UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM EPIDEMIOLOGIA

"The Role of Oral Glucose Tolerance Test Phenotypes in Type 2 Diabetes Progression and Remission"

"O Papel dos Fenótipos do Teste Oral de Tolerância à Glicose na Progressão e Remissão do Diabetes Tipo 2"

Thaís Soares Ferreira

Orientador: Prof. Dr. Bruce Bartholow Duncan

Co-orientador: Profª Drª. Maria Inês Schmidt

Porto Alegre, abril de 2025

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Tese apresentada ao Programa de Pós-Graduação em Epidemiologia da Faculdade de Medicina da Universidade Federal do Rio Grande do Sul como requisito parcial para obtenção do título de doutor em Epidemiologia.

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THAÍS SOARES FERREIRA

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BANCA EXAMINADORA

Prof Dr. Rodrigo Citton Padilha dos Reis, Programa de Pós-graduação em Epidemiologia, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brasil

Dra Gabriela Wunsch Lopes, Laboratório de Educação em Ambiente e Saúde – Instituto Oswaldo Cruz, Fundação Oswaldo Cruz

Profa. Dra Janine Alessi, Escola de Medicina da PUCRS e Serviço de Medicina Interna do Hospital São Lucas da PUCRS

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ABBREVIATIONS AND ACRONYMS

ADA – American Diabetes Association

AST - Aspartate Aminotransferase

ALT - Alanine Aminotransferase

BMI - Body Mass Index

DIADEM-I - Diabetes Intervention Accentuating Diet and Enhancing Metabolism - Estudo I

DiRECT - Diabetes Remission Clinical Trial

DPP – Diabetes Prevention Program

ELSA - Estudo Longitudinal da Saúde do Adulto

FLI – Fatty Liver Index

FPG – Fasting Plasma Glucose

GGT - Gamma-Glutamyl Transferase

GIP - Glucose-dependent Insulinotropic Polypeptide

GLP-1RA - Glucagon-Like Peptide-1 Receptor Aagonists

HbA1c - Glycated Hemoglobin

HDL-C - High Density Lipoprotein-Cholesterol

IDF - International Diabetes Federation

i-IFG – isolated Impaired Fasting Glucose

i-IGT – isolated Impaired Glucose Tolerance

IFG/IGT – impaired Fasting Glucose and Glucose Tolerance

LDL-C - Low Density Lipoprotein-Cholesterol

Look AHEAD - Action for Health in Diabetes

MAFLD - Metabolic-Associated Fatty Liver Disease

NAFLD - Non-Alcoholic Fatty Liver Disease

OGTT - Oral Glucose Tolerance Test

ReTUNE - Reversal of Type 2 diabetes Upon Normalization of Energy intake in the non-obese

SGLT2i - Sodium-Glucose Contransporter-2 inhibitors

T2D – Type 2 Diabetes Mellitus

UKPDS - United Kingdom Prospective Diabetes Study

WHR - Waist-to-Hip Ratio

2hPG - 2-hour Plasma Glucose

ABSTRACT

BACKGROUND: The heterogeneity of type 2 diabetes is complex and involves dynamic interactions between genetic predisposition, environmental exposures, and distinct metabolic phenotypes. Historically regarded as a chronic and inevitably progressive disease, type 2 diabetes has had its paradigm increasingly challenged by evidence from studies involving patients undergoing bariatric surgery, dietary interventions, and novel pharmacological therapies. These studies have demonstrated that diabetes remission is achievable in a subset of individuals. Since then, scientific interest has grown substantially, accompanied by efforts to identify factors associated with type 2 diabetes remission. Despite the lack of a widely accepted consensus on the definition of remission, disease duration and glycemic control have consistently emerged as key determinants. However, aspects related to the heterogeneity of diabetes pathophysiological pathways have received comparatively limited attention and diabetes is often used as a broad diagnostic label, overlooking the distinct metabolic phenotypes that constitute the disease spectrum. A better understanding of the clinical and metabolic profiles associated both with the onset of distinct T2D phenotypes and with remission is essential to support targeted prevention and personalized care strategies. In this context, the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), a multicenter cohort with standardized and centralized data collection, offers a unique opportunity to investigate the dynamic metabolic profiles associated with incident T2D phenotypes and remission among individuals with newly diagnosed disease.

METHODS: We analyzed data from ELSA-Brasil, which enrolled 15,105 civil servants aged 35–74 from six Brazilian cities between 2008 and 2010, with follow-up assessments conducted in 2012–2014 and 2017–2019. For the incidence analysis, we included participants without diabetes at baseline, confirmed by oral glucose tolerance test (OGTT) and the absence of glucose-lowering medication. Incident T2D was classified into isolated abnormal fasting glucose (FPG ≥126 mg/dL and 2hPG <200 mg/dL) or isolated abnormal 2-hour post-load glucose (2hPG ≥200 mg/dL and FPG <126 mg/dL), excluding those with both abnormalities. For the remission analysis, we included individuals newly diagnosed with T2D at Visit 1 or 2, with follow-up OGTT data available and no history of bariatric surgery. Remission was defined as achieving FPG <126 mg/dL, 2hPG <200 mg/dL, and HbA1c <6.5%, without glucose-lowering medication. Clinical, laboratory, and sociodemographic data were obtained using standardized protocols. Insulin

sensitivity was estimated using the Matsuda Index, and hepatic steatosis was assessed by the Fatty Liver Index (FLI). Associations between metabolic factors and diabetes phenotypes or remission were estimated using robust Poisson regression models.

RESULTS: Among 845 participants with incident T2D, after excluding those with abnormally elevated glycemia at both moments, 605 were classified with isolated abnormal fasting glucose (34%) or isolated abnormal 2hPG (66%). Higher LDL-Cholesterol was inversely associated with the isolated abnormal fasting phenotype (RR per 50 mg/dL=0.69; 95%CI: 0.55–0.88), while insulin sensitivity remained positively associated across models (RR=1.17; 95%CI 1.03–1.32). Higher levels of the Fatty Liver Index (FLI) were positively associated with fasting phenotype (RR=1.34; 95%CI: 1.02–1.77), but lost significance when BMI, hypertension and lifestyle characteristics were added into the model. Heavy alcohol consumption was associated with a higher risk of developing the isolated abnormal fasting glucose phenotype (RR=1.82; 95%CI 1.10–2.93). In the remission analysis, 752 participants with incident T2D were evaluated, among whom 100 were in diabetes remission at follow-up. Most cases of remission occurred among those initially classified with isolated abnormal 2hPG. In multivariable models, this group showed a higher probability of remission compared to those with isolated fasting glucose impairment (RR=1.95; 95%CI 1.17–3.39), whereas individuals with both abnormalities had a lower probability of remission (RR=0.19; 95%CI 0.04–0.60). Higher levels of HbA1c and fatty liver index (FLI) were inversely associated with remission across all models (RR=0.39; 95%CI 0.26–0.58 and RR=0.54; 95%CI 0.33–0.88, respectively). In contrast, anthropometric measures, lipid parameters, and insulin sensitivity (Matsuda index) were not significantly associated with remission in the multivariate models. Stratified analysis by body mass index (BMI) revealed effect modification for certain predictors. Among individuals without obesity (BMI<30 kg/m²), the inverse association between FLI and remission remained significant and slightly stronger (RR=0.44; 95%CI 0.26–0.73), whereas in individuals with obesity the association was attenuated. The positive association between isolated abnormal 2-hour post-load glucose and remission was more pronounced among individuals with obesity (RR: 4.50; 95%CI 1.43–14.15). Higher triglyceride levels were positively associated with remission in the BMI<30 group (RR=1.17; 95%CI 1.03–1.33), while no significant associations were found among individuals with BMI≥30 kg/m².

CONCLUSION: The two studies based on the ELSA-Brasil cohort highlight the prognostic relevance of OGTT phenotypes and their association with distinct metabolic profiles in type 2 diabetes. Individuals with isolated abnormal post-load glucose exhibited a lower probability of remission, particularly in the presence of obesity, and were characterized by lower insulin sensitivity and lower hepatic steatosis. Elevated LDL-Cholesterol was independently associated with this phenotype, pointing to a potential role of lipid metabolism in its development, beyond insulin resistance and hepatic dysfunction. These findings reinforce the need to move beyond a one-size-fits-all model of diabetes, emphasizing phenotypic stratification at diagnosis. Incorporating simple tools such as the OGTT and Fatty Liver Index into routine care may help identify individuals with greater remission potential and guide targeted cost-effective interventions. Recognizing the heterogeneity of type 2 diabetes is essential for advancing both research and clinical practice toward more personalized approaches.

Keywords: type 2 diabetes mellitus, Glucose Tolerance Test.

RESUMO

INTRODUÇÃO**:** A heterogeneidade do diabetes tipo 2 é complexa e envolve interações dinâmicas entre predisposição genética, exposições ambientais e fenótipos metabólicos distintos. Historicamente considerada uma doença crônica e invariavelmente progressiva, o paradigma do diabetes tipo 2 tem sido cada vez mais desafiado por estudos com pacientes submetidos à cirurgia bariátrica, intervenções dietéticas e novas terapias farmacológicas, cujos achados demonstram que a remissão do diabetes é possível em certos subgrupos de indivíduos. Desde então, o interesse científico tem crescido substancialmente, acompanhado por esforços para identificar fatores associados à remissão do diabetes tipo 2. Apesar da falta de um consenso amplamente aceito sobre a definição de remissão, a duração da doença e o controle glicêmico têm surgido consistentemente como determinantes-chave. No entanto, aspectos relacionados à heterogeneidade das vias fisiopatológicas do diabetes têm recebido atenção comparativamente limitada, e o termo diabetes é frequentemente utilizado como um rótulo diagnóstico amplo, negligenciando os distintos fenótipos metabólicos que constituem o espectro da doença. Uma melhor compreensão dos perfis clínicos e metabólicos associados tanto ao surgimento de distintos fenótipos de diabetes tipo 2 (DM2) quanto à remissão é essencial para apoiar estratégias de prevenção direcionadas e cuidados personalizados. Nesse contexto, o Estudo Longitudinal Brasileiro de Saúde do Adulto (ELSA-Brasil), uma coorte multicêntrica com coleta de dados padronizada e centralizada, oferece uma oportunidade única para investigar os perfis metabólicos dinâmicos associados ao surgimento de fenótipos de DM2 e à remissão em indivíduos com diagnóstico recente da doença.

MÉTODOS: Analisamos dados do ELSA-Brasil, que recrutou 15.105 servidores públicos com idades entre 35 e 74 anos, de seis cidades brasileiras, entre 2008 e 2010, com avaliações de acompanhamento realizadas entre 2012 e 2014 e entre 2017 e 2019. Para a análise de incidência, incluímos participantes sem diabetes no início do estudo, confirmado por teste oral de tolerância à glicose (TOTG) e ausência de uso de medicação hipoglicemiante. O diabetes tipo 2 (DM2) incidente foi classificado em glicemia de jejum anormal isolada (glicemia de jejum ≥126 mg/dL e glicemia 2 horas após sobrecarga de glicose <200 mg/dL) ou glicemia 2 horas após sobrecarga de glicose anormal isolada (glicemia 2 horas após sobrecarga de glicose ≥200 mg/dL e glicemia de jejum <126 mg/dL), excluindo aqueles com ambas as anormalidades. Para a análise de remissão,

incluímos indivíduos com diagnóstico recente de DM2 na Visita 1 ou 2, com dados de TOTG de acompanhamento disponíveis e sem histórico de cirurgia bariátrica. A remissão foi definida como a obtenção de glicemia de jejum (GJ) <126 mg/dL, glicemia 2 horas após sobrecarga de glicose (G2h) <200 mg/dL e hemoglobina glicada (HbA1c) <6,5%, sem o uso de medicamentos hipoglicemiantes. Dados clínicos, laboratoriais e sociodemográficos foram obtidos utilizando protocolos padronizados. A sensibilidade à insulina foi estimada pelo Índice de Matsuda e a esteatose hepática foi avaliada pelo Fatty Liver Index (FLI). As associações entre fatores metabólicos e fenótipos de diabetes ou remissão foram estimadas utilizando modelos robustos de regressão de Poisson.

RESULTADOS: Entre os 845 participantes com diabetes tipo 2 incidente, após a exclusão dos participantes com glicemia elevada em ambos os momentos, 605 foram classificados com glicemia de jejum anormal isolada (34%) ou glicemia 2 horas após sobrecarga de glicose anormal isolada (66%). Níveis mais elevados de colesterol LDL foram inversamente associados ao fenótipo de glicemia de jejum anormal isolada (RR por 50 mg/dL = 0,69; IC 95%: 0,55–0,88), enquanto a sensibilidade à insulina permaneceu positivamente associada em todos os modelos (RR = 1,17; IC 95%: 1,03–1,32). Níveis mais elevados do pelo Fatty Liver Index (FLI) foram associados ao fenótipo de glicemia de jejum (RR = 1,34; IC 95%: 1,02–1,77), mas perderam significância quando o IMC, a hipertensão e as características do estilo de vida foram adicionadas ao modelo. O consumo excessivo de álcool foi associado a um maior risco de desenvolver o fenótipo de glicemia de jejum anormal isolada (RR = 1,82; IC 95% 1,10–2,93). Na análise de remissão, 752 participantes com diabetes tipo 2 incidente foram avaliados, dos quais 100 estavam em remissão do diabetes no acompanhamento. A maioria dos casos de remissão ocorreu entre aqueles inicialmente classificados com glicemia de jejum 2 horas anormal isolada. Em modelos multivariáveis, esse grupo apresentou maior probabilidade de remissão em comparação àqueles com alteração isolada da glicemia de jejum (RR = 1,95; IC 95% 1,17–3,39), enquanto indivíduos com ambas as anormalidades apresentaram menor probabilidade de remissão (RR = 0,19; IC 95% 0,04–0,60). Níveis mais elevados de HbA1c e Fatty Liver Index (FLI) foram inversamente associados à remissão em todos os modelos (RR = 0,39; IC 95% 0,26–0,58 e RR = 0,54; IC 95% 0,33–0,88, respectivamente). Em contraste, medidas antropométricas, parâmetros lipídicos e sensibilidade à insulina (índice de Matsuda) não apresentaram associação significativa com a remissão nos modelos multivariados. A análise estratificada por índice de massa

corporal (IMC) revelou modificação do efeito para alguns preditores. Entre indivíduos sem obesidade (IMC < 30 kg/m²), a associação inversa entre IFG e remissão permaneceu significativa e ligeiramente mais forte (RR = 0,44; IC 95% 0,26–0,73), enquanto em indivíduos com obesidade a associação foi atenuada. A associação positiva entre glicemia anormal isolada 2 horas após a sobrecarga de glicose e remissão foi mais pronunciada entre indivíduos com obesidade (RR: 4,50; IC 95% 1,43–14,15). Níveis mais elevados de triglicerídeos foram associados positivamente à remissão no grupo com IMC < 30 (RR = 1,17; IC 95% 1,03–1,33), enquanto nenhuma associação significativa foi encontrada entre indivíduos com IMC ≥ 30 kg/m².

CONCLUSÃO: Ambos os estudos baseados na coorte ELSA-Brasil destacam a relevância prognóstica dos fenótipos do TOTG e sua associação com perfis metabólicos distintos no diabetes tipo 2. Indivíduos com glicemia pós-prandial anormal isolada apresentaram menor probabilidade de remissão, particularmente na presença de obesidade, e foram caracterizados por menor sensibilidade à insulina e menor grau de esteatose hepática. Níveis elevados de colesterol LDL foram associados independentemente a esse fenótipo, apontando para um possível papel do metabolismo lipídico em seu desenvolvimento, além da resistência à insulina e da disfunção hepática. Esses achados reforçam a necessidade do avanço para além de um modelo único aplicável a todos os indivíduos com diabetes, enfatizando a estratificação fenotípica no momento do diagnóstico. A incorporação de ferramentas simples como o TOTG e o Fatty Liver Index (FLI) na prática clínica pode auxiliar na identificação de indivíduos com maior potencial de remissão e orientar intervenções direcionadas e custo-efetivas. Reconhecer a heterogeneidade do diabetes tipo 2 é essencial para o avanço da pesquisa e da prática clínica em direção a abordagens mais personalizadas.

Palavras-chave: diabetes mellitus tipo 2, Teste Oral de Tolerância à Glicose (TOTG).

APRESENTATION

This work consists of the doctoral thesis titled "**The Role of Oral Glucose Tolerance Test Phenotypes in Type 2 Diabetes Progression and Remission** " which will be submitted to the Postgraduate Program in Epidemiology at the Federal University of Rio Grande do Sul. The work is presented in four parts, in the following order:

1. Introduction, Literature Review, Objectives

2. Article 1: **“Remission in Newly Diagnosed Type 2 Diabetes: Does Glucose Tolerance Test Phenotype Matter?”**

3. Article 2: “**Association Between Metabolic Profile and Distinct OGTT Phenotypes of Incident Type 2 Diabetes Mellitus”**

INTRODUCTION

Type 2 diabetes constitutes a condition that significantly impacts public health and the economy of societies due to its high potential to cause debilitating complications and increase the risk of premature mortality. Concernedly, a considerable rise in its prevalence has been observed in recent years, and projections for the coming decades are alarming, indicating a global increase, particularly in countries transitioning from low to middle-income status (International Diabetes Federation, 2025).

Until recently, type 2 diabetes was considered an invariably progressive disease, associated with the gradual deterioration of glycemic control and its subsequent macro- and microvascular complications (Turner et al., 1999). However, the observation of normalized blood glucose levels following bariatric surgery (Pories et al., 1995), along with a growing body of evidence demonstrating the effectiveness of bariatric surgery in glycemic control led to a paradigm shift, recognizing the possibility of disease remission (Schauer, Philip R., et al, 2016). Studies on dietary interventions (Lean et al., 2018) and, more recently, strategies involving new therapeutic agents (McInnes, Natalia, 2022) have reinforced the view that type 2 diabetes is a condition with potential for remission.

Recent efforts have been focused on understanding which individuals respond to, and which do not, the strategies aimed at achieving disease remission (Wang, Guo-Feng, et al, 2015; Steven et al., 2016a; Thom et al., 2021). Factors such as disease duration and glycemic control have consistently been identified as important predictors of remission. However, there has been limited attention given to the pathophysiological differences of the disease. Although the heterogeneity of diabetes is well recognized, and several studies attempt to subtype the disease considering outcomes such as glycemic control and progression to complications (Nair et al., 2022), many studies assessing remission use type 2 diabetes as a generic term to describe the various phenotypes of the disease. Considering phenotypic differences among patients with type 2 diabetes could not only prevent misleading conclusions regarding the efficacy of interventions but also help identify groups that may benefit more or less from the proposed strategies to achieve type 2 diabetes remission.

The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil), which has followed the development of type 2 diabetes and its subsequent remission in a cohort of middle-aged and elderly adults since 2008, provides an excellent opportunity to

investigate the factors associated with remission, considering different phenotypes of the disease.

LITERATURE REVIEW

The Diabetes Epidemic

In recent years, the global population has seen a significant rise in the prevalence of Type 2 Diabetes Mellitus, along with a growing number of adults at high risk of developing the condition. This increase has been particularly pronounced in low- and middle-income countries, mainly due to aging population, economic growth, and rising urbanization, resulting in more sedentary lifestyles and greater consumption of unhealthy foods linked with obesity (International Diabetes Federation, 2025).

The diabetes epidemic and its complications continue to be an escalating global threat. According to estimates from the International Diabetes Federation (IDF), in 2015, one in every 11 adults worldwide, aged 20 to 79, was living with diabetes. Projections for 2050 estimate that the number of people with diabetes will rise to 853 million, with the greatest increase expected in regions undergoing economic transitions from low to middle-income status (International Diabetes Federation, 2025).

The growing prevalence of the disease has a significant impact on public health and the economy of societies, due to its high potential to cause debilitating complications and increase the risk of premature death. In 2024, diabetes was responsible for 9.3% of global deaths among adults aged 20 to 79, with around 40% of these deaths occurring in people of working age (under the age of 60) (International Diabetes Federation, 2025).

Worryingly, in recent years, there has been a rise in diabetes cases among younger populations, which extends the duration of the disease and, consequently, increases the risk of developing complications (International Diabetes Federation, 2025).

A Paradigm Shift

Until recently, Type 2 Diabetes Mellitus (T2D) was considered a chronic, progressive disease related to a progressive depletion of β-cells and chronic macro and microvascular diabetes-related complications. Prospective studies, such as those conducted by the UKPDS group (UK Prospective Diabetes Study (UKPDS) Group, 1998), showed that, although better glycemic control was achieved with the use of antidiabetic drugs compared to dietary intervention alone, this effect was not sustained in the long term. Participants experienced a progressive deterioration in glycemic control and an increasing need for higher doses of antidiabetic medications. It was shown that,

nine years after diagnosis, most individuals with diabetes would need to add insulin therapy to their treatment regimen to achieve proper glycemic control (Turner et al., 1999).

At the same time, studies involving individuals with obesity and diabetes who underwent bariatric surgery challenged the traditional view of the disease as invariably progressive (Pories et al., 1995). With the observation that blood sugar levels returned to normal within hours to days after bariatric surgery in individuals with obesity and T2D, even before significant weight loss occurred (Guidone, Caterina, et al, 2006), and the growing body of evidence demonstrating bariatric surgery's effectiveness in glycemic control and T2D remission (Cohen et al., 2012; Purnell, Jonathan Q., et al, 2016; Batterham and Cummings, 2016; Schauer, Philip R., et al, 2016), a paradigm shift has occurred that recognizes the possibility of disease remission.

Contributing to the growing body of clinical evidence on the reversibility of T2D, dietary intervention studies were developed to evaluate the effects of a sudden and significant reduction in caloric intake on T2D remission (Lim, Ee Lin, et al, 2011; Steven et al., 2016). Long-term studies, such as the "Diabetes Remission Clinical Trial" (DiRECT), provided valuable insights into the possibility of T2D remission (Lean et al., 2018). In this study, patients with early-stage diabetes who were not undergoing insulin therapy and were placed on a hypocaloric diet achieved a 46% diabetes remission rate after 12 months. Remission was influenced by weight loss, with a remission rate of 86% observed in participants who lost 15 kg or more. Other studies, such as "Look AHEAD" (Gregg et al., 2012) and DIADEM-I (Taheri et al., 2020), further reinforced the idea that weight loss, however achieved, dramatically impacts the natural history of T2D, favoring glycemic control and even remission (Valabhji et al., 2024).

In addition to dietary interventions, new strategies have recently been explored to achieve T2DM remission. Over the past 15 years, new therapeutic agents have been discovered for the treatment of T2D, allowing for more personalized treatment options. Sodium-glucose contransporter-2 inhibitors (SGLT2i) (McInnes, Natalia, 2022), Glucagon-like peptide-1 receptor agonists (GLP-1RA) (Davies, Melanie, et al, 2021; ME Lunati, 2024) and more recently GLP-1/glucose-dependent insulinotropic polypeptide (GIP) dual agonists (Prato et al., 2021), and GLP-1/GIP/glucagon tri-agonists (Rosenstock et al., 2023) have emerged as promising classes in T2D research. Although incretin-based medications do not fully meet the definition of remission and their efficacy

primarily depends on the maintenance of weight loss, particularly with continued use of the medication, the consistent results are noteworthy, demonstrating not only glycemic control but also cardiovascular benefits (Jabbour, Serge A., et al, 2018; Husain, Mansoor, et al, 2019; Prato et al., 2021; Sattar et al., 2021) and even potential effect of reducing liver fat content (Petit, J-M. and Bruno Vergès, 2017).

While advances in therapeutic approaches have made T2D remission an achievable goal, and the concept is increasingly recognized within clinical guidelines, new challenges have arisen, such as establishing a clear and widely accepted definition of diabetes remission and gaining a better understanding of the individual variability in responses to the interventions.

Challenge 1: A Clear and Consensus Definition of Diabetes Remission

The lack of a widely accepted definition of remission criteria makes it difficult to interpret clinical study results, implement effective treatment strategies, and assess the long-term sustainability of the benefits. With growing evidence that effective interventions can lead to the normalization of glucose levels, T2D remission has emerged as a desirable therapeutic goal. However, the definition of T2D remission remains unclear, with different studies adopting varying criteria, making it difficult to compare results and generalize conclusions (Mas-Lorenzo et al., 2014; Captieux et al., 2020).

Defining remission of type 2 diabetes has not yet achieved consensus among various organizations and there is no single internationally acceptable definition. The existing definitions, however, have some gaps. For example, the required duration for glucose normalization to be considered remission is not uniformly accepted. The time intervals used are arbitrary and lack a solid foundation that would allow for the precise establishment of the conditions under which remission can be sustained in the long term (Captieux et al., 2020).

Another limitation in defining T2D remission is the lack of a standardized methodology for assessing glucose levels and related metabolic markers (Captieux et al., 2020). While the oral glucose tolerance test (OGTT) remains one of the most essential diagnostic tools for assessing normal glycemic profiles (Jagannathan et al., 2020; Kuo et al., 2021), the definition of remission often relies solely on FPG e/or HbA1c measurement (Captieux et al., 2020), even though these parameters have limitations and do not offer a full understanding of the pathophysiology in people with T2D, as underlying

pathophysiology, including pancreatic dysfunction and insulin resistance, can still be present in the case of normalized HbA1c and FPG.

The most widely used consensus to date has undergone recent changes. In 2021, the ADA revised the definition of diabetes remission by evaluating only the HbA1c value, which must be <6.5% (7.8mmol/l) for at least 3 months after surgery and hypoglycemic therapies have been stopped, thus excluding use of the fasting glucose measurement from this determination. (Riddle et al., 2021)

Challenge 2: Understanding Response Variability in Intervention Studies

The factors contributing to the remission of type 2 diabetes are multifaceted. Weight loss achieved through dietary control and pharmacological therapy, and bariatric surgery in individuals with obesity and T2D are interventions that have been shown to induce remission in some individuals (Purnell, Jonathan Q., et al, 2016; Schauer, Philip R., et al, 2016; Lean et al., 2018; McInnes, Natalia, 2022). However, these approaches have not proven equally effective in all patients. Factors such as the duration of diabetes, the severity of the disease, and the extent of weight loss have been identified as potential determinants of the variability in responses among individuals (Wang, Guo-Feng, et al, 2015; Steven et al., 2016b; Thom et al., 2021). This variability in response to therapeutic interventions and in maintaining long-term remission poses challenges to the concept of T2D remission and highlights the heterogeneity of the disease.

Due to the new demands that intensive weight control programs place on healthcare services and patients seeking disease remission, efforts to identify potential responders who will benefit from the proposed strategies have been more recently employed (Steven et al., 2016; Thom et al., 2021). However, there is still a lack of studies that account for the heterogeneity of T2D pathophysiology to explore potential predictors and identify subgroups for which remission is a worthwhile target (de Hoogh, Iris M., et al, 2021).

Lessons from Dietary Intervention and Bariatric Surgery Studies

Recent systematic reviews and meta-analyses have identified low-calorie diets as the most effective nutritional approach for promoting weight loss and potentially achieving remission in individuals with T2D (Churuangsuk et al., 2022). The first experimental evidence came from a secondary analysis of the Look AHEAD study (Gregg

et al., 2012), which examined the effectiveness of a low-calorie diet within an intensive lifestyle intervention aimed at T2D remission. The results showed an 8.6% weight loss in the intervention group, with a T2D remission rate of about 12% after one year of follow-up.

The DiRECT study (Lean et al., 2018) was later conducted, being the first randomized, controlled, multicenter trial, with the primary goal of achieving diabetes remission through dietary intervention in overweight individuals (BMI 27-45 kg/m²) with a disease duration under 6 years. After one year, a quarter of the participants in the intervention group reached the weight loss target of 15 kg, and nearly half achieved T2D remission. The remission rate remained significantly high even after two years of intervention, although it dropped to 35.6%, alongside some weight regain.

A post-hoc analysis of the DiRECT study (Thom et al., 2021) revealed that remission was more common in men, due to greater weight loss, and in those who were taking fewer anti-diabetic medications at the start of the study. On the other hand, remission was less likely in individuals with anxiety or depression, primarily due to the lower weight loss observed in this group.

Similarly, meta-analyses evaluating preoperative clinical factors predictive of remission found that younger patients, those with a shorter duration of diabetes, better glucose control, and preserved β-cell function were more likely to achieve remission of T2D after bariatric surgery (Wang, Guo-Feng, et al, 2015).

T2D Remission Without Weight Loss?

Following the observation of improvements in the metabolic state of individuals with obesity and T2D after bariatric surgery, the procedure has come to be recognized not only as a weight loss intervention but also as a metabolic approach capable of inducing T2D remission (Schauer, Philip R., et al, 2016). Although the underlying mechanisms are not yet fully understood, early improvements in glycemia can occur immediately after surgery, even prior to weight loss, suggesting a potential glycemic control mechanism independent of weight reduction (Sandoval, Darleen A. and Mary Elizabeth Patti, 2023). It is hypothesized that the effects of the surgery occur in two phases: an initial hypoglycemic effect, related to the reduction in gastric volume and consequently decreased nutrient absorption, enhanced hepatic insulin response, and increased gastrointestinal hormone secretion; followed by a later effect involving improved insulin

sensitivity due to the reduction of total, visceral, and pancreatic adipose tissue, which is dependent on weight loss and contributes to the long-term maintenance of T2D remission (Sandoval, Darleen A. and Mary Elizabeth Patti, 2023).

Is Baseline BMI Not a Predictor of T2D Remission?

Although an exploratory analysis of the DiRECT study showed that the remission rate increases proportionally with weight loss, no significant effect of baseline BMI on the probability of diabetes remission was observed (Thom et al., 2021). This finding can be explained by the limitation of BMI in indicating, on its own, an abnormal distribution of body fat and the presence of metabolically harmful ectopic fat.

In line with this hypothesis, the ReTUNE study was conducted, which included patients with diabetes and intra-hepatic and/or intra-pancreatic fat accumulation, measured by abdominal Magnetic Resonance Imaging (MRI), despite having a BMI indicative of normal weight or mild overweight (< 27 kg/m²). The patients followed weight loss protocols with a low-calorie diet. After one year of follow-up, with an average weight loss of 7.7 kg, diabetes remission was observed in 70% of participants, along with a reduction in total body fat, accompanied by a more pronounced decrease in intra-hepatic and intra-pancreatic fat (Taylor, Roy, et al, 2023) .

Could Intra-Hepatic Fat Be Involved in T2D Remission?

Positive associations between Non-Alcoholic Fatty Liver Disease (NAFLD) and incident type 2 diabetes have been well documented (Mantovani et al., 2021; Faria et al., 2023). Studies show that people with T2D have higher levels of intra-hepatic fat compared to individuals of the same age, sex, and weight (Kotronen et al., 2008). Additionally, changes in liver enzymes can precede the development of T2D, likely linked to the increase in intra-hepatic fat (Mantovani et al., 2021).

In early 2020, aligned with this concept of the close relationship between liver fat deposition and metabolic abnormalities, an international group of experts, through a consensus statement, recommended changing the name of non-alcoholic fatty liver disease (NAFLD) to metabolic-associated fatty liver disease (MAFLD) to better reflect the current knowledge of the disease (Eslam et al., 2020). The criteria for MAFLD follows the same standard for hepatic steatosis (≥5% liver fat without other liver conditions, including significant alcohol consumption), but requires the presence of metabolic

dysregulation as a prerequisite for considering the diagnosis. According to the MAFLD criteria, the metabolic risk factors include type 2 diabetes mellitus and overweight/obesity. To diagnose MAFLD in individuals with a healthy weight, an individual must have at least two out of the seven risk factors. The risk factors include waist circumference, blood pressure, plasma high-density lipoprotein cholesterol, plasma triglycerides, the homeostasis model assessment of insulin resistance score, prediabetes, and plasma high-sensitivity C-reactive protein.

According to researchers such as Taylor and colleagues, the accumulation of fat in the liver is implicated in the development of T2D, a phenomenon they describe as the "Twin-cycle hypothesis" (Taylor, 2008). This theory posits that chronic overconsumption of calories leads to the accumulation of fat in both the liver and pancreas, a process that is self-reinforcing but reversible. Therefore, reducing lipid deposition in these organs and tissues is considered essential for T2D remission. In intervention studies such as the DiRECT trial, Taylor and his team observed that a hypocaloric diet not only normalized glycemic control and increased liver insulin sensitivity within the first few days but also reduced triglyceride levels in both the liver and pancreas, restoring insulin response within 8 weeks. The removal of excess fat from these organs, secondary to weight loss, was associated with the recovery of β-cell function, evidenced by improved insulin secretion as measured by oral glucose tolerance tests. Additionally, the improvement in liver insulin sensitivity contributes to the normalization of hepatic glucose production during fasting, mitigating the toxic effects of hyperglycemia on β-cells.

In a prospective study investigating the effects of an 8-week hypocaloric diet followed by a controlled return to an isocaloric diet on the remission of T2D (Steven et al., 2016), it was found that remission was achieved in 41% of participants, with 60% of those having a shorter duration of the disease. The "good responders" were characterized by a shorter disease duration, younger age, lower fasting plasma glucose (FPG) and HbA1c levels, higher insulin levels, and lower concentrations of ketones and free fatty acids. Additionally, they exhibited a tendency toward increased hepatic insulin resistance, with elevated ALT levels and a greater likelihood of hepatic fat accumulation compared to the "non-responders" at baseline. Although there were no significant differences in weight or BMI between the two groups, the "poor responders" had a greater total fat mass. No differences were observed in pancreatic fat content, subcutaneous fat, or visceral fat

between the groups at baseline. Approximately 40% of the "good responders" maintained remission after 6 months.

Insights from Studies on Progression to T2D

For over 20 years, studies comparing individuals with intermediate hyperglycemia due to isolated impaired fasting glucose (i-IFG), isolated impaired glucose tolerance (i-IGT), and both altered (IFG/IGT) have demonstrated phenotypic differences among these groups (Weyer, Christian et al., 1999). These differences reflect distinct underlying pathophysiological mechanisms and varying risk profiles for progression to T2D (Fonseca, 2009). Additionally, cardiovascular risk differences have been observed, with the group exhibiting both altered parameters (IFG/IGT) showing a more unfavorable cardiovascular risk profile and a higher probability of progression to type 2 diabetes (Gerstein et al., 2007; Tabák et al., 2012) .

Later, the use of the term "prediabetes" as a general expression to describe the different types of intermediate hyperglycemia in intervention studies led to the appearance that lifestyle interventions, as currently applied, were effective in all cases, reducing the progression to type 2 diabetes. However, it was found that most of the significant clinical trials on lifestyle-related diabetes prevention programs (DPPs) recruited participants diagnosed with i-IGT, and these studies showed clear benefits of the interventions (Tuomilehto, Jaakko, et al, 2001; Diabetes Prevention Program Research Group, 2002; Campbell, Matthew D., et al, 2020). In contrast, the same effect was not observed in studies including patients with i-IFG, in which the progression to type 2 diabetes was not prevented (Saito, Toshikazu, et al, 2011; Campbell, Matthew D., et al, 2020). The discordant outcomes in reducing the risk of type 2 diabetes across the spectrum of intermediate hyperglycemia phenotypes (as defined by glucose levels) have been explained by the distinct metabolic states associated with the pathophysiology of i-IFG and i-IGT, which have been the subject of recent studies. These have yielded varying results based on the criteria used to classify the different intermediate hyperglycemia phenotypes (Sathish et al., 2023; Zila-Velasque et al., 2025).

Insights from Subtype Classification Studies of Type 2 Diabetes

The heterogeneity of type 2 diabetes is complex and multifaceted, involving interactions between genetic, environmental, and phenotypic factors, resulting in distinct risk profiles, disease progression, and treatment responses (Redondo and

Balasubramanyam, 2021; Suzuki, K and Hatzikotoulas, K., Southam, L., 2024). Although patients with diabetes exhibit a broad spectrum of clinical characteristics and a range of variables that directly impact glucose homeostasis, the multifaceted nature of the disease has only recently gained more attention.

To better understand the complexity of type 2 diabetes and gain deeper insights into its underlying pathophysiological mechanisms, treatment responses, and prognoses, recent studies have sought to identify subtypes of diabetes through various approaches (Misra et al., 2023). These include those based on the presence or absence of simple clinical characteristics or biomarkers, and more recently, advanced methods employing machine learning or omics data. While these studies offer promising directions for future research, there are still challenges that need to be addressed:

Lack of Robust Studies Evaluating Diabetes Subtypes in Relation to Remission

In a systematic review aimed at evaluating whether current strategies for subclassifying type 2 diabetes were supported by high-quality evidence, reproducible results, and improved patient outcomes (Misra et al., 2023), 51 studies were identified that employed simple stratification approaches, including stratification based on OGTT data. These studies found differences in glycemic control (Arslanian, Silva, et al, 2019), cardiometabolic risk (Færch et al., 2013), and measures of glucose homeostasis (Mitsui et al., 2006) between subgroups, but did not assess differences in disease remission rates. More complex stratifications were found in 62 studies, which included clustering strategies that considered clinical information at the time of diagnosis or clinical data combined with genetic information to characterize disease heterogeneity. These studies demonstrated inter-cluster differences regarding progression to complications or the need for insulin treatment; however, they also did not include diabetes remission as part of the outcomes assessed. For example, Ahlqvist and colleagues (Ahlqvist et al., 2018) grouped individuals based on six variables measured shortly after the diabetes diagnosis, including glycated hemoglobin, glutamate decarboxylase antibodies, and body mass index. The subgroups differed in terms of disease progression, use of antidiabetic treatments, and risks of diabetes-related complications. However, disease remission was not included as an outcome in the analysis of the different clusters.

The Selection of Variables Included in Subclassification Approaches and Clinical Applicability

Both in studies with more complex approaches and those using stratification based on simple clinical phenotypes, there is notable variability in the selection of variables to be included in the subclassification process. Variables such as pancreatic autoantibodies, measures related to beta-cell function, age, BMI, lipid profile/metabolic syndrome, glycemic tests, and genetic information have been used in various combinations (Misra et al., 2023). Importantly, many of these variables undergo changes as the disease progresses and throughout treatment. Therefore, the application of more complex approaches that include measures of variables not routinely available in clinical practice remains of uncertain utility, particularly when patients are assessed at different stages of the disease and/or after the initiation of treatment. Additionally, it is still uncertain whether many of the clinical biomarkers employed in cluster analyses so far are causal, consequential, or merely coincidental in the disease process, due to the lack of studies evaluating predictive factors for the proposed diabetes subtypes.

Uncertainty Regarding the Superiority of More Complex Approaches in Diabetes Subclassification

Simpler subclassification strategies are easier to implement across various resource settings, while more complex approaches may offer greater accuracy in classifying disease heterogeneity (Misra et al., 2023). However, there has been considerable debate regarding whether analyses based on subgroups defined through data-driven clustering methods are superior to those using simpler stratification approaches in assessing disease progression and treatment response. In fact, a study that compared simple clinical phenotypes with patient stratification based on Ahlqvist's classification found that models using basic clinical features to predict glucose response and guide treatment selection were significantly more effective than cluster-based approaches (Dennis et al., 2019). This brings into question whether segmenting continuous, multidimensional data into discrete clusters is clinically meaningful. In line with this perspective, an additional study demonstrated that the predictive capacity of diabetes subtypes, based on clustering, for cardiovascular events, renal function decline, and disease progression, showed no advantage over traditional risk scores (Aoki et al., 2021).

OBJECTIVES

General Objectives

To investigate OGTT phenotypes and their implications to type 2 diabetes pathophysiology and remission.

Specific Objectives

- Identify whether participants ascertained with Type 2 Diabetes by an abnormal 2h post-load glucose value following an oral glucose tolerance test, compared to those ascertained by an elevated fasting glucose, are more likely to have remitted upon retesting approximately four years later, and evaluate other predictors of remission in individuals newly diagnosed with diabetes (Article 1).

1. Identify the moment of glucose abnormality during the oral glucose tolerance test (OGTT phenotype) with the highest probability of remission.
2. Identify predictors of remission and assess whether this moment is an independent predictor.
3. Evaluate the association of hepatic steatosis and additional indicators of hepatic dysfunction with remission.

- To describe differences in sociodemographic and clinical characteristics between new onset diabetes based on an abnormal fasting glucose from that based on an abnormal 2h glucose. Additionally, to evaluate if hepatic steatosis is more associated with one of these pathways to diabetes (Article 2).

1. Identify exposures, considering anthropometrics, liver function, hepatic steatosis, and lipids, associated with incident diabetes detected by 2h glucose during an oral glucose test, as opposed to by fasting glucose.
2. Evaluate whether hepatic steatosis is more predictive of incident diabetes detected by fasting than by 2h glucose abnormality.

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RESUMO ARTIGO 1

Remissão no Diabetes Tipo 2 Recém-Diagnosticado: O Fenótipo do Teste de Tolerância à Glicose Importa?

Introdução: Historicamente, o diabetes foi compreendido como uma doença crônica e invariavelmente progressiva, associada à deterioração gradual da função das células β-pancreáticas à ocorrência de complicações micro e macrovasculares. No entanto, evidências crescentes provenientes de estudos com pacientes submetidos à cirurgia bariátrica, às intervenções dietéticas e às novas terapias farmacológicas têm desafiado esse paradigma ao demonstrar que a remissão do diabetes é possível em um subconjunto de indivíduos. A partir dessas constatações, houve um aumento do interesse científico e esforços têm sido empregados no sentido de identificar fatores associados à remissão do diabetes tipo 2. Apesar da ausência de um consenso amplamente aceito sobre a definição de remissão, fatores como a duração da doença e o controle glicêmico têm sido consistentemente apontados como determinantes importantes. Contudo, aspectos relacionados às diferentes vias fisiopatológicas do diabetes têm recebido atenção limitada. Recentemente, estudos têm sido conduzidos visando à identificação de subtipos de DM2 com maior propensão ao controle glicêmico, risco cardiometabólico e desenvolvimento de complicações. Esses estudos utilizam desde classificações fenotípicas simples até abordagens complexas baseadas em *machine learning*. Entretanto, há uma lacuna na literatura quanto à investigação de fenótipos com maior propensão ao desfecho remissão. A compreensão dos fatores clínicos e metabólicos associados à remissão da doença é essencial para subsidiar estratégias de manejo personalizadas. Nesse contexto, o Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil) representa uma oportunidade única para explorar tais determinantes em uma coorte extensa e bem caracterizada de adultos com diagnóstico recente de diabetes tipo 2.

Métodos: Este estudo utilizou dados da coorte ELSA-Brasil, composta por 15.105 servidores públicos com idades entre 35 e 74 anos, recrutados em seis centros de pesquisa no Brasil entre 2008 e 2010, com seguimentos realizados em 2012–2014 e 2017–2019. Foram incluídos participantes com diagnóstico recente de DM2, identificado por meio do teste oral de tolerância à glicose (TOTG) na Visita 1 ou 2, e que apresentavam dados de TOTG no acompanhamento subsequente. Excluíram-se indivíduos submetidos à cirurgia bariátrica ou com informações insuficientes para avaliação da remissão. A remissão foi definida como a regressão a níveis de glicemia abaixo do limiar diagnóstico para diabetes

(glicemia de jejum < 126 mg/dL, glicemia 2h pós-TOTG < 200 mg/dL e HbA1c < 6,5%) na ausência de uso de medicamentos hipoglicemiantes. Informações clínicas, laboratoriais e sociodemográficas foram obtidas por meio de protocolos padronizados. A sensibilidade à insulina foi estimada pelo índice de Matsuda, e a presença de esteatose hepática foi avaliada por meio do Fatty Liver Index (FLI). Modelos de regressão de Poisson com variância robusta foram utilizados para estimar riscos relativos (RR) e intervalos de confiança de 95% (IC95%) para a ocorrência de remissão, ajustando-se para variáveis sociodemográficas, clínicas e metabólicas.

Resultados: Foram incluídos na análise 752 participantes com diagnóstico recente de DM2. Durante o período de acompanhamento, 100 casos de remissão foram identificados, sendo a maioria pertencente ao grupo com alteração isolada da glicemia de 2h. Nos modelos multivariados, esse grupo apresentou maior probabilidade de remissão em comparação aos indivíduos com alteração isolada da glicemia de jejum (RR=1,95; IC95% 1,17–3,39), enquanto aqueles com ambas as alterações apresentaram menor probabilidade de remissão (RR=0,19; IC95% 0,04–0,60). Níveis mais elevados de HbA1c e do Fatty Liver Index (FLI) estiveram inversamente associados à remissão em todos os modelos (RR=0,39; IC95% 0,26–0,58 e RR=0,54; IC95% 0,33–0,88, respectivamente). Por outro lado, medidas antropométricas, parâmetros lipídicos e sensibilidade à insulina (índice de Matsuda) não se associaram significativamente à remissão nos modelos ajustados. A análise estratificada por índice de massa corporal (IMC) revelou modificação de efeito para certos preditores. Entre os participantes sem obesidade (IMC <30 kg/m²), a associação inversa entre FLI e remissão manteve-se significativa (RR=0,44; IC95% 0,26–0,73), enquanto nos indivíduos com obesidade essa associação foi atenuada. A associação positiva entre alteração isolada da glicemia pós-carga e remissão foi mais pronunciada no grupo de indivíduos com obesidade (RR=4,50; IC95% 1,43–14,15). Níveis mais elevados de triglicerídeos estiveram positivamente associados à remissão no grupo com IMC<30 (RR=1,17; IC95% 1,03–1,33).

Conclusões: Os achados deste estudo indicam que a remissão do diabetes está fortemente relacionada ao fenótipo inicial identificado pelo TOTG, ao controle glicêmico basal e à presença de alterações metabólicas hepáticas, sendo essa relação modulada pela presença de obesidade. Os resultados reforçam a importância da caracterização fenotípica baseada em dados clínicos rotineiramente disponíveis no momento do diagnóstico, permitindo uma estratificação mais individualizada do potencial de remissão. Essa abordagem pode

orientar intervenções personalizadas, voltadas àqueles indivíduos com maior probabilidade de alcançar a remissão da doença.

ARTICLE 1

Remission in Newly Diagnosed Type 2 Diabetes: Does Glucose Tolerance Test Phenotype Matter?

Thaís S Ferreira[1]

Rodrigo Citton Padilha dos Reis[1]

Maria Inês Schmidt[1]

Bruce B Duncan[1]

1.Postgraduate Program in Epidemiology, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Corresponding Author: Bruce B Duncan, Postgraduate Program in Epidemiology, Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos, 2600/518, Porto Alegre 90035-003, Brazil. Email: bbduncan@ufrgs.br.

Abstract

BACKGROUND**:** Type 2 diabetes mellitus (T2D) has long been considered a chronic and irreversible condition, progressing steadily over time. Yet, growing evidence from studies involving bariatric surgery, dietary interventions, and novel pharmacological treatments has challenged this paradigm by demonstrating that remission is achievable in selected individuals. Our aim was to identify factors linked to remission, including that based on the baseline oral glucose tolerance test (OGTT) results, in The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).

METHODS: We evaluated 752 participants from ELSA-Brasil cohort with newly diagnosed T2D, based on a single OGTT at baseline, with OGTT data at follow-up visits approximately 4 and 9 years later. Remission was defined as presenting non-diabetic glycemic criteria (FPG <126 mg/dL, 2hPG <200 mg/dL and HbA1c <6.5%) in the absence of glucose-lowering medications at follow-up. Clinical, laboratory, and sociodemographic variables were collected using standardized procedures. Insulin sensitivity was estimated via the Matsuda Index, and hepatic steatosis through the Fatty

Liver Index (FLI). Adjusted robust Poisson regression was used to estimate relative risks (RR) for remission.

RESULTS**:** Among the 752 individuals with new onset diabetes, 100 returned to follow-up in remission. Remission was more likely in participants with isolated abnormal post-load glucose (RR=1.95; 95%CI 1.17–3.39), while those with both fasting and 2hPG abnormalities had a much lower probability of remission (RR=0.19; 95%CI 0.04–0.60). Higher baseline HbA1c and FLI were inversely associated with remission (RR=0.39 and 0.54, respectively). Stratified analyses showed that among individuals without obesity, FLI (RR=0.44; 95%CI 0.26-0.73) but not the isolated 2hPG abnormality (RR=1.35; 95%CI 0.73-2.50) remained associated, while in individuals with obesity the isolated 2hPG abnormality was a considerably strong predictor of remission (RR=4.50; 95%CI 1.43-14.15). Higher triglycerides levels also predicted remission (RR=1.17; 95%CI 1.03-1.33) among participants without obesity.

CONCLUSION**:** Our findings highlight the role of OGTT phenotype in predicting T2D remission. Lower baseline HbA1c levels, and reduced hepatic steatosis were associated with higher remission rates. Obesity acting was a strong effect modifier. These findings support the use of routine clinical data for identifying patients with greater potential for remission and reinforce the notion that early-stage diabetes may be reversible, even through low-intensity interventions in metabolically favorable phenotypes.

Introduction

Until recently, Type 2 Diabetes Mellitus was considered a chronic, progressive disease related to a progressive depletion of β-cells and chronic macro and microvascular diabetes-related complications (1). With the observation that blood glucose levels returned to normal within hours to days after bariatric surgery in individuals with obesity and diabetes, even before significant weight loss occurred (2,3), and the growing body of evidence demonstrating bariatric surgery's effectiveness in glycemic control and diabetes remission (3–6), a paradigm shift has occurred that recognizes the possibility of disease remission.

Contributing to the growing body of clinical evidence on the reversibility of diabetes, dietary intervention studies were developed to evaluate the effects of a sudden

RESUMO ARTIGO 2

Associação Entre Perfil Metabólico e Fenótipos Distintos de TOTG no Diabetes Mellitus Tipo 2 Incidente

INTRODUÇÃO: A heterogeneidade do diabetes tipo 2 é complexa e envolve interações dinâmicas entre predisposição genética, exposições ambientais e fenótipos metabólicos distintos. Embora amplamente reconhecida a contribuição de sua natureza heterogênea para a variabilidade em sua apresentação clínica, sua progressão e resposta às intervenções terapêuticas, o termo "diabetes" é frequentemente utilizado de forma ampla, abrangendo os diferentes fenótipos que compõem o espectro da doença. Como resultado, são frequentemente observadas inconsistências na direção das associações entre variáveis ligadas ao desenvolvimento da doença, a depender do método diagnóstico utilizado para definir sua incidência. Estratificar indivíduos em fenótipos distintos de diabetes tipo 2 recentemente diagnosticado pode ampliar a compreensão dos determinantes etiológicos da doença e apoiar o desenvolvimento de estratégias de prevenção e tratamento mais direcionadas. Nesse contexto, o Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil), uma ampla coorte multicêntrica com coleta de dados padronizada e centralizada, oferece uma oportunidade única para a investigação de características clínicas e metabólicas associadas à incidência de diferentes fenótipos de diabetes tipo 2, contribuindo assim para avanços na compreensão fisiopatológica e no aprimoramento das abordagens terapêuticas.

MÉTODOS: Foram analisados dados da coorte ELSA-Brasil, que incluiu 15.105 servidores públicos com idades entre 35 e 74 anos de seis cidades brasileiras, recrutados entre 2008 e 2010, com visitas de seguimento realizadas entre 2012–2014 e 2017–2019. Foram incluídos participantes sem diagnóstico de diabetes, conforme confirmado por teste oral de tolerância à glicose (TOTG) e sem uso de medicamentos hipoglicemiantes. A incidência de diabetes tipo 2 foi classificada como alteração isolada da glicemia de jejum (glicemia de jejum ≥126 mg/dL e glicemia 2h pós-carga <200 mg/dL) ou alteração isolada da glicemia 2h pós-carga (glicemia 2h pós-carga ≥200 mg/dL e glicemia de jejum <126 mg/dL), sendo excluídos indivíduos com ambas as glicemias alteradas. Dados clínicos, laboratoriais e sociodemográficos foram coletados por protocolos padronizados. A sensibilidade à insulina foi estimada por meio do Índice de Matsuda, e a presença de esteatose hepática foi avaliada pelo *Fatty Liver Index* (FLI). As associações entre fatores metabólicos basais e fenótipos de diabetes definidos pelo TOTG foram estimadas por

modelos de regressão de Poisson robusta, ajustados sequencialmente para covariáveis sociodemográficas, metabólicas e comportamentais.

RESULTADOS: Entre os participantes avaliados, 845 desenvolveram diabetes, confirmado pelo teste oral de tolerância à glicose (TOTG), sendo 605 classificados como portadores de alteração isolada da glicemia de jejum (34%) ou alteração isolada da glicemia 2h pós-carga (66%). Nos modelos ajustados, níveis mais elevados de colesterol LDL-C estiveram inversamente associados ao fenótipo com alteração isolada da glicemia de jejum (RR por 50 mg/dL = 0,69; IC95%: 0,55–0,88), enquanto a sensibilidade à insulina permaneceu positivamente associada ao mesmo fenótipo em todos os modelos avaliados (RR = 1,17; IC95%: 1,03–1,32). Níveis mais altos do FLI estiveram positivamente associados ao fenótipo com alteração da glicemia de jejum (RR = 1,34; IC95%: 1,02–1,77), porém a associação perdeu significância após o ajuste para IMC, hipertensão e características de estilo de vida, como tabagismo e consumo de álcool. O consumo excessivo de álcool foi associado a um maior risco de desenvolver o fenótipo com alteração isolada da glicemia de jejum (RR = 1,82; IC95%: 1,10–2,93).

CONCLUSÃO: Os achados destacam a presença de mecanismos fisiopatológicos distintos nos diferentes fenótipos analisados, ressaltando a importância de sua identificação durante o diagnóstico e nas etapas iniciais de manejo de indivíduos em risco para o desenvolvimento da doença. Essas distinções podem refletir processos metabólicos divergentes, enfatizando a necessidade de abordagens mais personalizadas para a prevenção e manejo do diabetes.

ARTICLE 2

Association Between Metabolic Profile and Distinct OGTT Phenotypes of Incident Type 2 Diabetes Mellitus

Thaís S Ferreira[1]

Rodrigo Citton Padilha dos Reis[1]

Maria Inês Schmidt[1]

Bruce B Duncan[1]

1.Postgraduate Program in Epidemiology, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Corresponding Author: Bruce B Duncan, Postgraduate Program in Epidemiology, Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos, 2600/518, Porto Alegre 90035-003, Brazil. Email: bbduncan@ufrgs.br.

BACKGROUND: The heterogeneity of type 2 diabetes is complex and involves dynamic interactions. Stratifying individuals into distinct phenotypes of recently diagnosed type 2 diabetes may enhance our understanding of its etiological determinants and support the development of targeted prevention and treatment strategies. The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) provides a unique opportunity to investigate clinical and metabolic characteristics associated with the incidence of different type 2 diabetes phenotypes.

METHODS: We included participants without diabetes at baseline and absence of glucose-lowering medication. Incident type 2 diabetes was classified as either isolated abnormal fasting glucose (FPG ≥126 mg/dL and 2hPG <200 mg/dL) or isolated abnormal 2-h post-load glucose (2hPG ≥200 mg/dL and FPG <126 mg/dL), excluding individuals with both altered. Clinical, laboratory, and sociodemographic data were collected using standardized protocols. Insulin sensitivity was estimated using the Matsuda Index, and hepatic steatosis was assessed using the Fatty Liver Index (FLI). Associations between baseline metabolic factors and diabetes OGTT phenotypes were estimated using robust Poisson regression models.

RESULTS: 845 participants developed incident diabetes confirmed by oral glucose tolerance test (OGTT), with 605 classified as having either isolated abnormal fasting glucose (34%) or isolated abnormal 2-hour post-load glucose (66%). Higher LDL-Cholesterol was inversely associated with the isolated abnormal fasting phenotype (RR per 50 mg/dL=0.69; 95%CI: 0.55–0.88), while insulin sensitivity remained positively associated across models (RR=1.17; 95%CI 1.03–1.32). Higher levels of the Fatty Liver Index (FLI) were positively associated with fasting phenotype (RR=1.34; 95%CI: 1.02–1.77), but lost significance when BMI, hypertension and lifestyle characteristics were added. Heavy alcohol consumption was associated with a higher risk of developing the isolated abnormal fasting glucose phenotype (RR=1.82; 95%CI 1.10–2.93).

CONCLUSION: The findings highlight the presence of distinct pathophysiological mechanisms underlying the diabetes phenotypes examined, underscoring the importance of recognizing these differences during diagnosis and in the early stages of managing individuals at risk for diabetes. These distinctions likely reflect divergent metabolic processes, emphasizing the need for more tailored approaches to diabetes prevention and care.

Introduction

The heterogeneity of type 2 diabetes is complex and multifaceted, involving interactions between genetic, environmental, and phenotypic factors, resulting in distinct risk profiles, disease progression, and treatment responses (1,2). Recent efforts to subclassify diabetes aim to improve understanding of its underlying pathophysiological mechanisms and patient outcomes, using both simple clinical criteria and more advanced methods such as machine learning and omics data (3). However, challenges remain including the selection of variables used in subclassification approaches and their clinical applicability.

In this context, important questions remain regarding the characterization and clinical significance of the different phenotypes of early onset type 2 diabetes. Characterizing the sociodemographic and metabolic profiles of different phenotypes, in addition to deepening the understanding of the pathophysiological mechanisms of the disease, will aid in understanding the extent to which of individuals of different

CONCLUSIONS AND FINAL CONSIDERATIONS

The findings from the two studies presented, both conducted using data from the ELSA-Brasil cohort, make a substantial contribution to the understanding of the phenotypic heterogeneity of type 2 diabetes and its clinical and metabolic determinants. Collectively, the results suggest that OGTT phenotypes, traditionally underrecognized in routine clinical practice, hold significant prognostic relevance with respect to diabetes remission and may reflect distinct pathophysiological trajectories of the disease.

In the first study, isolated abnormal post-load glucose was independently associated with a higher probability of diabetes remission, especially among individuals with obesity. Complementing this, the second study showed that the same phenotype tends to present a more favorable metabolic profile, marked by a lower hepatic steatosis index scores. Taken together, these features not only seem to influence the development of the specific phenotype but also to shape the probability of disease remission.

Another relevant observation relates to the consistent association between lower LDL-Cholesterol levels and the phenotype defined by isolated abnormal fasting glucose. While LDL-Cholesterol is traditionally viewed as a cardiovascular risk marker in the context of diabetes, our findings suggest it may also play a distinct role in the pathogenesis of diabetes itself. Importantly, unlike other metabolic factors evaluated, LDL-C levels remained significantly associated with this phenotype even after adjusting for insulin sensitivity and hepatic steatosis, indicating that this relationship may occur through mechanisms relatively independent of hepatic dysfunction or systemic insulin sensitivity. This raises important questions about the role of lipid metabolism in the onset and progression of specific phenotypes of type 2 diabetes – questions that merit further investigation.

From both clinical and public health perspectives, these findings have important implications. Incorporating phenotypic assessment at the time of diabetes diagnosis, using simple, non-invasive tools widely available in clinical practice, such as the Fatty Liver Index (FLI), may allow for early stratification and more efficient allocation of therapeutic resources. This approach could help identify individuals with a higher potential for remission, who may benefit from more intensive intervention strategies aimed at diabetes remission, rather than defaulting to glycemic control strategies centered on HbA1c. Furthermore, the results highlight the importance of phenotype-based approaches in the

design and interpretation of studies assessing factors related to both the progression and remission of type 2 diabetes. The use of phenotypic classifications, such as the distinction between isolated abnormal fasting glucose and isolated abnormal post-load glucose, enables the capture of nuanced pathophysiological patterns that would otherwise be obscured in analyses treating diabetes as a homogeneous condition.

In conclusion, the insights gained from these studies not only reinforce the complex and heterogeneous nature of type 2 diabetes, but also support the importance of adopting a more refined, phenotype-driven approaches to its early diagnosis, treatment, and potential remission