignancies is beyond the scope of this consensus.

## Chapter 7. Complications

### Recommendation 7.1 Acute complications

**7.1 Acute hyperglycemic complications like diabetic ketoacidosis (DKA) are less common in T3cD but can occur in those requiring insulin in the presence of precipitating factors like severe sepsis.** (LOE : 4 , Consensus : 90 %, SOR : C)

**7.2 Patients with T3cD are at high risk for hypoglycemia and can have a brittle form of diabetes with wide glycemic fluctuations, underscoring the need for close monitoring**

**specially in those on insulin and not receiving PERT.** (LOE : 3 , Consensus : 95 %, SOR : B)

DKA is believed to be rare in T3cD, especially in FCPD. Postulated mechanisms for ketosis resistance include decreased alpha cell and lower glucagon reserve, lesser subcutaneous adipose tissue leading to reduced non-esterified fatty acids (NEFA), carnitine deficiency secondary to fat malabsorption and partial preservation of beta cell function. However, studies from India, Bangladesh and Taiwan with large countrywide cohorts show 13-15% incidence of DKA, hyperosmolar hyperglycemic state (HHS) or DKA-HHS overlap in T3cD. (145)(146,147) Greater than 90% of these patients had significant precipitating factors for DKA like severe sepsis, omission of insulin. The DKA episodes were usually mild in severity.(145)

Patients with T3DM are known to run a high risk for hypoglycemia, which is attributable to several mechanisms including the lack of the decline in insulin levels as a first line defence to hypoglycemia, extensive pancreatic destruction causing lack of glucagon secretion in advanced phase of the disease.(44) Some studies have reported that patients with T3cD have a brittle form of diabetes with wide glycemic fluctuations and high GV compared to T2D, mainly due to high post-meal glycemic excursions whereas hypoglycemia rates were similar to T2D though some studies suggest otherwise. (148,149) In an Indian study, however, patients with T3cD on insulin had lower GV and hyperglycemia but similar hypoglycemia rates as seen in T1D.(140) In another study, hypoglycemia unawareness has been evidenced in as high as 73% of patients with FCPD. Significant hypoglycaemia, nocturnal hypoglycaemia, duration of hypoglycaemia and poor cardiac autonomic functions were significantly more prominent in the “unaware” group, who also had significantly low fasting and postprandial glucagon levels.(150) A study using continuous glucose monitoring (CGM) in T3cD reported significantly higher time below range (TBR), LBGI (low blood glucose index) in FCPD compared to non-FCPD subtypes of T3cD.(28) Acute onset non-choreoballistic movement disorders (hemifacial spasm, myoclonus) have been reported as the first presenting manifestation of T3cD and any patient of T3cD presenting with acute onset involuntary

movements should be screened for their glycemic status.(151,152) Management of hyperglycemia alone generally leads to complete reversal of the movement disorders. Hypoglycemia has been reported as a major cause of death in T3cD and the rates are higher in T3cD patients on insulin, those with continuous alcohol intake and those not receiving PERT. (153,154) As expected, large epidemiologic studies have reported higher hypoglycemia rates with insulin use compared to those receiving oral anti-diabetic agents like metformin.(155)

**Recommendation 7.2 Chronic complications**

**7.2.1 Screening for microvascular complications in T3cD should follow the same principles as for T2D, with yearly screening starting at 5 years from diagnosis, or earlier in those not receiving PERT or having clinical and/or biochemical evidence of PEI**. (LOE : 3, Consensus : 97 %, SOR : B)

**7.2.1.1. Patients with advanced FCPD should be additionally screened for cardiac autonomic neuropathy.** (LOE : 4, Consensus : 85 %, SOR : C)

**7.2.2 Macrovascular complications occur at slightly lesser frequency than in T2D but there is lack of adequate evidence currently to make recommendations regarding the frequency and protocol for screening**. (LOE : 5, Consensus : 92 %, SOR : B)

**7.2.3 Blood pressure should be monitored at each visit and management of hypertension should be as per standard guidelines.** (LOE : 3, Consensus : 88 %, SOR : C)

Journal Pre-proof

**7.2.4 Dyslipidemia may occur at a lesser frequency than in T2D but annual screening with fasting lipid profile should be done.** (LOE : 4, Consensus : 94 %, SOR : B)

**7.2.5 Adequate control of risk factors that affect the risk of target organ complications in T3cD like obesity, hypertension and dyslipidemia is important.** (LOE: 5, Consensus : 94 %, SOR : B)

**7.2.6 In absence of adequate evidence and the possibility of FIB-4 being prone to inaccuracy in this population, we suggest that screening for metabolic-dysfunction associated steatotic liver disease (MASLD) in T3cD should use vibration controlled transient elastography (VCTE) as the initial tool.** (LOE: 5, Consensus: 82 %, SOR : C)

People with FCPD harbour a similar risk of microvascular diabetes-related complications like retinopathy, nephropathy, and neuropathy as seen in T2D.(27) In a study conducted on a group of patients with DM detected below 30 years of age, microvascular complications of diabetes were seen in similar proportions in all groups, with peripheral neuropathy being more common in FCPD.(156) Other studies have also confirmed higher prevalence of peripheral neuropathy assessed by Vibration Perception Threshold (VPT) in FCPD (26.7%) as compared to T2D (30%).(157) The increased incidence of peripheral neuropathy is possibly due to coexisting nutritional deficiencies in FCPD though vitamin $B_{12}$ and other nutrients have not been systematically assessed in these studies. Annual neurologic assessment and foot evaluation must be done. Studies have reported lower frequency of retinopathy inT3cD than T2D. (156) As in all persons with diabetes, dilated fundus examination, preferably examined by ophthalmologists are needed in patients with T3cD at annual intervals or more frequently in those with established retinopathy. Notably, in a study from Bangladesh, a high prevalence of

cataract has been seen in children with FCPD further necessitating periodic ophthalmologic examinations.(158) Nephropathy screening should include serum creatinine elevation with estimated glomerular filtration rate (eGFR) calculation and a spot urine albumin-creatinine ratio (ACR) sample with chronic kidney disease (CKD) staging done as per standard guidelines. It may be noted here that cystatin-C based formulae for eGFR calculation may be more appropriate than Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) or other formulae in these patients especially for those not receiving adequate PERT and having low BMI and poor muscle mass. There is a high incidence of cardiac autonomic neuropathy (CAN) in FCPD (40% to 60% depending on duration of diabetes), parasympathetic dysfunction being predominant. (157,159) FCPD patient with CAN had more advanced disease (lower fecal elastase, worse glycemic control) and significantly higher occurrence of end organ damage (neuropathy/ nephropathy/ retinopathy).(157)

Unlike in T2D, a prolonged pre-diabetes phase has not been reported clearly in T3cD, but the presentation of diabetes is not very florid. In youth with T1D, the recommended age of initiation of screening for microvascular complications like neuropathy and retinopathy is after 5 years of diagnosis of diabetes. In the absence of adequate evidences regarding the onset and progression of microvascular complications in T3cD, it seems reasonable to screen for microvascular complications in T3cD following the same protocol as for T2D.

Unlike microvascular complications, macrovascular complications are expected to be lower in T3cD, especially FCPD due to lesser chances of atherogenic dyslipidemia, younger age and a lean phenotype among other factors.(27) In a study from Bangladesh, macrovascular complications like ischemic heart disease and peripheral vascular disease were less frequently observed than microvascular complications in FCPD. (146) Few studies have focussed on comparing macrovascular complications in T3cD to other forms of diabetes. Shivaprasad et al showed prevalence of coronary artery disease and stroke to be significantly lower in T3cD than

in T2D.(160) Risk of macrovascular complications correlated with duration of diabetes, HbA1c and age of patient.

Observational studies on comorbidities in T3cD or FCPD had variable study designs with small samples.(146,157,159,160) Prospectively, smoking, hypertension, hyperlipidaemia, and obesity are expected to influence target organ complications and should be timely screening and management is important. The recommended systolic and diastolic blood pressure goals are 130 mmHg and 80 mmHg, respectively, or 90th percentile for age and sex for children. Cholesterol levels are low in T3cD, specially FCPD due to poor absorption of fat and low BMI but dyslipidemia may occur in individuals receiving adequate PERT as reported in patients of CFRD. However, following existing guidelines for dyslipidemia in individuals with diabetes and considering the benefits vs. low risk of dyslipidemia management, annual lipid profile is recommended for all adult patients with T3cD, prioritising those with additional risk factors like obesity, family history of coronary artery disease, and longer duration of diabetes.(161) Since there is no increased risk of other autoimmune disorders and endocrinopathies, screening for these is not needed.(162)

Despite the increasing interest in detection and treatment of MASLD till date, there is no evidence regarding the prevalence of MASLD in T3cD. Increasing number of studies in T1D and T2D have unearthed multiple mechanisms which explain the increasing prevalence of MASLD in diabetes. Intriguingly, though quite a few of these mechanisms are well applicable to T3cD, presence of MASLD in them has not been adequately researched in them. There are multiple factors like prolonged insulin exposure, frequent hypoglycemia, hyperglucagonemia and reduced GLP-1 secretion in T3cD which might contribute to hepatic lipogenesis and MASLD in T3cD.(163–165) On the contrary, low BMI, low glucagon, and malabsorption may play antagonistic roles. Thus, in the absence of adequate evidence, screening for MASLD in T3cD may follow the same principles as T2D. (165) It is to be noted however that in some

patients with FCPD, due to the loss of hepatotropic effects of both insulin and glucagon, elevation of liver enzymes specially serum glutamic pyruvic transaminase (SGPT) and alkaline phosphatase (ALP) have been seen and focal necrosis and inflammatory changes have been seen in histopathology in the absence of fatty changes.(166) Thus, the consensus suggests that non-invasive scores like FIB-4 may not be accurate as the initial screening test for MASLD in T3cD making VCTE the preferred initial screening modality.

## Chapter 8. Monitoring

### Recommendation 8.1 Monitoring of glycemic parameters

**8.1.1 Glycemic monitoring in T3cD should be done using FPG and PPPG for short term and HbA1c% for long term control, the targets for therapy being the same as for other diabetes.** (LOE : 1, Consensus: 100%, SOR : A)

**8.1.2 CGM should be considered in all T3cD patients, especially those receiving insulin. If CGM is unavailable, frequent self-monitoring of blood glucose (SMBG) should be practised.** (LOE : 1, Consensus : 100%, SOR: A)

International recommendations support the notion that T3cD should be diagnosed and followed up with FPG, PPPG (preferably an OGTT) and HbA1c as other types of diabetes.(10) Past study from resource-constrained settings have shown that FCPD patients have poorly controlled glycemic status compared to T2D.(146,160) On the other hand, a study from Germany showed that in comparison with T1D, pediatric T3cD cases had better long-term glycemic control with similar rates of severe hypoglycemic events.(167) A case-control study

in Indian settings involving newly diagnosed pediatric T1D and T3cD found significantly higher FPG in T1D than FCPD, but no difference in PPPG and HbA1c at presentation. (117)

As discussed before, T3cD may be having a high propensity to have high GV as compared to T2D or even T1D.(28,160) Multiple CGM based studies have reported high indices of GV and low Time-in-range (TIR) compared to T2D.(140,148,168) Indices of hypoglycemia like TBR have been variable and may depend on factors like the etiology of pancreatitis or whether receiving PERT as well as the type of treatment.(28,168). One study which studied CGM parameters in T3cD with relatively shorter duration and preserved C-peptide showed no differences in CGM parameters from T1D or T2D. (149) Current guidelines recommend the same TIR, TAR and TBR for adults with T1D and T2D. The need for CGM is particularly high among T3cD with longer duration of diabetes, more severe disease with PEI and others at high risk for hypoglycemia. Until more data in this particular population is available, the same targets might be applied for T3cD (TIR [70 – 180 mg/dl] > 70% , TBR [< 70 mg/dl] < 4% , [< 54 mg/dl] < 1% and TAR [> 180 mg/dl] < 25% and [> 250 mg/dl] < 5%).(44)

This not only poses significant challenge in keeping the glycemic equipoise, but also heralds various angiopathic complications and hypoglycemia unawareness.(150,169,170). Thus, CGM is necessary for patients of T3cD especially those receiving multiple daily doses of insulin. In resource constrained settings, frequent SMBG can be performed as an alternative to CGM.

**Recommendation 8.2: Monitoring patients with PEI**

**8.2.1 Clinical and anthropometric parameters should be used to assess the nutritional status of all patients with T3cD having PEI, at baseline and during follow-up.** ( LOE : 3 ; Consensus : 96 % , SOR : B)

Journal Pre-proof

**8.2.2 Response to PERT is indicated by improvement in the nutritional status.** (LOE : 2 , Consensus : 97% , SOR : A)

**8.2.3 Measurement of serum levels of fat-soluble vitamins, trace elements (Mg, Se, Zn) are not recommended to diagnose PEI, but it may be used as a surrogate marker to assess the response to PERT.** (LOE : 3 , Consensus : 82%, SOR : C)

**8.2.4 Fecal elastase should not be measured to monitor the treatment response to PERT.** (LOE : 5, Consensus : 97%, SOR : B)

**8.2.5 Dual-energy x-ray absorptiometry (DXA) scan for assessment of bone mineral density (BMD) should be obtained at baseline and repeated at an interval of every 1-2 years.** (LOE: 5, Consensus : 96%, SOR : B )

**8.2.6 Adequate calcium and vitamin D intake should be advised for all patients.** (LOE : 3, Consensus : 98%, SOR : B )

Nutritional status should be monitored in all patients with PEI. Clinical assessment regarding dietary habits and the severity of gastrointestinal symptoms such as steatorrhea, postprandial abdominal pain, and bloating should be done at baseline and during follow-up.(171) Abdominal symptoms often improve once adequate PERT is initiated. Anthropometric parameters such as body weight and BMI should be measured. In addition, the assessment of muscle mass, muscle strength, and muscle function should be performed, as sarcopenia is not uncommon in PEI. Measurement of mid-arm circumference and calf circumference gives a clinical idea about muscle mass. Hand grip strength, the sit to stand test, and the 6-minute walk test are commonly

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used for the functional assessment of muscle strength and function.(172) With adequate PERT administration, patients experience gains in body weight and muscle mass. Muscle strength and muscle function are also expected to improve. It is not recommended to measure serum levels of fat-soluble vitamins and trace elements (Mg, Se, Zn) to diagnose PEI. However, if the baseline level is available, then it may be used as a surrogate marker to assess the response to PERT during follow up. (173) Initiation of PERT does not alter fecal elastase levels therefore should not be measured to assess treatment response. Osteopenia or osteoporosis is frequently observed in CP. As CP is a common cause of PEI, it is advisable to assess BMD using a DXA scan in all patients with PEI at baseline and at intervals of 1-2 years. (173)

**Recommendation 8.3: Monitoring for pancreatic carcinoma**

**8.3.1 Patients with T3cD who develop features suspicious of malignancy should be monitored for the early diagnosis of PDAC.** (LOE : 2, Consensus : 98% , SOR : A )

**8.3.2 Worsening of glycemic status that was well controlled previously, along with a history of recent-onset weight loss, are the initial clues that should alert the clinician regarding the possibility of underlying pancreatic carcinoma.** (LOE : 2, Consensus : 100 % , SOR : A )

**8.3.3 Individuals with FCPD and hereditary pancreatitis due to the PRSS1 mutations should be monitored more frequently for pancreatic carcinoma than those who have pancreatic diabetes due to other causes.** (LOE : 5, Consensus : 95% , SOR : B )

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**8.3.4 In the presence of suspicion for PDAC, imaging of the pancreas along with the measurement of serum carbohydrate antigen 19-9 (CA-19-9) levels should be performed.** (LOE : 3, Consensus : 97% , SOR : B )

**8.3.5 We recommend against routine CA–19–9 screening in asymptomatic individuals with T3cD given its poor sensitivity in the absence of a pancreatic mass lesion.** (LOE : 3 , Consensus : 97% , SOR : B )

**10.3.6 Tri-phasic pancreatic-protocol CT is the best initial imaging modality for the diagnosis and staging of PDAC.** (LOE : 5, Consensus : 99% , SOR : B )

**10.3.7 CT findings should be reviewed by a radiologist having expertise in pancreatic diseases, as the morphological features of certain inflammatory pancreatic conditions may resemble PDAC.** (LOE: 5, Consensus : 96 % , SOR : B )

**8.3.8 MRI scan should be employed for imaging when pancreatic lesions are poorly visible on CT scan and/or when imaging with CT scan is contraindicated.** (LOE : 5, Consensus: 97% , SOR : B )

**8.3.9 In doubtful cases, EUS guided FNAC/FNB may be performed from the suspicious lesions to differentiate CP from PDAC that has arisen in the context of CP.**

(LOE : 5 , Consensus : 80% , SOR : C )

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PDAC accounts for 90% of all pancreatic malignancies and carries a high mortality rate.(174) Individuals with FCPD and hereditary pancreatitis due to inherited *PRSS1* mutations are at particularly high risk of developing pancreatic carcinoma. Pancreatic carcinoma detected at an early stage is often resectable. However, clinical features are mostly absent in the early stages of PDAC.(175) Symptoms such as anorexia, jaundice with pruritus, and abdominal pain that persist despite the withdrawal of aggravating factors such as alcohol intake and smoking usually appear once the disease is advanced. Weight loss is often observed in the initial stages of disease.(23,176). New onset diabetes has also been recognized as the early manifestation of PDAC.(177) In fact, diabetes usually occurs 2-5 years before the diagnosis of carcinoma in these patients, even when the tumor is very small. The worsening of glycemic status despite weight loss, requiring an increase in the dosage of ongoing antidiabetic medications, should raise the suspicion of underlying PDAC.(178)

Early diagnosis in asymptomatic stage allows for detection of disease when it is surgically resectable. So far, none of the available tests is sensitive and specific enough to be used for screening purposes in asymptomatic individuals. All efforts, therefore, should be directed towards the diagnosis of the disease at an early stage when resection is possible.

Although an established biomarker for pancreatic carcinoma, CA-19-9 has poor sensitivity in detecting PDAC in asymptomatic individuals in the absence of a detectable mass. Moreover, it has low specificity as elevated level can occur even in pure inflammatory lesions. However, age over 60 years and CA 19-9 more than 100 IU/mL are independent risk factors for pancreatic carcinoma in patients with CP.(179). CECT scan is the primary imaging modality for PDAC. It detects locally advanced and metastatic disease reliably and allow for disease staging therefore provides an idea about resectability of the tumor. However, metastases to normal sized lymph nodes, small peritoneal and hepatic metastases are often missed on CT scan.(180) Tri-phasic pancreatic-protocol CT, including non-contrast phase, pancreatic parenchymal

phase, and portal venous phase, should be performed to identify and stage PDAC. The non-contrast phase is useful for the detection of calcifications. Following intravenous contrast injection, the pancreatic parenchymal phase and portal venous phase are acquired at 40-50 seconds and 65-70 seconds, respectively.(181) . PDAC is typically hypovascular and appears hypo-enhancing in comparison to the rest of parenchyma on the pancreatic parenchymal and portal venous phases. The portal venous phase additionally assesses metastases and venous staging.(182) Some PDAC appears iso-attenuating during the pancreatic parenchymal phase. The addition of delayed phase sequences (at 4 minutes) allows for visualization of this subset of PDAC wherein the mass appears hyperattenuating on delayed images.(183) At times, it becomes difficult to discern the radiological abnormalities pertinent to PDAC against the structurally distorted background caused by CP. (184) . Furthermore, the appearance of some inflammatory pancreatic conditions may mimic PDAC on imaging.

MRI scan has better sensitivity than CT scan for the identification of smaller tumors. T1-weighted fat-suppressed and gadolinium-enhanced gradient recalled echo (GRE) sequences should be acquired. On T1-weighted fat-suppressed sequences, pancreatic carcinoma appears hypointense against the pancreatic parenchyma, which usually displays high signal intensity due its proteinaceous content. The tumor enhances less than the surrounding parenchyma on gadolinium-enhanced GRE sequences. (180) About 10% of pancreatic carcinomas appear iso-attenuating on CT scans. MRI with diffusion-weighted imaging can help identify iso-attenuating pancreatic lesions.(181) EUS is another imaging modality to visualize lesions which may go undetected on a CT scan due to their small size and indeterminate nature. (182) Besides visualizing the pancreatic mass, EUS also allows sampling from the suspicious lesion for histopathological diagnosis. However, it is sometimes difficult to perform sampling from very hypo-echoic and calcified lesions. All Cases of T3cD with suspicion of pancreatic carcinoma should be referred to a centre with specialized gastrosurgeons, oncosurgeons,

oncologists and gastroenterologists with experience in pancreatic carcinoma for further management.

**Conclusion:**

T3cD is a unique type of diabetes with multiple issues in diagnosis and management that are still shrouded with controversies. Although it is not very rare, but data is less and this forms an area of immense research potential. It is imperative that endocrinologists and physicians, especially in South-east Asian countries, where FCPD is a common diagnosis, be guided by the best possible evidence-based strategies to optimize patient care.

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## Tables and Figures

### Figures

**Figure 1 .PRISMA flow diagram for literature review**

### Tables

**Table 1. Modified evidence grading Table 1A . Levels of Evidences (LOE) and 1B. Strengths of recommendation (SOR)**

**Table 2: Etiologies of type 3c diabetes**

**Table 3: Differences between fibro calculus pancreatic diabetes (FCPD) and diabetes due to other forms of chronic calcific pancreatitis (CCP)**

**Table 4. Preferred imaging modality and findings in different etiologies of T3cD**

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**Table 1A**

| Level of evidence (LOE) | Evidence quality | Eligible study design and sources |
|---|---|---|
| **1** | Highest | Systematic reviews, meta-analyses and high quality randomised controlled trials (RCTs) |
| **2** | High | Lesser quality RCTs, prospective cohort studies or well-designed controlled trials without randomisation |
| **3** | Moderate | Retrospective cohort studies, case-control studies, or cross-sectional studies |
| **4** | Low | Case series, poor-quality cohort/ case-control studies |
| **5** | Lowest | Expert opinion, mechanism-based reasoning or in-vitro/animal research |

**Table 1B**

| | LOE 1 -2 | LOE 3 - 4 | LOE 5 |
|---|---|---|---|
| **High consensus agreement ( >= 90 %)** | SOR Grade A | SOR Grade B | SOR Grade B |
| **Moderate consensus agreement ( 80 – 89 %)** | SOR Grade B | SOR Grade C | SOR Grade C |
| **Low Consensus agreement ( < 80 %)** | No recommendation | No recommendation | No recommendation |

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**Table 2 : Etiologies of type 3c diabetes(9,15)**

1. Pancreatitis (both acute and chronic)- Includes new onset diabetes after pancreatitis (NODAP)
2. Pancreatic neoplasm, including new-onset diabetes in pre-symptomatic pancreatic ductal adenocarcinoma (NOD-PDAC) and pancreatic cancer-related diabetes (PCRD)
3. Fibrocalculous pancreatic diabetes (FCPD) or diabetes from tropical chronic pancreatitis
4. Cystic fibrosis- Cystic fibrosis related diabetes (CFRD)
5. Hemochromatosis
6. Trauma (both surgical or others)
7. Congenital structural defects in pancreas, such as pancreatic agenesis [except those already included under maturity onset diabetes of young (MODY) due to transcription factor defect such as *IPF-1/PDX-1*]
8. Idiopathic
9. Others

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**Table 3: Differences between fibrocalculus pancreatic diabetes (FCPD) and diabetes due to other forms of chronic calcific pancreatitis (CCP)**(18,26–28)

| **Characteristics** | **FCPD** | **Diabetes due to other forms of CCP** |
|---|---|---|
| Geographical distribution | More prevalent in tropical countries | No such predilection |
| Sex difference | Male : Female = 70 : 30 | Almost exclusively in males |
| Age of onset | Childhood to young adulthood | Middle age |
| Socioeconomic strata | More commonly affects individuals from low socioeconomic status | Affects all |
| Relationship with alcohol | None | Alcoholic pancreatitis is the most common etiology |
| Pattern of calcification | Large dense intraductal calculi with discrete margin | Small speckled calculi mainly in the smaller ducts and parenchyma |
| Fibrosis and ductal dilatation | More marked | Less marked |
| Risk of pancreatic ductal adenocarcinoma | 100 times more than general population | 10 times more than general population |
| Malnutrition | Common | Less typical |
| Incidence of diabetes | Development of diabetes after fibrocalculous pancreatopathy is almost 90% | Development of diabetes after alcoholic pancreatitis is around 50% |
| Course of diabetes | More aggressive | Less aggressive |
| Glycemic variability | Very high | High |

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**Table 4. Preferred imaging modality and findings in different etiologies of type 3c Diabetes (T3cD)**

| Etiology | Preferred Imaging | Key Imaging Findings |
|---|---|---|
| Alcoholic Pancreatitis | CT, MRCP | • Fine, speckled calcifications (hazy margins)<br>• Mainly in parenchyma & small ducts<br>• Mild ductal dilatation |
| FCPD | US, CT, MRCP | • Dense, large intraductal calculi (in head)<br>• Rare parenchymal calcification<br>• Marked ductal dilatation |
| Pancreatic Carcinoma | CECT, MRI, EUS | • Hypodense mass with delayed enhancement<br>• Abrupt MPD cutoff<br>• Parenchymal atrophy |
| Post-Pancreatectomy | CT, MRI, MRCP | • Post-surgical changes<br>• Remnant atrophy<br>• Fatty replacement<br>• Fluid collections |
| Hemochromatosis | MRI, CT | • Low T2 signal<br>• Pancreatic atrophy<br>• No ductal changes |
| Cystic Fibrosis | MRI, MRCP, CT, US | • Fatty replacement<br>• Rare ductal calcification<br>• Late: calcification, atrophy, small cysts (1–3 mm) |

FCPD : Fibrocalculous pancreatic diabetes CT = Computed Tomography, MRI = Magnetic Resonance Imaging, US = Ultrasound, MRCP = Magnetic resonance cholangiopancreatography, CECT = Contrast enhanced CT, EUS = Endoscopic ultrasound

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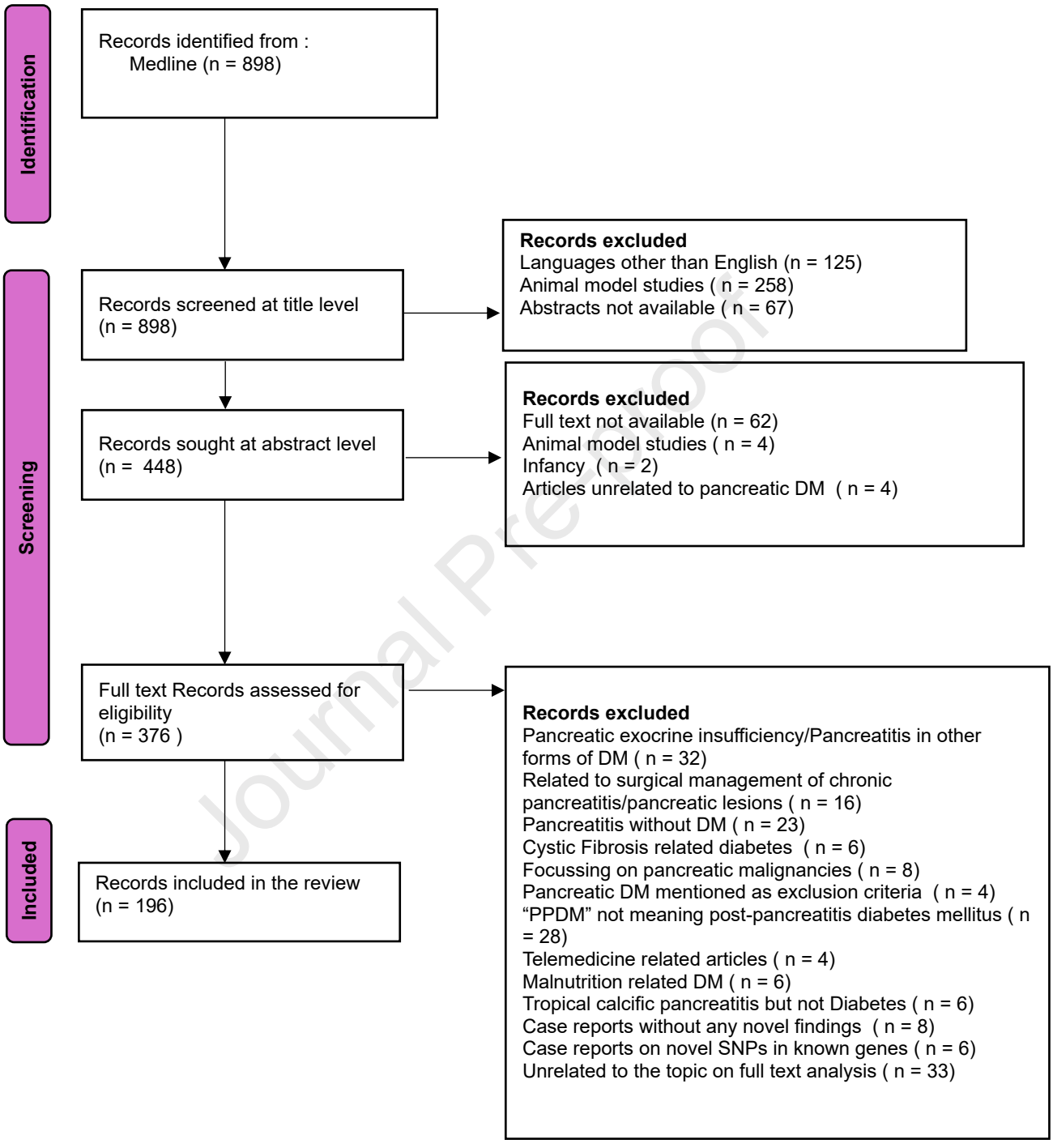


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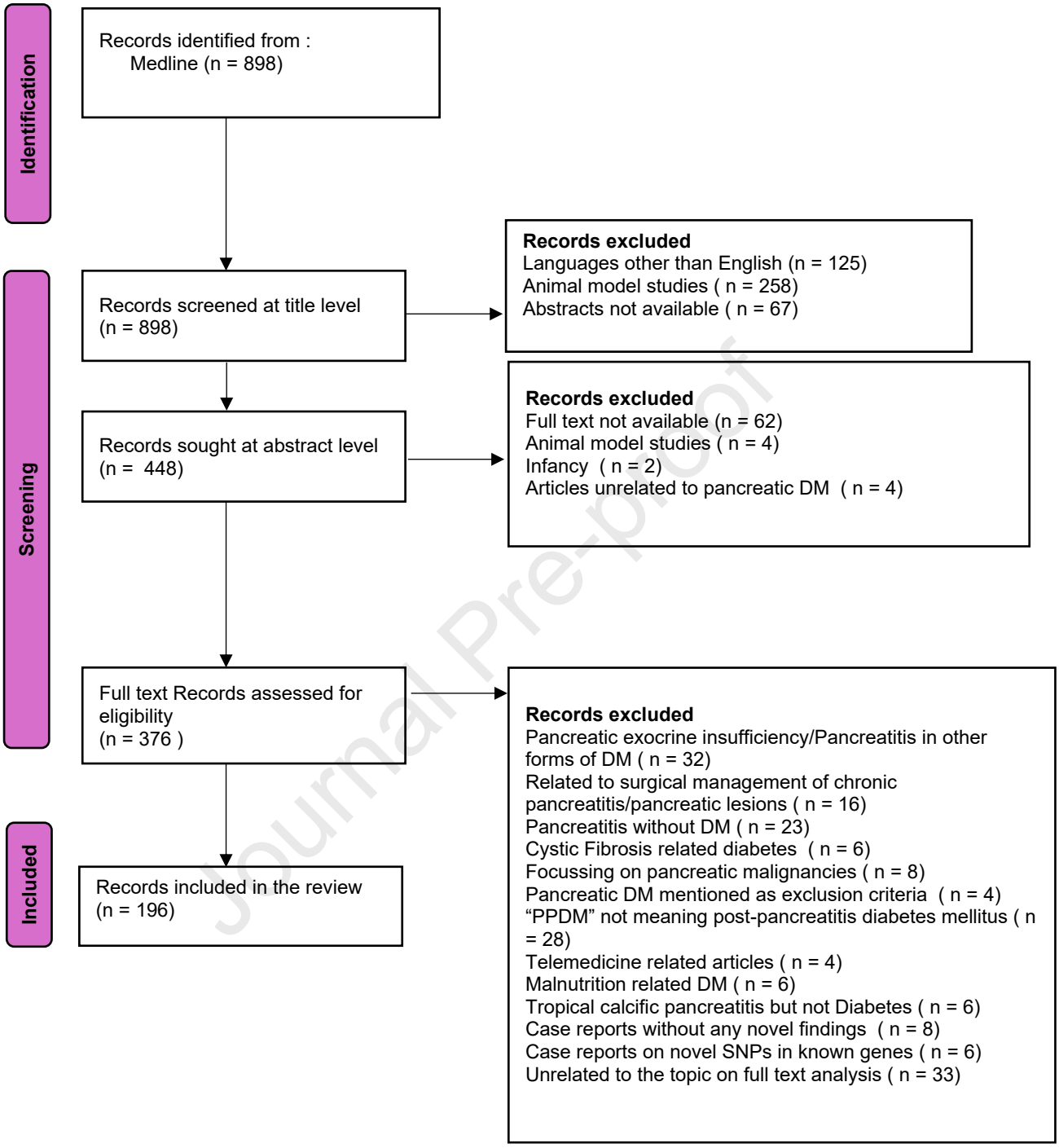


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**Highlights**

- T3cDM is a common cause for young onset diabetes especially in tropical countries.
- Multiple controversies exist from its nomenclature, diagnosis and management.
- No comprehensive guidelines exist till date.
- This consensus gives a holistic updated evidence-based statements for T3cDM.
- It covers diagnosis, classification, management – endocrine and gastroenterological and monitoring in short and long term.

**Clinical Relevance :**

Despite being a common cause for diabetes in many parts of the world, there is dearth of data and lack of guidelines for the management of T3cDM. This is the first multidisciplinary consensus giving a holistic updated evidence-based clinical-practice points for diagnosis and management of T3cDM.

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