Brazilian Journal of TRANSPLANTATION

https://doi.org/10.53855/bjt.v28i1.706_ENG

ORIGINAL PAPER

# Construction and Validation of a Bundle for Screening and Diagnosis of Posttransplant Diabetes Mellitus in Kidney Transplant Recipients

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Seccion editor: Ilka de Fátima Santana F. Boin

Received: May 31, 2025 | Approved: June 23, 2025

## ABSTRACT

**Introduction:** Posttransplant diabetes mellitus (PTDM) is a potential consequence of kidney transplantation (KTx), and its prompt identification has a beneficial effect on patient longevity and graft maintenance. Although the diagnostic standards for PTDM remain identical to those used for the general public, the reliability of the assessments differs in KTx patients, and their recognition is often overlooked when fasting glucose (FG) is utilized as the sole screening method. **Objectives:** We intended to design and authenticate a care bundle for the screening and identification of PTDM in KTx individuals. **Methods:** The following procedures were carried out: a) literature survey; b) development of the bundle; and c) expert validation by qualified reviewers. The integrative review served as a resource in formulating the bundle. We assessed the experts' feedback using the content validity index (CVI). A binomial analysis was executed to determine the consensus among the reviewers. **Results:** The bundle was organized to deliver guidance regarding: 1) which examination(s) to order; 2) the optimal timing to request them to distinguish PTDM from temporary hyperglycemia; and 3) which individuals require further assessments beyond FG. Every component was deemed validated, with an overall CVI of 0.99. **Conclusion:** The bundle was judged reliable for supporting clinical judgment in conducting PTDM screening and diagnosis in KTx individuals in a straightforward and efficient manner. We propose integrating this instrument into clinical routines due to its ease of use, affordability, and potential to enhance the care of these patients.

**Descriptors:** Posttransplant Diabetes Mellitus; Kidney Transplant; Diagnosis; Clinical Protocols; Validation Study.

## *Construção e Validação de um Conjunto de Medidas para Triagem e Diagnóstico do Diabetes Mellitus Pós-Transplante em Receptores de Transplante Renal*

## RESUMO

**Introdução:** O diabetes mellitus pós-transplante (DMPT) é uma possível complicação do transplante renal (TR), e sua detecção precoce tem um impacto favorável na sobrevida do paciente e na preservação do enxerto. Apesar de os critérios diagnósticos para DMPT permanecerem os mesmos da população em geral, a acurácia dos testes muda em receptores de TR, e sua detecção é subestimada quando a glicemia de jejum (GJ) é usada isoladamente para triagem. **Objetivos:** Nosso objetivo foi construir e validar um pacote de cuidados para triagem e diagnóstico de DMPT em receptores de TR. **Métodos:** As seguintes etapas foram realizadas: a) revisão da literatura; b) elaboração do pacote; e c) validação de conteúdo por juízes especialistas. A revisão integrativa foi considerada um auxílio na construção do pacote. Analisamos as avaliações dos especialistas usando o índice de validade de conteúdo (IVC). O teste binomial foi realizado para avaliar a concordância dos juízes. **Resultados:** O pacote foi estruturado para fornecer informações sobre: 1) qual(is) teste(s) solicitar; 2) quando solicitá-los para melhor diferenciação entre DMPT e hiperglicemia transitória; e 3) para quem solicitar exames adicionais além da GJ. Todos os itens foram considerados validados, com IVC geral de 0,99. **Conclusão:** O pacote foi considerado válido para facilitar a tomada de decisão do médico na condução do rastreamento e diagnóstico de DMPT em receptores de transplante renal de forma prática e eficaz. Recomendamos a incorporação dessa ferramenta ao cuidado médico, considerando sua fácil aplicabilidade, baixo custo e potencial para contribuir para o manejo desses pacientes.

**Descritores:** Diabetes Mellitus Pós-Transplante; Transplante Renal; Diagnóstico; Protocolos Clínicos; Estudo de Validação.

## INTRODUCTION

Posttransplant diabetes mellitus (PTDM) refers to diabetes mellitus (DM) first identified in the posttransplant phase and is linked to negative outcomes, including overall graft failure, infections, and cardiovascular complications.[1] It most commonly develops within the initial year following solid organ transplantation, with reported incidence ranging from 7% to 30%, depending on the cohort.[2] In most cases, PTDM involves impaired β-cell performance and diminished insulin responsiveness in hepatic, muscular, and adipose tissues.[3]

As a result of surgical and anesthetic stress, elevated exposure to calcineurin inhibitors (CNIs), reestablished renal insulin elimination, and glucocorticoid-based induction regimens, hyperglycemia manifests in over 90% of kidney transplant (KTx) patients within the early posttransplant weeks.[4] Temporary hyperglycemia may also arise due to interventions for graft rejection, infections, or other critical illnesses. Although transient posttransplant hyperglycemia is a significant predisposing factor for PTDM, it should not be misinterpreted as PTDM itself.

Implementing strategies for prompt PTDM identification improves both patient and graft outcomes by mitigating cardiovascular issues and long-term graft dysfunction.[5]

Establishing standardized testing protocols for PTDM screening is crucial, given the substantial inconsistency across transplant institutions regarding testing approaches and timing. Numerous centers rely solely on fasting glucose (FG) and glycated hemoglobin (HbA1c) for screening and diagnosing PTDM in KTx individuals, methods that have demonstrated lower sensitivity compared to the oral glucose tolerance test (OGTT).[6,7]

Early recognition of PTDM permits timely clinical and pharmacologic measures, which can decrease the likelihood of unfavorable results. Therefore, to define criteria for early and precise diagnosis, as well as to ensure appropriate follow-up and care for PTDM, our objective is to design and validate a bundle for PTDM screening and diagnosis in KTx patients. By "bundle," we refer to a structured set of care actions systematically aligned with the most robust evidence-based recommendations.[8]

## METHODS

### Participants

This study employed a methodological approach to develop and validate a care bundle for the screening and diagnosis of PTDM in KTx recipients. The process of constructing and validating the bundle took place from December 2022 to January 2023. The validation phase involved 13 physicians specializing in nephrology and endocrinology, all with expertise in KTx. The research protocol was approved by the ethics committee of a high-complexity hospital center in northeastern Brazil under approval number 5.835.225.

### Research phases

The development and validation of the bundle followed three main phases: a) literature review; b) bundle elaboration; and c) content validation by expert judges.[9]

### Integrative review

The literature review was performed using an integrative approach to identify evidence on the diagnostic accuracy of tests for glucose metabolism disorders in KTx recipients. Searches were conducted in the Medline/PubMed, Lilacs, Scopus, and Embase databases. The research question was structured using the PICO framework (P = Population, I = Intervention or interest, C = Comparison, O = Outcome).[10] In this context, "P" referred to KTx recipients, "I" to diagnostic tests for glucose metabolism disorders, "C" was not applicable, and "O" referred to the diagnosis of prediabetes or DM.

Only original scientific papers published in Portuguese, English, or Spanish and fully accessible online in the past 15 years were included. Excluded materials comprised review articles, conference abstracts, book chapters, editorials, dissertations, and theses. Study selection and data extraction were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, including the checklist and flow diagram.

### Development of the bundle

The insights from the integrative review supported the creation of the initial version of the bundle, which targeted KTx surgeons and physicians specializing in endocrinology and nephrology. The goal was to create a tool to enhance diagnostic strategies for glucose metabolism abnormalities, including transient hyperglycemia, prediabetes, and PTDM.

The bundle was organized to offer guidance on: 1) which diagnostic test(s) to order; 2) the appropriate timing to differentiate PTDM from transient hyperglycemia; and 3) which patients require tests beyond FG.

The supporting evidence was classified according to the evidence hierarchy defined by Melnyk and Fineout-Overholt.[11]

## Validation of the bundle

After the initial version of the bundle was developed, it underwent a "content validation" process to ensure it effectively served its intended purpose. This phase is a critical step in instrument development, providing greater "credibility and trustworthiness" among end-users.

Expert judges were selected based on a modified scoring system proposed by Joventino,12 designed to assess professional suitability for validation studies, emphasizing clinical and academic experience (Table 1). A minimum score of 5 points was required to qualify. The selection process used the Lattes Platform, a Brazilian academic *curriculum vitae* (CV) database, applying the following filters: all regions of Brazil; academic qualifications at the specialization, master's, or doctoral level; major area in health sciences; subarea in clinical medicine; and specialization in nephrology or endocrinology. Invitations were sent via email.

**Table 1.** Judge selection score, Fortaleza, state of Ceará, 2023.

| Evaluation criteria | Points |
|---|---|
| Working with KTx recipients | 2.5 |
| Recent clinical practice of at least 1 year in the area of interest* | 1 per year |
| Specialization in the area of interest* | 1 |
| Master's degree in the area of interest* | 2 |
| Doctorate or post-doctorate in the area of interest* | 2.5 |
| Published articles in the area of interest* | 1 per article |

Source: Elaborated by the authors, based on Joventino.[12] * Area of interest: KTx.

Those who agreed to participate received the initial version of the bundle and an evaluation tool,[13] divided into three sections: a) Block 1: objectives; b) Block 2: structure and presentation; c) Block 3: relevance. Responses were recorded using a Likert-type scale with the following options: 1 – completely disagree; 2 – slightly disagree; 3 – mostly agree; and 4 – completely agree. At the end of the instrument, evaluators could provide comments, corrections, or recommendations.

Feedback from the reviewers was analyzed and used to finalize the version of the bundle. A summary table consolidated all suggestions to facilitate the incorporation of improvements, resulting in an updated and final version of the bundle.

## Statistical analysis

The quantitative validation of the bundle utilized the content validity index (CVI), which reflects the proportion of agreement among experts for each item and across the entire tool.[14]

The CVI was calculated by summing the number of responses rated 3 or 4 and dividing that by the total number of responses. A threshold of 0.80 was considered acceptable.[15]

CVI scores were computed for each item, each block, and overall.[15] To further examine item-level agreement, a binomial distribution was applied using the exact test, appropriate for small sample sizes. Statistical significance was set at $p > 0.05$, and the CVI statistical reliability was benchmarked against a proportion of 0.80.[16] The reliability of scoring consistency across experts was evaluated using the intraclass correlation coefficient (ICC) and its 95% confidence intervals (95%CI), applying a two-way mixed-effects model with a consistency definition. ICC values are interpreted as follows: < 0.5 = poor reliability; 0.5-0.75 = moderate reliability; 0.75-0.9 = good reliability; and > 0.9 = excellent reliability.[17]

# RESULTS

## Integrative review

A total of 19 studies were included, published from 2006 to 2020, with 12 of them released from 2013 to 2018.[6,18-35] The majority originated from Australia (n = 4), followed by Norway (n = 3), Japan (n = 2), and Brazil (n = 2). One study each was published from Germany, China, the United States, the United Kingdom, Belgium, India, Poland, and Turkey. The studies were categorized based on their primary aim: 12 studies focused on evaluating the performance of diagnostic tests in the posttransplant setting, and seven studies aimed to identify pretransplant markers predictive of PTDM onset. In terms of study design, the distribution

was as follows: retrospective cohort, seven studies; cross-sectional, seven studies; and prospective cohort, five studies. All were considered to have level IV strength of evidence (Table 2).

**Table 2.** Characterization of integrative review studies.

| Variables | n | % |
|---|---|---|
| **Country of origin** | | |
| Australia | 4 | 21.2 |
| Norway | 3 | 15.9 |
| Brazil | 2 | 10.6 |
| Japan | 2 | 10.6 |
| Germany | 1 | 5.3 |
| China | 1 | 5.3 |
| United States | 1 | 5.3 |
| United Kingdom | 1 | 5.3 |
| India | 1 | 5.3 |
| Turkey | 1 | 5.3 |
| Poland | 1 | 5.3 |
| Belgium | 1 | 5.3 |
| **Year of publication** | | |
| 2006 | 1 | 5.3 |
| 2008 | 1 | 5.3 |
| 2009 | 1 | 5.3 |
| 2013 | 3 | 15.9 |
| 2014 | 2 | 10.6 |
| 2015 | 3 | 15.9 |
| 2016 | 1 | 5.3 |
| 2017 | 1 | 5.3 |
| 2018 | 3 | 15.9 |
| 2019 | 2 | 10.6 |
| 2020 | 1 | 5.3 |
| **Type of study** | | |
| Cross-sectional | 7 | 36.8 |
| Prospective cohort | 5 | 26.4 |
| Retrospective cohort | 7 | 36.8 |

Source: Elaborated by the authors.

## Specialist characterization

Seventy-one experts were invited via the Lattes Platform, a comprehensive database of academic and professional profiles in Brazil. Considering the predetermined period of 15 initial days and 10 additional days after new contact for those who did not respond, there were 13 respondents. All participants met the criteria established for the selection of professionals.

The number of expert judges was deemed appropriate, considering the lack of consensus in the literature regarding the ideal panel size. Some authors recommend a minimum of five and a maximum of ten professionals for this stage, while others suggest between six and 20 experts, with at least three individuals representing each selected professional group.[14]

Regarding sociodemographic characteristics, 53.8% of expert judges were female. The age range varied between 32 and 61 years old, predominantly between 30 and 40 years old (46.1%), 84.6% were nephrologists, and 38.5% had between 15 and 20 years of experience in the area. More than 60% are involved in medical assistance, and the rest dedicate themselves to teaching and assistance simultaneously. Additionally, 38.5% of professionals had scientific publications (books or articles) in the field. The judges resided predominantly in Fortaleza (66.7%), and the rest were distributed across São Paulo, Rio de Janeiro, and Brasília.

## Validation of the bundle's content and appearance

An analysis of the CVI for the items used to assess the bundle demonstrated that all components met the validation criteria (CVI > 0.80). Among the individual items, the statement "*The font size of the title and headings is adequate*" received the lowest

CVI (0.85), though it remained above the threshold for validation. The overall CVI of the assessment instrument was 0.99 (95%CI 0.91-0.98) (Table 3).

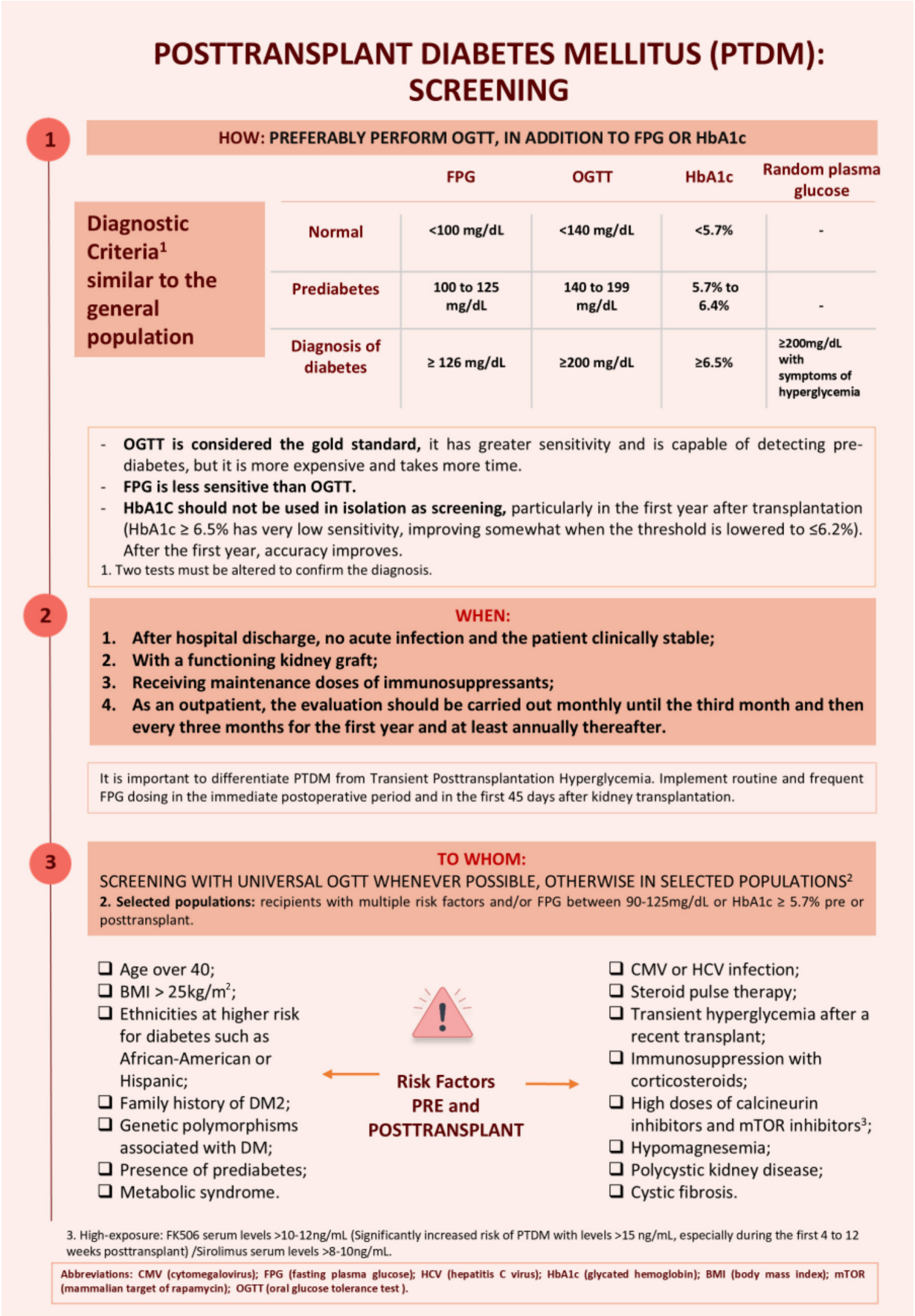
**Table 3.** Validation of the content of the bundle.

| Instrument items | CVI | Agreement | | *p*-value |
|---|---|---|---|---|
| | | MA | CA | |
| | | *f*(%) | *f*(%) | |
| **Block 1: Objectives** | 1.00 | | | |
| 1.1. The information/content is pertinent to the needs of the target audience regarding this issue. | 1.00 | 3 (23.1) | 10 (76.9) | 0.135* |
| 1.2. The information/content can help specialized physicians in diagnosing glucose metabolism disorders in KTx recipients. | 1.00 | 2 (15.4) | 11 (84.6) | 0.225* |
| 1.3 The instrument promotes and/or encourages the use of new practices, including behavior and attitude changes in physicians in the assistance of KTx recipients. | 1.00 | 2 (15.4) | 11 (84.6) | 0.225* |
| 1.4. The instrument has potential for publication in the scientific field. | 1.00 | 5 (23.1) | 8 (61.5) | 0.025* |
| 1.5. The instrument attends to the goals of the institutions that attend/work with the target audience. | 1.00 | 3 (23.1) | 10 (76.9) | 0.135* |
| **Block 2: Structure and presentation** | 0.98 | | | |
| 2.1. The bundle is appropriate for its target audience. | 1.00 | 5 (23.1) | 8 (61.5) | 0.025* |
| 2.2. The messages are present clearly and objectively. | 1.00 | 4 (30.8) | 9 (69.2) | 0.093* |
| 2.3. Information presented is scientifically correct. | 1.00 | 1 (7.7) | 12 (92.3) | 0.487* |
| 2.4. The material is appropriate for the scientific level of the target audience. | 1.00 | 3 (23.1) | 10 (76.9) | 0.137* |
| 2.5. The content is provided in a logical sequence. | 1.00 | 2 (15.4) | 11 (84.6) | 0.225* |
| 2.6. Information is well structured regarding orthography and concord. | 1.00 | 1 (7.7) | 12 (92.3) | 0.487* |
| 2.7. The writing style is in accordance with the scientific level of the target audience. | 1.00 | 2 (15.4) | 11 (84.6) | 0.225* |
| 2.8. The size of the font of the title and the topics is adequate. | 0.85 | | | 0.025* |
| 2.9. The material (paper) is adequate. | 1.00 | 4 (30.8) | 9 (69.2) | 0.093* |
| 2.10. The number of pages is adequate. | 1.00 | 1 (7.7) | 12 (92.3) | 0.487* |
| **Block 3: Relevance** | 1.00 | 2 (15.4) | 9 (69.2) | 0.025* |
| 3.1. Topics provide key aspects that should be reiterated. | 1.00 | 1 (7.7) | 12 (92.3) | 0.487* |
| 3.2. The bundle allows generalization and the transference of knowledge in many contexts. | 1.00 | 4 (30.8) | 9 (69.2) | 0.093* |
| 3.3. The bundle proposes the construction of the knowledge. | 1.00 | 1 (7.7) | 12 (92.3) | 0.487* |
| 3.4. The bundle addresses the topics essential to increasing the level of knowledge of the target audience. | 1.00 | 3 (23.1) | 10 (76.9) | 0.135* |
| 3.5. The bundle is adequate to be used by any physician specialized in the care of KTx recipients. | 1.00 | 4 (30.8) | 9 (69.2) | 0.093* |
| General bundle CVI | 0.99 | 0.91 | 0.98 | - |

Source: Elaborated by the authors. CA = completely agree; MA = mostly agree. *p*-value = exact binomial test (* alternative hypotheses state that the proportion of cases in the first group is less than 0.80).

Regarding score distribution, some discrepancies among expert evaluators were observed, particularly in the following items: 1.4: "*The instrument has potential for publication in the scientific field*"; 2.1: "*The bundle is appropriate for its intended audience*"; and 2.8: "*The font size of the title and headings is appropriate.*" It is noteworthy that for items 1.4 and 2.1, the variance occurred between the "mostly agree" and "completely agree" options, both of which are still considered acceptable responses.

The reliability of the scoring distribution was deemed "good," as evidenced by the ICC (ICC = 0.841, 95%CI 0.682-0.942). Figure 1 presents the finalized version of the bundle following validation.




Source: Elaborated by the authors.

**Figure 1.** Final version of the bundle.

## DISCUSSION

In this integrative literature review, it was possible to identify, analyze, and synthesize the results of independent studies from various nationalities on the peculiarities of diagnosing PTDM in KTx recipients, which led to the development of a bundle. After the review, it became quite clear that professionals who work in the healthcare of KTx recipients need to recognize the particularities of screening and diagnosing prediabetes and PTDM. Maintaining diagnostic criteria similar to those of the general population may not respect the particularities of this population.

The OGTT is regarded as the gold-standard examination for identifying PTDM or prediabetes, but it is expensive, unpleasant, and more time-consuming than other approaches. Because PTDM generally manifests as post-meal hyperglycemia, OGTT might detect PTDM earlier than FG. Indeed, diminished renal insulin clearance could be accountable for increased postprandial blood sugar levels, despite fasting measurements being within the normal range. The OGTT permits the identification of impaired glucose tolerance, an independent risk factor for the long-term onset of PTDM, cardiovascular conditions, and death, both when assessed before and after transplantation.[36]

In a study conducted by Caillard et al.,[5] FG alone diagnosed PTDM in only three-quarters of KTx recipients in a sample composed of 120 patients, with the remaining quarter being diagnosed only after OGTT, which is more sensitive and specific than FG. In another study, Valderhaug et al.[19] concluded that, in the recent posttransplant period, KTx recipients with FG between 95 and 120 mg/dL or HbA1c ≥ 5.8%, or with FG ≥ 90 mg/dL combined with HbA1c ≥ 5.7% must undergo an OGTT for diagnostic investigation of PTDM.

The utilization of HbA1c for the diagnosis of DM in patients with chronic kidney disease undergoing dialysis is not advised due to several physiological and analytical factors that can influence HbA1c outcomes, such as uremia, hemodialysis, and administration of erythropoietin.[37] HbA1c, in turn, presents some limitations in the KTx population, such as the possibility of false-negative results due to anemia, common in the recent posttransplant period, and interferences resulting from blood transfusion or the use of erythropoietin.[37] The 2014 International Expert Panel recommended that although HbA1c can be used to diagnose PTDM if elevated (greater than or equal to 6.5%), it should not be used alone as a screening test, particularly in the 1st year after transplantation.[36]

HbA1c measurement, nevertheless, may be more practical and less time-intensive in clinical settings. Modifying the HbA1c threshold in the transplant population seems to be a feasible option, particularly 12 months post-transplantation. A systematic review and meta-analysis assessed the overall diagnostic performance of HbA1c for detecting PTDM in KTx recipients. It demonstrated that HbA1c levels of 6.5 and 6.2% exhibited high specificity to confirm the presence of PTDM between 10 weeks and 4 months after transplantation, but with low to moderate sensitivity. Comparable findings were observed in the assessment after 12 months post-transplant. Lowering the HbA1c cutoff to 6.2% preserved high specificity (89%) and enhanced sensitivity (48% sensitivity with HbA1c > 6.5% versus 76% with HbA1c > 6.2%).[38]

In a recent review of PTDM, Jenssen and Hartmann[3] recommended performing OGTT in all patients to diagnose PTDM, unless FG was already diagnostic. However, they recommended that OGTT should not be conducted before 2 months post-transplantation or prior to stabilization of immunosuppressant doses. If universal screening using OGTT is unfeasible, they proposed that this test be administered to patients with metabolic syndrome and elevated triglycerides or, alternatively, it could be limited to patients with HbA1c above 5.7%. Identifying the risk factors present in the pre- or post-KTx period is essential to determine how and when the patient will be screened for PTDM.

Determining the time point for screening and diagnosis of PTDM is challenging, as several factors influence the choice and interpretation of the method to be used. Therefore, updates must be routinely implemented. Furthermore, the accuracy of the tests is different in KTx recipients, making it challenging to choose the most appropriate method and even contributing to underdiagnosis.

The objective of the construction of this bundle is to produce a "package" of good practices, based on scientific evidence, which would help professionals in the screening and diagnosis of prediabetes and PTDM, through the selection of the most suitable tests for specific situations and periods, allowing early diagnosis and assertive behavior. As limitations, the final version of the bundle was not validated in clinical practice. Although the number of expert judges was small, it was deemed adequate based on current literature regarding health instrument validation. We acknowledge the lack of diversity in the panel of judges, with an overrepresentation of nephrologists, as well as the absence of experts from other states in Brazil, which limits the external validity of the bundle. Further studies are recommended to confirm the validity of this tool and to assess the impact of its implementation in clinical practice.

PTDM is a contributing cause of illness and death in solid organ transplantation and is recognized as one of the primary complications linked to transplantation. In the meantime, the 3rd International Consensus Meeting on PTDM was held, which included statements of opinion on aspects related to the recognition and diagnosis of PTDM.[39]

The implementation of an OGTT, starting on the waiting list, for screening and diagnosis is a relevant tool, given that metabolic variability is a milestone in the longitudinal evolution of PTDM. In cases of patients with prediabetes or with risk factors for developing PTDM, performing OGTT tests repeated annually may benefit them.[39,40]

The use of the 1-hour OGTT as a diagnostic tool for prediabetes and DM has been suggested more recently and is considered more practical, with similar reproducibility compared to the 2-hour OGTT.[41] From this perspective, it is recommended that glycemia in the 1-hour OGTT ≥ 209 mg/dL be configured as a diagnostic criterion for DM, since it helps to identify individuals with prediabetes, DM, and retinopathy. Therefore, the 1-hour OGTT enables early detection of these cases and allows greater chances of longitudinal intervention and, consequently, reduces the risk of complications associated with DM.

In parallel, the identification of prediabetes with glycemia values ≥ 155 mg/dL in the 1-hour OGTT was detected earlier than glycemia ≥ 140 mg/dL in the 2-hour OGTT.[41] Furthermore, knowledge of the effects of prediabetes and PTDM should be emphasized, since PTDM is related to graft loss, cardiovascular and microvascular involvement, and, consequently, overall mortality.[39] Thus, screening and early diagnosis of PTDM are fundamental requirements for the comprehensive and longitudinal care of posttransplant patients.[39]

As mentioned above, the results obtained in the present study are comparable with publications after the period covered by the integrative review. Based on this, the future possibility of including the 1h-OGTT as a diagnostic criterion for PTDM tends to be better evaluated together with other criteria similar to those used in the general population, as portrayed by the consensus. It is also inferred that there is a perception of specific and distinct criteria or targets for individuals with PTDM in relation to the general public, since the consensus addresses similar cutoff points among populations with peculiar specificities.

## CONCLUSION

This tool should not serve as a substitute for the personalized assessment of patients performed by the attending physician. We believe that the adoption of the bundle for screening and diagnosing DM following KTx will assist in achieving early diagnosis, decreasing the occurrence and rate of underdiagnosis, and, consequently, potential complications resulting from this condition. Therefore, it is essential that other review studies and/or clinical trials addressing the topic be carried out. The constructed bundle was developed based on the data provided in the article.

## CONFLICT OF INTEREST

Nothing to declare.

## AUTHOR'S CONTRIBUTION

**Substantive scientific and intellectual contributions to the study:** Dallago CM, Brasil IRC, Souza TCS, Freitas TVS. **Conception and design:** Dallago CM, Brasil IRC, Souza TCS, Freitas TVS, Gouveia EBC. **Data analysis and interpretation:** Dallago CM, Brasil IRC, Souza TCS, Freitas TVS, Rabelo FCS, Gouveia EBC. **Article writing:** Dallago CM, Souza TCS, Rabelo FCS. **Critical revision:** Dallago CM, Rabelo FCS. **Final approval:** Dallago CM, Rabelo FCS

## DATA AVAILABILITY STATEMENT

All data were generated or analyzed in this study.

## FUNDING

Nothing to declare.

## ACKNOWLEDGEMENT

Not applicable.

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