UNIVERSIDADE FEDERAL DO RIO GRANDE DO NORTE
CENTRO DE CIÊNCIAS DA SAÚDE
DEPARTAMENTO DE FISIOTERAPIA
PROGRAMA DE PÓS-GRADUAÇÃO EM FISIOTERAPIA

Aprendizagem de máquina aplicada à execução da marcha em diabéticos tipo 2

Machine learning applied to gait performance in type 2 diabetes

Patrícia Mayara Moura da Silva

Natal

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Tese apresentada ao curso de Doutorado do Programa de Pós-Graduação em Fisioterapia da Universidade Federal do Rio Grande do Norte, como requisito à obtenção do Grau de Doutor.

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Resumo

Introdução: A diabetes caracteriza-se por um conjunto de doenças metabólicas que podem causar diversas alterações. Uma delas ocorre na função sensório-motora que gera modificações na execução da marcha, como: fase de apoio mais longa, passos mais curtos e inadequada distribuição da pressão plantar. Métodos quantitativos de avaliação das alterações do padrão de marcha podem ser decisivos para traçar estratégias de tratamento. Além disso, eles podem ajudar na prevenção de complicações causadas pela diabetes. Com os avanços das técnicas de aprendizagem de máquina (AM), o reconhecimento automatizado de padrões diante da enorme quantidade de dados vem se tornando uma ferramenta essencial na área médica devido à capacidade de prever complicações clínicas antes que a doença se agrave. **Objetivos:** investigar modelos de AM sobre dados de avaliação da marcha de pacientes diabéticos, tipo 2, a fim de identificar os padrões de execução de marcha que possam prever complicações clínicas da diabetes. **Métodos:** O estudo envolveu duas etapas metodológicas: 1) Elaboração de protocolo e Revisão Sistemática; 2) Desenvolvimento e aprimoramento de modelos preditivos de AM não supervisionada e supervisionada para análise exploratória de dados, detecção da diabetes e detecção de complicações clínicas na diabetes baseadas nos níveis de hemoglobina glicada (HbA1c). Os dados para execução do estudo foram fornecidos mediante parceria com a *Florida International University* (FIU) durante doutorado sanduíche (Edital No. 02/2020 – CAPES/PRINT) entre setembro de 2021 e junho de 2022. Os dados foram pré-processados e implementados em diferentes modelos de AM. Os modelos de AM utilizados foram avaliados quanto a sua eficiência baseando-se na análise de *silhouette* para AM não supervisionada, métricas de AM supervisionada baseadas na matriz de confusão e estatística convencional adotando-se o nível de significância de 5%. **Resultados:** Etapa 1 resultou em dois artigos: Artigo 1 - O protocolo já publicado definiu a metodologia a ser seguida na revisão; Artigo 2 - A revisão sistemática, em apreciação, resultou em quatro estudos (208 participantes) incluídos. Dois usaram AM como método preditivo, um utilizou estatística convencional baseada em regressão múltipla *stepwise* e um o classificador Fuzzy que é um método de incerteza. Os estudos atingiram pelo menos 75% em reportar adequadamente 19 itens do *Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis* (TRIPOD). Três dos estudos incluídos foram classificados como alto risco de viés. Etapa 2 resultou em três artigos, em processo de submissão: Artigo 3 – K-Médias separou o conjunto de dados em dois grupos (*silhouette* = 0,47). Os padrões de velocidade, comprimento do passo e distribuição de pressão plantar da marcha foram estatisticamente diferentes ($p < 0,05$) entre diabéticos e não diabéticos. Além disso, entre os diabéticos, observou-se uma diferença de estatística significativa ($p < 0,05$) nos padrões de distribuição de pressão plantar. Artigo 4 – Algoritmos de AM supervisionada usando dados de marcha mostraram alta sensibilidade na distribuição da pressão plantar na região do calcanhar para classificar diabéticos de não diabéticos. Artigo 5 – O classificador XGB apresentou melhores resultados para classificar complicações na diabetes baseados no nível de HbA1c, alcançando AUC de 0,99, precisão de 0,91, recall de 0,90 e f1-score de 0,89. As características da marcha mais relevantes para essa classificação foram base de apoio esquerda, pressão esquerda média ao longo do tempo na região dos metatarsos (I-III) e média da área do sensor ativo nas falanges (III-IV). **Conclusão:** A literatura mostra poucos estudos sobre o uso de dados de marcha como preditores da diabetes. Diabéticos tipo 2 apresentam alterações alterações execução da marcha, com diferenças na distribuição da pressão plantar dos indivíduos com maiores níveis glicêmicos. Regiões diferentes de distribuição da pressão plantar foram relevantes na classificação de diabéticos ou não diabéticos e na detecção de complicações na diabetes. Ambos achados são respaldados na literatura.

Palavras-chaves: Diabetes, Marcha, Aprendizagem de Máquina.

Abstract

Introduction: Diabetes is characterized by a set of metabolic diseases that can cause several changes. One of them occurs in the sensorimotor function, which generates changes in gait execution, such as longer stance phase, shorter steps and inadequate plantar pressure distribution. Quantitative methods for assessing changes in gait patterns can be decisive in designing treatment strategies. Also, they can help in preventing complications caused by diabetes. With advances in machine learning (ML) techniques, automated pattern recognition in the face of massive amounts of data has become an essential tool in the medical field due to its ability to predict clinical complications before the disease gets worse. **Objectives:** To investigate ML models on gait assessment data from type 2 diabetic patients in order to identify gait patterns that may predict clinical complications of diabetes. **Methods:** The study involved two methodological phases: 1) Protocol and Systematic Review elaboration; 2) Development and improvement of predictive models of unsupervised and supervised BF for exploratory data analysis, detection of diabetes and detection of clinical complications in diabetes based on glycated hemoglobin (HbA1c) levels. The data for carrying out the study was provided through a partnership with Florida International University (FIU) during a sandwich doctorate (Edital No. 02/2020 – CAPES/PRINT) between September 2021 and June 2022. The data were pre-processed and implemented in different ML models. The ML models used were evaluated for their efficiency based on the silhouette analysis for unsupervised ML, metrics based on the confusion matrix for supervised ML, and conventional statistics, adopting a significance level of 5%. **Results:** Phase 1 resulted in two articles: Article 1 - The published protocol defined the methodology that guided the review; Article 2 - The systematic review, under consideration, resulted in four studies (208 participants) included. Two used ML as a predictive method, one used conventional statistics based on multiple stepwise regression, and one used the Fuzzy classifier, an uncertainty method. Studies achieved at least 75% in adequately reporting 19 Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) items. Three of the included studies were classified as high risk of bias. Phase 2 resulted in three articles in the submission process: Article 3 – K-Means separated the data set into two groups (silhouette = 0.47). Gait speed, step length and plantar pressure distribution patterns were statistically different ($p < 0.05$) between diabetics and non-diabetics. Among diabetics, there was a statistically significant difference ($p < 0.05$) in plantar pressure distribution patterns. Article 4 – Supervised ML algorithms using gait data showed high sensitivity in the distribution of plantar pressure in the heel region to classify diabetics from non-diabetics. Article 5 – The XGB classifier showed better results in classifying diabetes complications based on HbA1c levels, reaching an AUC of 0.99, a precision of 0.91, a recall of 0.90 and an f1-score of 0.89. For this classification, the most relevant gait characteristics were left support base, mean left pressure over time in the metatarsal region (I-III) and mean active sensor area in the phalanges (III-IV). **Conclusion:** The literature shows few studies using gait data as predictors of diabetes. Type 2 diabetics presented changes in gait performance, with differences in plantar pressure distribution in individuals with higher glycemic levels. Different regions of plantar pressure distribution were relevant in the classification of diabetics or non-diabetics and in detecting complications in diabetes. These findings have been supported in the literature.

Keywords: Diabetes, Gait, Machine Learning.

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"What do we live for, if it is not to make life less difficult for each other?"

(George Eliot).

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Lista de Acrônimos e Abreviações

ACP – Análise de Componentes Principais

ADA – American Diabetes Association

AM – Aprendizagem de Máquina

API – Interface de Programação de Aplicação

AUC – Área sobre a Curva de Característica de Operação do Receptor

CAPES – Coordenação de Aperfeiçoamento de Pessoal de Nível Superior

Curva ROC – Curva de Característica de Operação do Receptor

DPN – Neuropatia Periférica Diabética

DT – Árvore de Decisão

EMG – Eletromiografia

FIU – Florida International University

HbA1c – Hemoglobina glicada

IA – Inteligência Artificial

IIN-ELS – Instituto Internacional de Neurociências Edmond e Lily Safra

IMC – Índice de Massa Corporal

KNN – K-Vizinhos Mais Próximos

LDA – Análise Discriminante Linear

LIPERV – Laboratório de Intervenção e Pesquisa em Realidade Virtual

LR – Regressão Logística

ML – Machine Learning

MLP – Máquinas de Vetores de Suporte

NB – Bayes Ingênuo

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

R^2 – Coeficiente de Determinação

RF – Floresta Aleatória

RFE – Eliminação de Características Recursivas

RMSE – Raiz do Erro Quadrático Médio

SMOTE – Synthetic Minority Oversampling Technique

SNC – Sistema Nervoso Central

SNP – Sistema Nervoso Periférico

SUS – Sistema Único de Saúde

SVM – Máquinas de Vetores de Suporte

TRIPOD – Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis

XGB Classifier – Extreme Gradient Boost Classifier

Prefácio

A presente Tese contém 5 estudos e versa sobre a utilização de diversas abordagens de modelos preditivos de aprendizagem de máquina (AM) em um banco de dados fornecidos por uma parceria estabelecida com *Florida International University* (FIU). Os dados são relacionados a dados clínicos e de execução da marcha de diabéticos e não diabéticos. O delineamento desse estudo baseou-se na hipótese de que complicações neurológicas motoras para execução da marcha em pacientes diabéticos podem preceder as alterações sensoriais que são características mais graves da doença. Assim, uma vez detectadas as alterações motoras da marcha de forma precoce, tratamentos adequados poderão ser direcionados para que sejam evitadas complicações sensoriais mais graves como a neuropatia diabética periférica.

Para facilitar a leitura, esta Tese está organizada em 6 partes. Iniciando pela introdução que apresenta uma breve problematização sobre o tema trabalhado, compreendendo as características da diabetes, as complicações e os padrões de execução de marcha encontrados na literaturatura. Nessa parte ainda são discutidos sobre os vários métodos de análise de marcha utilizados na prática clínica, finalizando com uma explanação sobre o que seria a aprendizagem de máquina, seus subtipos e métricas de avaliação.

Já na segunda e na terceira parte encontram-se, respectivamente, a justificativa e os objetivos da presente Tese. Na quarta parte, os materiais e métodos empregados são explanados de forma sucinta.

Enquanto na quinta parte intitulada "Resultados e Discussão", compreende todos os artigos resultantes da presente Tese. Cada artigo apresenta suas próprias referências bibliográficas e materiais suplementares. O artigo 01 apresenta-se publicado na revista *"BMJ Open"* (Qualis A2 - *Scopus* 81%). O artigo 02 apresenta-se submetido a revista *"Diabetes & Metabolic Syndrome: Clinical Research & Reviews"* (Qualis A1 - *Scopus* 90%). Os artigos 03, 04 e 05 estão em fase de correções e serão submetidos para as revistas *"International Journal of Medical Informatics"* (Qualis A2 - *Scopus* 84%), *"Gait and Posture"* (Qualis A2 - *Scopus* 85%) e *"Journal of Diabetes Science and Technology"* (Qualis A2 - *Scopus* 80%), respectivamente.

Por fim, na última parte é abordado um panorama geral das conclusões dos principais resultados encontrados na realização desta Tese.

1 Introdução

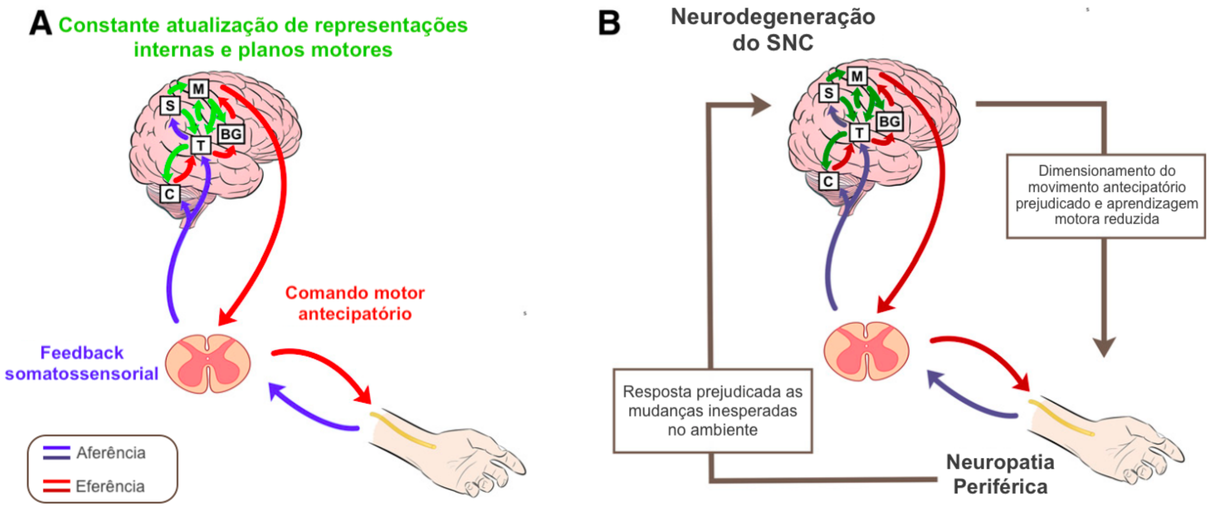
1.1 Diabetes: complicações e repercussão na execução da marcha

A diabetes caracteriza-se por ser uma doença metabólica gerada por defeitos na secreção e/ou na ação da insulina, resultando em quadros de hiperglicemia (CHATTERJEE *et al.*, 2017; ARIK *et al.*, 2019; RODEN; SHULMAN, 2019). Mundialmente há mais de 430 milhões de pacientes com diabetes, sendo a mais comum a diabetes mellitus tipo 2 (GOLBERT *et al.*, 2020). Estima-se que 13 milhões de brasileiros apresentam diabetes mellitus, sendo o país classificado como o quarto mais prevalente no mundo (FLORÊNCIO *et al.*, 2021). Além disso, projeta-se 23 milhões de brasileiros com a doença até o ano de 2045, enquanto a nível global projeta-se 629 milhões de indivíduos. Esta projeção global poderá resultar em grandes impactos econômicos nos sistemas de saúde dos países (GOLBERT *et al.*, 2020; FLORÊNCIO *et al.*, 2021).

Entre esses indivíduos, a população idosa é a mais comum de apresentar a doença devido a diversos fatores relacionados ao envelhecimento. Dentre eles estão o aumento da resistência à insulina, a obesidade, o baixo nível de atividade física e o uso de medicamentos (ARIK *et al.*, 2019; RODEN; SHULMAN, 2019; STANDL *et al.*, 2019). Detectar precocemente a diabetes permite iniciar o tratamento de forma mais efetiva a fim de melhorar o controle glicêmico e minimizar danos (CHATTERJEE *et al.*, 2017) que poderão afetar o sistema nervoso. Uma dessas complicações decorrentes de alterações do sistema nervoso é a neuropatia periférica diabética (DPN).

A DPN é a complicação crônica mais comum da diabetes mellitus tipo 2 (MELESE *et al.*, 2020). Ela caracteriza-se por uma degeneração progressiva dos nervos periféricos, principalmente dos membros inferiores, afetando seus componentes sensoriais, motores e autônomos (CREWS *et al.*, 2013; MELESE *et al.*, 2020). Pacientes com DPN apresentam sensação plantar diminuída que afeta a quantidade e a qualidade das informações aferentes envolvidas na geração e controle da marcha (HUANG *et al.*, 2019; MELESE *et al.*, 2020). Deficiências na realização do movimento de indivíduos com diabetes são atribuídas às complicações decorrentes da DPN. No entanto, comprometimentos motores eferentes também vêm sendo observados em pacientes diabéticos que não apresentam DPN, como alterações na marcha e no equilíbrio e comprometimento no controle de preensão (FERRIS *et al.*, 2020). Ainda existem achados sugestivos de que a doença também pode apresentar alterações no sistema nervoso central (SNC) além das alterações, bastante evidenciadas, no sistema nervoso peri-

Figura 1.1 – Esquema de como ocorre a relação entre o Sistema Nervoso Central (SNC) e Sistema Nervoso Periférico (SNP) no controle motor íntegro (A) e comprometido devido à diabetes (B) com a degeneração de regiões do SNC e aferência sensorial comprometida no SNP (neuropatia periférica) comprometendo as funções sensório-motoras. BG: gânglios basais; C: cerebelo; M: córtex motor; S: córtex somatossensorial; T: tálamo.



Fonte: Adaptado de Ferris *et al.* (2020).

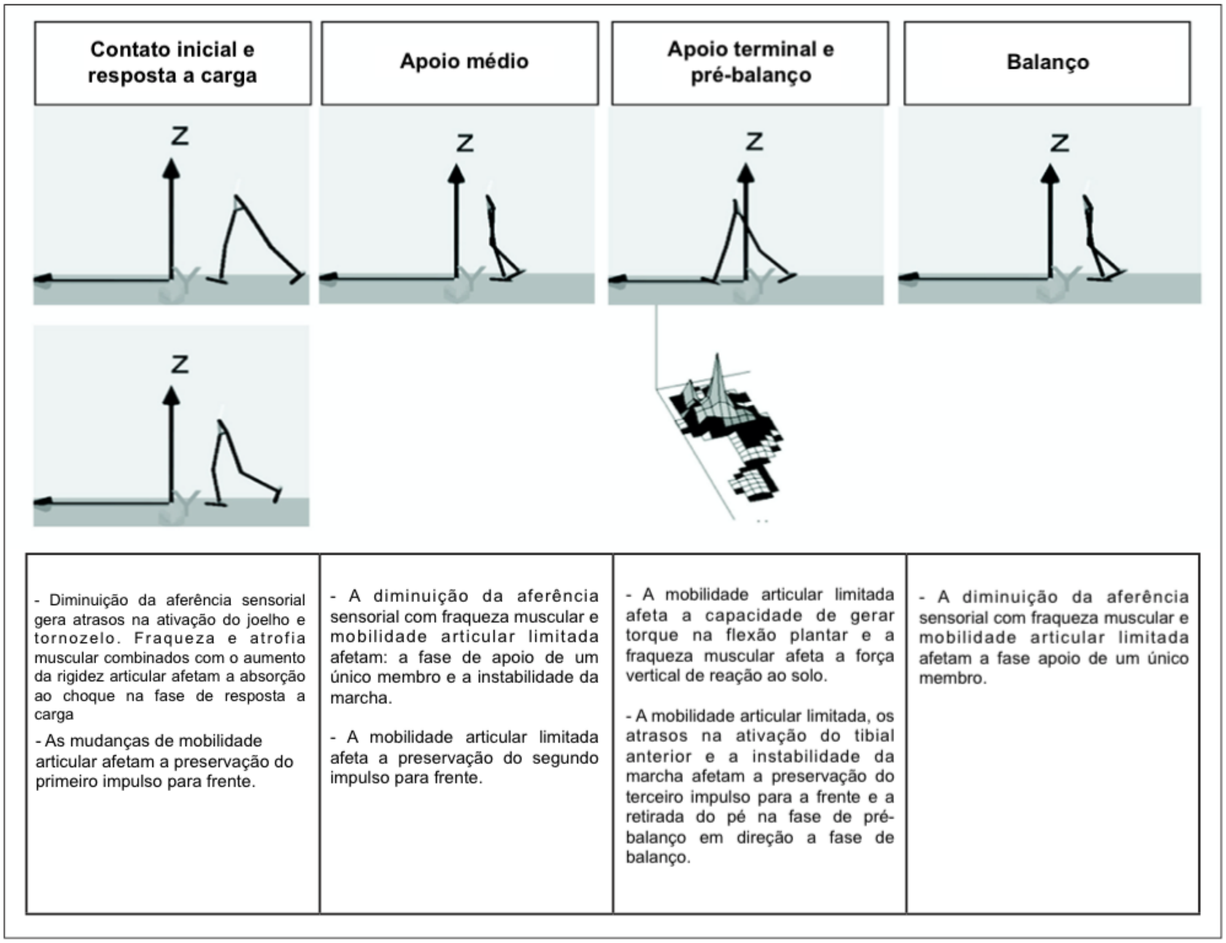
férico (SNP) (Figura 1.1B).

Os recentes avanços em neuroimagem vem mostrando evidências de que a diabetes pode afetar diferentes áreas cerebrais como o córtex somatossensorial (S), córtex motor (M), cerebelo (C) e gânglios da base (BG) (FERRIS *et al.*, 2020). Estudos recentes apontados por Ferris *et al.* (2020) mostram que a hiperglicemia crônica e a perda da sinalização da insulina geram uma cascata inflamatória, estresse oxidativo e disfunção endotelial, resultando em subsequente perda da integridade da barreira hematoencefálica. Isso permite lesões microvasculares cerebrais e uma de suas consequências é a neurodegeneração cortical de regiões do SNC (Figura 1.1B). Essas evidências mostram que mais pesquisas precisam ser realizadas a fim de elucidar como ocorrem as alterações do SNC, se elas ocorrem de forma simultânea às alterações do SNP ou se uma independe da outra (FERRIS *et al.*, 2020). Bem como envolver as relações recíprocas entre esses dois sistemas no controle e na aprendizagem motora. O que se sabe é que a falha na função sensório-motora pode levar à redução da mobilidade, da amplitude de movimento e da força muscular. O somatório dessa tríade pode resultar em alterações no controle do equilíbrio (estático e dinâmico) e na mecânica da marcha (CREWS *et al.*, 2013; HUANG *et al.*, 2019; MELESE *et al.*, 2020).

A marcha é caracterizada por um movimento cíclico e contínuo alternando períodos de apoio e balanço. Segundo o sistema desenvolvido por Perry *et al.* (1992), um ciclo da marcha é dividido em duas grandes fases, a fase de apoio que normalmente constitui 60% do ciclo da marcha e a fase de balanço que constitui os 40% restantes (TUNCA *et al.*, 2017). A mudança em alguma fase do ciclo reflete em todas as outras fases (KIRKWOOD *et al.*, 2019). Os pacientes com diabetes tipo 2 apresentam distribuição inadequada da pressão plantar, fase de apoio mais longa, passos mais curtos, aumento da cadência, diminuição da velocidade e maior base de suporte (PETROFSKY *et al.*, 2005; ALLET *et al.*, 2008; KIRKWOOD *et al.*, 2019; GNANASUNDARAM *et al.*, 2020). Já nos estágios iniciais da doença, as alterações na marcha precedem as perdas sensoriais (SAWACHA *et al.*, 2009; WROBEL; NAJAFI, 2010; GNANASUNDARAM *et al.*, 2020) com os pacientes tendendo a apresentar um tempo de reação maior para realização das atividades, resultando em um padrão de marcha menos eficiente e requerendo maior esforço na sua execução (WROBEL; NAJAFI, 2010; KO *et al.*, 2011).

A ineficiência da marcha é decorrente de uma execução mais lenta e cautelosa dos movimentos com gradativa redução da mobilidade articular e aumento da rigidez dos tendões (WROBEL; NAJAFI, 2010; GNANASUNDARAM *et al.*, 2020), reduzindo as demandas sobre os principais grupos musculares dos membros inferiores (BOULTON *et al.*, 2006). A doença também gera redução da força muscular, principalmente nos músculos mais distais do membro inferior (BOULTON *et al.*, 2006). Assim, os passos mais curtos envolvem menor torque em torno das articulações dos membros inferiores e consequente redução de força muscular requerida para realizar o movimento (Figura 1.2).

Figura 1.2 – Resumo das alterações da marcha de pacientes diabéticos nas cinco subfases da fase de apoio (contato inicial, resposta a carga, apoio médio, apoio terminal e pré-balanço) e na fase de balanço.



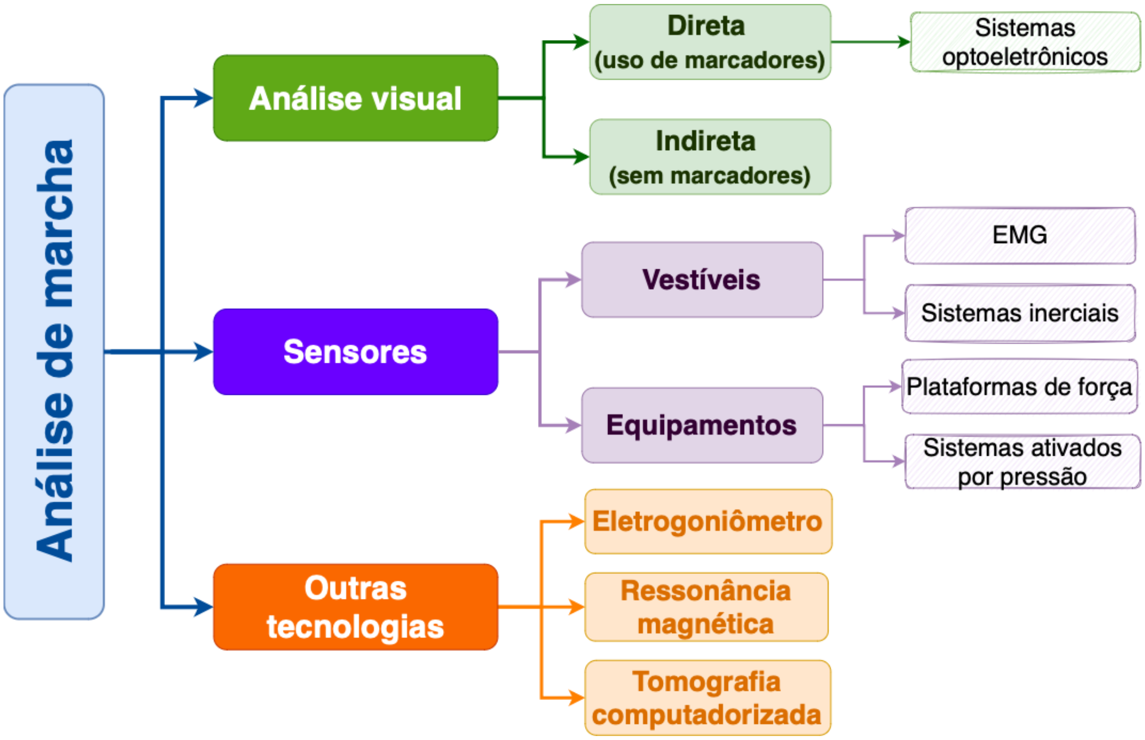
Contato inicial e resposta a carga	Apoio médio	Apoio terminal e pré-balanço	Balanço
- Diminuição da aferência sensorial gera atrasos na ativação do joelho e tornozelo. Fraqueza e atrofia muscular combinados com o aumento da rigidez articular afetam a absorção ao choque na fase de resposta a carga - As mudanças de mobilidade articular afetam a preservação do primeiro impulso para frente.	- A diminuição da aferência sensorial com fraqueza muscular e mobilidade articular limitada afetam: a fase de apoio de um único membro e a instabilidade da marcha. - A mobilidade articular limitada afeta a preservação do segundo impulso para frente.	- A mobilidade articular limitada afeta a capacidade de gerar torque na flexão plantar e a fraqueza muscular afeta a força vertical de reação ao solo. - A mobilidade articular limitada, os atrasos na ativação do tibial anterior e a instabilidade da marcha afetam a preservação do terceiro impulso para a frente e a retirada do pé na fase de pré-balanço em direção a fase de balanço.	- A diminuição da aferência sensorial com fraqueza muscular e mobilidade articular limitada afetam a fase apoio de um único membro.

Fonte: Adaptado de Wrobel e Najafi (2010).

1.2 Métodos de análise de marcha

A análise quantitativa da marcha é uma ferramenta clínica importante no diagnóstico e tratamento das anormalidades apresentadas durante a execução dessa habilidade motora (BENSON *et al.*, 2018). Também é usada para avaliar os efeitos do tratamento (BENSON *et al.*, 2018). Técnicas mais simples de análise de marcha incluem a quantificação de características espaço-temporais, como: tempo e comprimento do passo e da passada, velocidade de execução e cadência (PRAKASH *et al.*, 2018). Enquanto técnicas mais robustas e avançadas incluem análise cinética (como as forças de reação ao solo) e cinemática (como a velocidade angular e ângulos articulares) da marcha (BENSON *et al.*, 2018; CALDAS *et al.*, 2020). Para Prakash *et al.* (2018), com o advento de novas técnicas computacionais a partir de 1960, as análises da marcha humana podem ser classificadas em três grandes grupos. O primeiro grupo baseia-se na análise visual, o segundo na análise baseada em sensores o terceiro em tecnologias menos usuais (PRAKASH *et al.*, 2018) (Figura 1.3).

Figura 1.3 – Métodos de análise de marcha.



Fonte: Adaptado de Prakash *et al.* (2018)

A análise visual da marcha a partir de imagens capturadas por sistemas optoeletrônicos é geralmente realizada com uso de marcadores reflexivos acoplados no corpo do indivíduo. O uso de marcadores auxilia na análise da cinemática de um indivíduo (GOR-GARCÍA-FOGEDA *et al.*, 2016; TUNCA *et al.*, 2017; PRAKASH *et al.*, 2018), sendo o padrão ouro da análise direta da marcha (CALDAS *et al.*, 2020). Alguns sistemas optoeletrônicos se utilizam de câmeras de infravermelho que detectam o reflexo dos marcadores fixados ao corpo do indivíduo, recriando-o para análises computacionais (PRAKASH *et al.*, 2018; PUCHAUD *et al.*, 2020). Apesar da precisão, esses sistemas de certa forma impedem o movimento natural do indivíduo, uma vez que a movimentação dele é realizada em um espaço restrito e previamente delimitado pelas câmeras (PRAKASH *et al.*, 2018; BENSON *et al.*, 2018; SARAVANAN *et al.*, 2020). Também existe a análise visual de imagens sem o uso de marcadores, dita como análise indireta da marcha, caracteriza-se por ser um método observacional e subjetivo, deixando margem para diferentes interpretações entre os avaliadores (GOR-GARCÍA-FOGEDA *et al.*, 2016; ROBERTS *et al.*, 2017; SILVA *et al.*, 2022).

Além disso, pode gerar imprecisões durante avaliação e diagnóstico do movimento do paciente, prejudicando a tomada de decisões para a realização do tratamento (ROBERTS *et al.*, 2017).

As análises da marcha baseadas em sensores variam quanto ao posicionamento e o tipo do sensor. O sensor poderá ser posicionado no corpo do indivíduo (sensor vestível) ou posicionado em um equipamento (externo ao indivíduo) (PRAKASH *et al.*, 2018). Dentre os sensores vestíveis encontra-se a eletromiografia (EMG) de superfície e os sistemas inerciais (CALDAS *et al.*, 2017; SUNARYA *et al.*, 2020). A EMG é usada para avaliar a atividade elétrica muscular durante a execução da marcha, podendo detectar qual grupamento muscular encontra-se mais ativo no decorrer das fases da marcha (PRAKASH *et al.*, 2018; PAPAGIANNIS *et al.*, 2019).

Já os sistemas inerciais são usados para medir a mudança de movimento do corpo humano em um sistema de coordenadas tridimensional que vão desde mudanças na aceleração do movimento com uso de acelerômetros até mudanças angulares com uso de giroscópios (SEEL *et al.*, 2014; TAMURA, 2014; CALDAS *et al.*, 2017). Outros tipos de sensores vestíveis são os sensores de pressão que podem ser colocados no calçado que o indivíduo usa durante o dia a dia (GIOVANELLI; FARELLA, 2016; MARTINI *et al.*, 2020; MUNDT *et al.*, 2020). A maioria dos sensores vestíveis, como os sensores inerciais e os sensores de pressão, tem a vantagem de captar o movimento natural do indivíduo, sem que haja interferência do avaliador ou do próprio sistema de avaliação (PRAKASH *et al.*, 2018; BENSON *et al.*, 2018; MARTINI *et al.*, 2020).

Equipamentos utilizados para análise de marcha que apresentam sensores acoplados a eles incluem as plataformas e as passarelas ativadas por sensores de pressão. As plataformas de força são equipamentos utilizados para obter a cinética do movimento, como as forças de reação ao solo e a distribuição de pressão plantar durante a execução do movimento (PRAKASH *et al.*, 2018; MAEDA *et al.*, 2018). As passarelas ativadas por sensores de pressão, como o GAITRite® consistem em uma espécie de tapete contendo uma grade de sensores de pressão (MOTIIAN *et al.*, 2015). À medida que o indivíduo caminha sobre o equipamento, o sistema capta a geometria e o contato do pé com o solo e por meio da distribuição da pressão plantar fornece os parâmetros espaço-temporais (MOTIIAN *et al.*, 2015; KIRKWOOD *et al.*, 2019; ERDEM *et al.*, 2020). Apesar de serem considerados equipamentos padrão ouro na avaliação da marcha, para que haja uma correta medição, ambos apresentam a desvantagem de necessitar consciência do indivíduo para executar o movimento correto dentro do espaço requerido pela plataforma ou pela passarela (PRAKASH *et al.*, 2018; SARAVANAN *et al.*, 2020). Ademais, ambos equipamentos limitam a quantidade de passos a serem executados pelos indivíduos (GADALETA *et al.*, 2019; SARAVANAN *et al.*, 2020).

Outras abordagens tecnológicas menos usuais utilizadas para análise de marcha incluem o eletrogoniômetro, os sistemas de imagens por ressonância magnética e tomografia computadorizada. O eletrogoniômetro avalia a variação angular articular durante a execução do movimento (GONZALEZ-ISLAS *et al.*, 2019). Essa abordagem consome bastante tempo na avaliação, pois precisa de calibração minuciosa do equipamento previamente a sua utilização (PRAKASH *et al.*, 2018; GONZALEZ-ISLAS *et al.*, 2019). Os sistemas de imagens por ressonância magnética e tomografia computadorizada são usados para recriar modelos computacionais do indivíduo e a partir disso avaliar a cinética e a cinemática desses modelos (PRAKASH *et al.*, 2018; PUCHAUD *et al.*, 2020). Esses sistemas são bastante sensíveis a interferências durante a coleta das imagens (PRAKASH *et al.*, 2018).

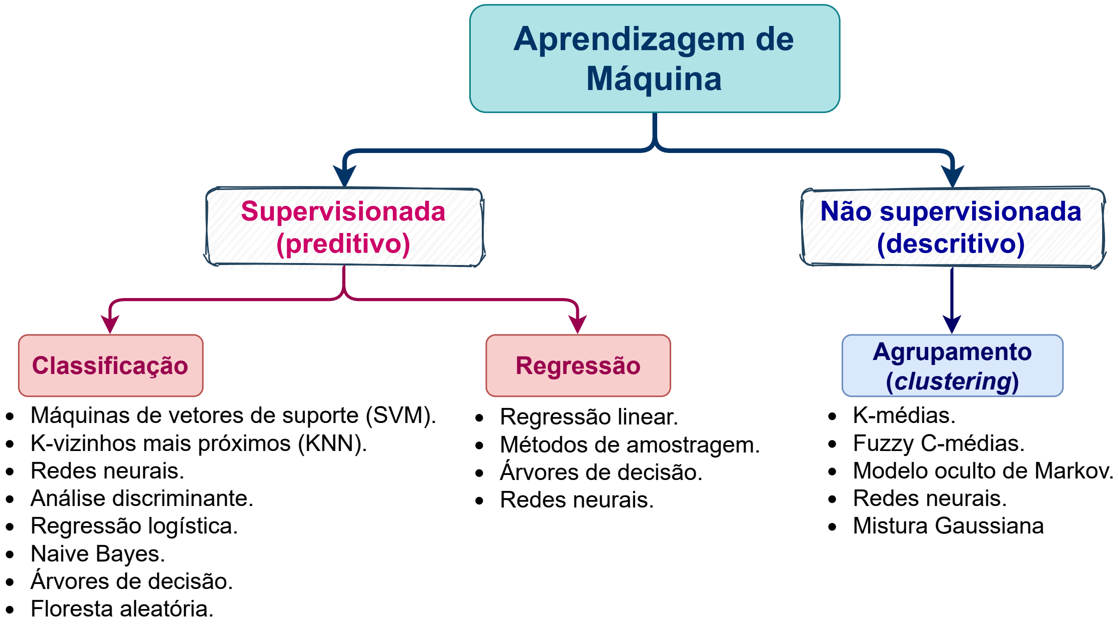
A análise da marcha combinando as diferentes ferramentas, previamente citadas, melhora a precisão das análises (BEGG; KAMRUZZAMAN, 2005; PRAKASH *et al.*, 2018). A disponibilidade de diferentes parâmetros quantitativos de execução da marcha auxilia na objetividade em detectar distúrbios (PRAKASH *et al.*, 2018; BENSON *et al.*, 2018). Além de auxiliar no direcionamento de tratamento mais adequado (PRAKASH *et al.*, 2018; BENSON *et al.*, 2018). A evolução de novos modelos e métodos para analisar marcha vem se tornando uma atividade contínua. Logo, detectar e/ou prever uma falha incipiente durante execução da marcha vem recebendo cada vez mais atenção na saúde, uma vez que esse contexto de triagem preventiva poderá evitar o agravamento ou aparecimento de futuras doenças.

1.3 A aprendizagem de máquina

A popularização de dispositivos móveis, como os *smartphones* e *smartwatches*, e o uso de aplicativos gerou um aumento no volume e na necessidade de exploração de dados, impossíveis de serem analisados manualmente. A expansão tecnológica ocorrida nas últimas décadas está desencadeando uma busca por novas ferramentas que ampliem e facilitem cada vez mais a vida humana. Uma dessas ferramentas, ramificada da ciência da computação, é a inteligência artificial (IA). De modo geral, a IA diz respeito ao uso do computador para reproduzir o comportamento inteligente com mínima intervenção humana (HAMET; TREMBLAY, 2017). É a capacidade de um sistema artificial de interpretar dados externos, aprender com esses dados e aplicar o aprendizado para atingir algum objetivo e/ou realizar tarefa específica (HAENLEIN; KAPLAN, 2019). Para alcançar esses objetivos é necessário usar comandos entendidos pela máquina (computador), chamados de algoritmos. Os algoritmos são sequências de instruções lógicas, não ambíguas, realizadas por um programador, a fim de que o computador execute cada passo para resolver um problema (ALPAYDIN, 2016).

A IA apresenta várias vertentes, como processamento de linguagem natural (para geração automática de textos e traduções), reconhecimento de padrões (de escrita, de voz e facial) e aprendizagem de máquina (AM). A AM é um campo de pesquisa baseado na interseção entre estatística e matemática em que seus algoritmos são utilizados para aprender a detectar determinados padrões (MÜLLER; GUIDO, 2016; HAMET; TREMBLAY, 2017). A análise manual de grande quantidade de dados disponíveis na atualidade é inviável, assim a AM surge para realizar esse processamento em busca de alguma informação útil (DANGETI, 2017). A AM simula o comportamento humano, buscando descobrir padrões significativos ou fórmulas matemáticas que expliquem o relacionamento entre os dados (DANGETI, 2017; THEOBALD, 2017). Em outras palavras, possibilita descobrir e generalizar padrões difíceis ou impossíveis de serem identificados manualmente (GOECKS *et al.*, 2020) e/ou criar uma regra desconhecida a partir de exemplos fornecidos (DANGETI, 2017).

Figura 1.4 – Hierarquia da classificação dos sistemas de aprendizagem de máquina.



Fonte: Adaptado de Gonzalez-Islas *et al.* (2019).

Faceli *et al.* (2011) defendem a importância de que os algoritmos de AM tenham viés indutivo para derivar conclusões gerais a partir de observações específicas. Os algoritmos de AM são utilizados em diversas tarefas e organizados de acordo com diferentes critérios (THEOBALD, 2017). Os dois grandes grupos de AM mais utilizados são os grupos preditivos e os descritivos (Figura 1.4). Além disso, existe uma terminologia comumente empregada quando se trata de AM (Tabela 1.1).

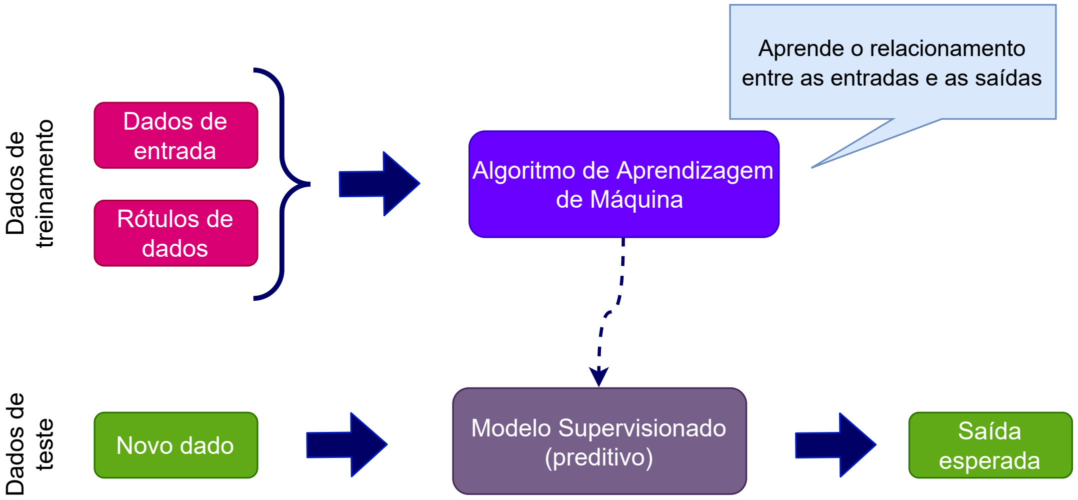
Tabela 1.1 – Glossário de terminologias empregadas na Aprendizagem de Máquina (AM).

Terminologia	**Significado**
Dados de entrada	São as variáveis de entrada que serão utilizadas em um modelo de AM. Por exemplo, dados das características antropométricas de uma amostra, dados da marcha. Esses dados poderão ser processados antes de serem empregados em um modelo de AM. Também conhecidos como características (*features*).
Dados de saída	São os resultados preditivos ou descritivos após execução de algum modelo de AM.
Rotular	Identificar antes de utilizar um modelo de AM o que as variáveis de entrada e/ou saída representam. Por exemplo, em um modelo AM para classificar a marcha entre saudáveis e não saudáveis, o rótulo para cada participante seria identificar previamente os saudáveis dos não saudáveis.
Modelo ou algoritmo	São os tipos de algoritmos de AM frequentemente usados a fim de se obter um modelo final pronto para ser utilizado, por exemplo, máquinas de vetores de suporte (SVM), regressão linear, K-médias.
Treino	O treinamento consiste em empregar uma porcentagem dos dados totais disponíveis para o estudo em um ou mais modelos de AM. É o processo de ajustar os parâmetros do modelo de AM a fim de se obter a melhor resposta possível para o problema que se quer resolver.
Teste	Após treinamento do modelo, o teste consiste em empregar a porcentagem restante dos dados disponíveis para o estudo (os dados que não foram utilizados no treinamento) a fim de observar a eficiência e capacidade de resolução e generalização do(s) modelo(s) de AM treinado(s).

Fonte: Adaptado de Liu *et al.* (2019).

O grupo preditivo também é conhecido como AM supervisionada e seus modelos (ou algoritmos) são utilizados para a predição de eventos. Esses modelos buscam, no conjunto de dados que representam um problema, encontrar uma função ou hipótese, que possa prever um resultado ou caracterizar um novo dado, sem que esse tenha sido usado no treinamento do modelo (GÉRON, 2019). Nesse tipo de AM é necessário apresentar ao modelo um número suficiente de dados de entrada e de saída desejados, estando esses devidamente rotulados. Ou seja, caracteriza-se de antemão ao treinamento do modelo qual a saída esperada para cada entrada. O objetivo dos modelos de AM preditiva é aprender uma regra geral ou função que mapeie corretamente as entradas nas saídas e assim possam prever as saídas para novos

Figura 1.5 – Esquema de como é realizada a AM supervisionada. Os dados previamente rotulados são utilizados para o treinamento do modelo (algoritmo) de AM supervisionada, uma vez finalizado o treinamento, novos dados são empregados para testar o modelo que foi treinado.



Fonte: Adaptado de Sarker (2021).

dados que não foram utilizados durante o treinamento do modelo (Figura 1.5) (THEOBALD, 2017; PRAKASH *et al.*, 2018; GÉRON, 2019; GOECKS *et al.*, 2020). Assim, os modelos preditivos (ou supervisionados) buscam encontrar uma relação nos dados de entrada que permitam produzir dados de saída com menor risco e erro (PRAKASH *et al.*, 2018) guiados por intervenções humanas nas rotulações (THEOBALD, 2017).

Os modelos de AM supervisionada podem resolver dois tipos de problemas: os de classificação e os de regressão (Figura 1.4). Os problemas de classificação têm o intuito de prever categorias (variáveis qualitativas[1]) a partir de uma base de dados (Figura 1.6A), enquanto os de regressão preveem valores quantitativos[2] (Figura 1.6B) (RASHIDI *et al.*, 2019; GOECKS *et al.*, 2020).

A Figura 1.6A, apresenta o fluxograma resumindo um problema de classificação. Inicialmente a partir de uma base de dados, já rotulados, a mesma é dividida, de forma aleatória, em dois grupos, o grupo para treinar o modelo e o grupo para testar o modelo. Em seguida, o treinamento do modelo é realizado. Uma vez finalizado o treinamento, inicia-se o teste do modelo. No teste, retiram-se os rótulos da base de dados que foi previamente separada para o teste e utiliza esses dados no modelo de AM para que o modelo realize a predição de saída. A habilidade e eficiência do desempenho do modelo em classificar corretamente os exemplos da

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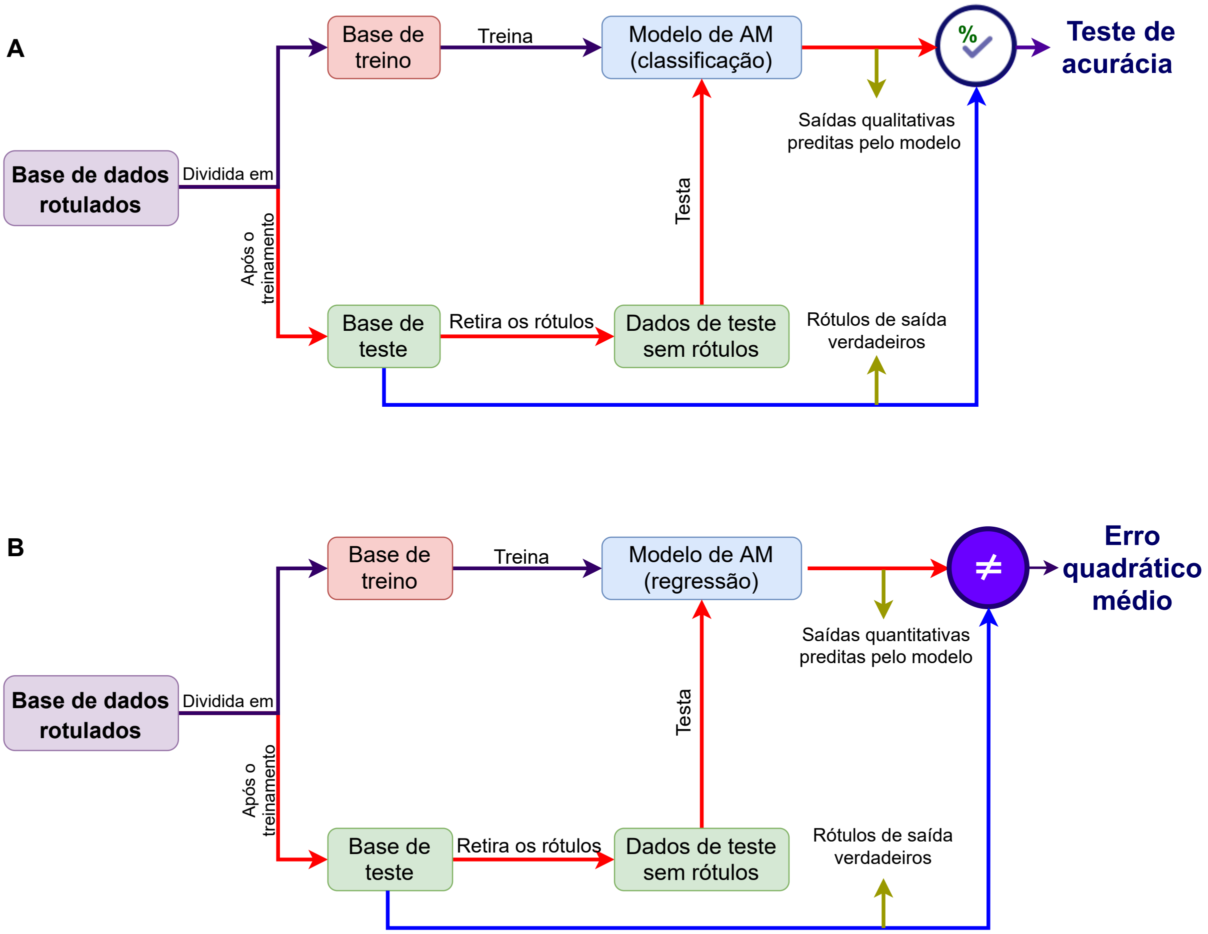
[1] Variáveis nominais ou ordinais. Ex.: sexo, estado civil e grau de escolaridade.

[2] Variáveis discretas ou contínuas. Ex.: idade, altura e peso.

Figura 1.6 – Resumo de como é o processo de predição nos problemas de classificação (A) e de regressão (B). Nos modelos supervisionados após finalizado o treinamento, inicia-se o teste do modelo com dados não utilizados no treinamento. Os modelos são avaliados quanto a sua eficiência mediante os resultados de saída preditos em relação as saídas conhecidas da rotulação inicial da base de dados. Nos problemas de classificacção (A) a eficiência do modelo é analisada pela acurácia e nos problemas de regressão (B) pelo erro quadrático médio.



Fonte: Adaptado de Rashidi *et al.* (2019).

base de teste é avaliada a partir de comparações entre as saídas preditas pelo modelo de AM e as saídas reais da base de teste, já conhecidas antes da retirada dos rótulos (ALPAYDIN, 2016).

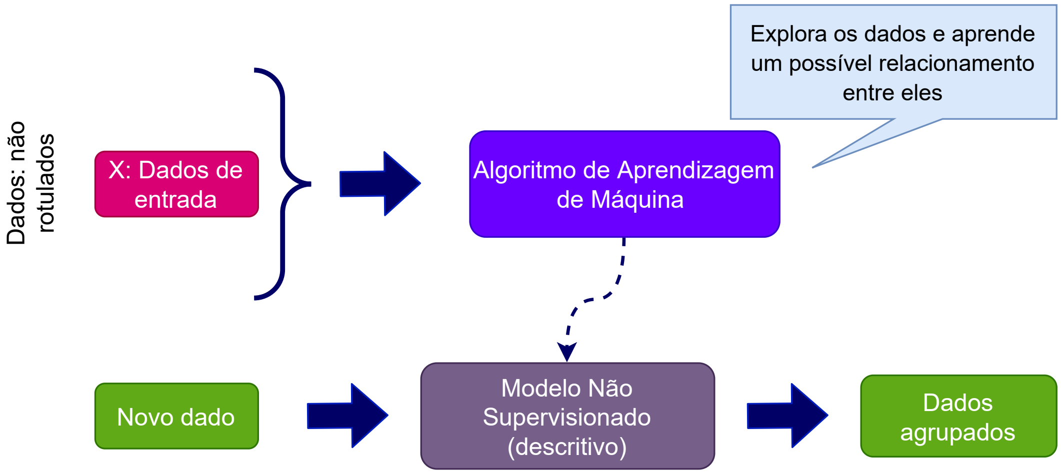
Nos problemas de classificação, as métricas de estimativas de desempenho mais utilizadas são a acurácia e a matriz de confusão. A acurácia representa o percentual de acerto de um modelo de classificação utilizado (MÜLLER; GUIDO, 2016; ALPAYDIN, 2016). Enquanto a matriz de confusão exibe, para cada saída, o número de classificações corretas em relação ao número de classificações preditas (MÜLLER; GUIDO, 2016; XU *et al.*, 2020). A matriz de confusão pode ser usada para calcular outras métricas como o número de falsos negativos ou positivos (respectivamente, erros do tipo II e I comumente vistos na estatística) e o número de verdadeiros positivos ou negativos (MÜLLER; GUIDO, 2016).

A Figura 1.6B, apresenta o fluxograma resumindo um problema de regressão. Ele tem as mesmas etapas do fluxograma dos problemas de classificação (Figura 1.6A), o que os diferenciam são as saídas dos problemas de regressão que são variáveis quantitativas. E as métricas de estimativas de desempenho que também mudam. As métricas de estimativas de desempenho mais utilizadas nos problemas de regressão são a raiz do erro quadrático médio (RMSE) e o coeficiente de determinação (R^2). Quanto menor o valor do RMSE, melhor é o modelo de regressão que está sendo analisado, já para o R^2, quanto mais próximo de 1, melhor (MÜLLER; GUIDO, 2016). Nos problemas de regressão, verifica-se a distância ou o erro entre a saída do modelo de AM e a saída desejada (as rotulações já conhecidas inicialmente na base de teste). Espera-se que a saída do modelo seja um valor numérico o mais próximo possível do valor desejado. A diferença entre esses dois valores fornece uma medida de erro que se estima para o algoritmo em análise.

Diferentemente dos modelos preditivos, os modelos descritivos objetivam encontrar alguma relação, regra ou padrão em um conjunto de dados, realizando associações, ou agrupamentos (conhecido como *clusters*) (PRAKASH *et al.*, 2018; GOECKS *et al.*, 2020; SARKER, 2021). O número de grupos (ou *clusters*) é previamente definido pelo programador (GOECKS *et al.*, 2020). O próprio modelo realiza a relação entre os vários dados de entrada para determinar a saída (KHERA; KUMAR, 2020). Esses modelos são conhecidos como AM não supervisionada (Figura 1.7), pois apresentam intervenção humana mínima, já que seus dados de entrada e saída não são rotulados, em outras palavras, não se ensina o modelo qual é o objetivo final (THEOBALD, 2017). Nesse tipo de AM são usadas diversas técnicas de agrupamentos e associações (PRAKASH *et al.*, 2018), sendo as técnicas de agrupamento as mais utilizadas na área de saúde (TULLOCH *et al.*, 2020).

Para se implementar um projeto que envolva AM deve-se seguir alguns passos iniciais

Figura 1.7 – Esquema de como é realizada a AM não supervisionada. São empregados dados, não rotulados, em um modelo de AM não supervisionada para que o modelo realize alguma associação ou agrupamento (*clusters*) dos dados.



Fonte: Adaptado de Sarker (2021).

antes de aplicar algum tipo de AM supervisionada ou não supervisionada. Primeiramente deve-se avaliar o problema que se deseja resolver para em seguida coletar e preparar os dados de forma adequada para serem implementados em algum tipo de AM e seus respectivos modelos. Também deve-se verificar a eficiência dos modelos de AM utilizados a fim de se chegar a um modelo satisfatório. Se necessário, durante a verificação da eficiência, pode-se voltar às etapas de coletas, preparação de dados ou de construção do modelo até chegar ao modelo final desejado. Um resumo dessas etapas pode ser visto na Tabela 1.2.

Há evidências na literatura que o desenvolvimento de métodos automáticos para discriminar os diferentes padrões de marcha, patológica ou não, poderão ser utilizados em diversas aplicações clínicas (MANNINI *et al.*, 2016; CARAMIA *et al.*, 2018; PRAKASH *et al.*, 2018; MUNDT *et al.*, 2020; SUNARYA *et al.*, 2020; TULLOCH *et al.*, 2020). Avaliação de doenças neurológicas, prevenção de quedas e diagnóstico de distúrbios ortopédicos são alguns exemplos em evidência (SUNARYA *et al.*, 2020). Métodos de AM têm sido utilizados para classificar várias patologias mediante identificação de marchas patológicas em relação à marcha de indivíduos saudáveis (HU *et al.*, 2018; SLIJEPCEVIC *et al.*, 2017).

Tabela 1.2 – Principais etapas para seguir em um projeto de AM.

Etapas
1) Entender o problema – qual o problema que pretendo resolver?
2) Quais informações vou precisar para resolver meu problema? Coletar e preparar os dados
3) Selecionar o(s) modelo(s) de AM.
4) Treinar o(s) modelo(s) de AM.
5) Avaliar a eficiência do(s) modelo(s) – o modelo resolve o problema?
6) Se necessário, ajuste o(s) modelo(s) e reavalie-o(s).
7) Apresente sua solução.
8) Monitore e mantenha seu sistema.

Fonte: Adaptado de Géron (2019).

2 Justificativa

Como já mencionado anteriormente, a análise da marcha visa quantificar os fatores que regem a funcionalidade dos membros inferiores, sendo crucial para detectar anormalidades, reconhecer instabilidades posturais, avaliar intervenções clínicas e programas de reabilitação (GUPTA *et al.*, 2020; KHERA; KUMAR, 2020). Antecipar diagnósticos e realizar correlações é fundamental na prevenção de eventuais complicações futuras, o que hoje é possível com o advento da AM. Técnicas de AM vêm sendo amplamente empregadas em vários campos, como: diagnóstico médico, reconhecimento de padrões, análise de predição e classificação, monitoramento e processamento de imagens e na redução do erro humano (PHINYOMARK *et al.*, 2018; KHERA; KUMAR, 2020; TULLOCH *et al.*, 2020). Portanto, tornando-as adequadas para serem utilizadas no estudo da marcha.

Ao que diz respeito à marcha, já se utiliza AM para diagnóstico precoce de distúrbios da marcha, riscos de quedas, seja por envelhecimento ou deficiência, planejamento de reabilitações e intervenções terapêuticas (KHERA; KUMAR, 2020). Diagnósticos precoces podem prevenir perda de mobilidade e complicações futuras, bem como reduzir custos de saúde, uma preocupação crescente nos países em desenvolvimento (GOECKS *et al.*, 2020; TULLOCH *et al.*, 2020). Acerca disso, Mundt *et al.* (2020) e Sunarya *et al.* (2020) discorreram sobre o uso de sensores vestíveis captando informações do indivíduo diariamente, e a importância de se analisar esse grande volume de informações com aplicações de AM. Ambos defendem que essa captação irrestrita de informações possibilita a detecção antecipada de alguma anormalidade na marcha que pode ser precocemente corrigida, evitando complicações futuras. O reconhecimento automatizado de padrões por meio da AM vem se tornando uma ferramenta essencial devido à enorme quantidade de dados biomédicos coletados, para os quais a análise manual torna-se inviável (GOECKS *et al.*, 2020).

Os modelos de AM também têm a capacidade de aprendizagem contínua, melhorando cada vez mais sua resposta em função do problema imposto (GOECKS *et al.*, 2020). Esses modelos diferenciam-se das ferramentas estatísticas convencionais, uma vez que a estatística convencional não apresenta poder preditivo para realizar suas análises de forma contínua (GOECKS *et al.*, 2020; KHERA; KUMAR, 2020) e lidar com grandes volumes de dados (PHINYOMARK *et al.*, 2018). Além de apresentar dificuldades em analisar dados não lineares. Logo, a capacidade de generalização da AM poderá ser um método a ser implantado em diversas ferramentas de análise de marcha, pois permitirá uma maior abrangência para que diferentes padrões de execução de marcha sejam analisados por essas ferramentas.

Na literatura, a grande maioria dos estudos utilizando AM na diabetes está relacionada com avaliação de equilíbrio, detecção dos níveis de glicose e a presença de retinopatia (JIANG *et al.*, 2017; RIGLA *et al.*, 2018; REN *et al.*, 2020), havendo pouco enfoque para a execução da marcha. Essa habilidade é apontada como um dos principais fatores para prevenção de quedas em pacientes diabéticos, sendo um aspecto importante o seu restabelecimento (ALLET *et al.*, 2008). Caracterizar as execuções da marcha ao longo da progressão da doença utilizando AM torna-se uma alternativa viável, uma vez que a capacidade preditiva da AM poderá direcionar o treinamento adequado antes que a doença avance para estágios mais graves, como na DPN. Um exemplo é o estudo de Botros *et al.* (2016) que, utilizando o modelo de máquinas de vetores de suporte (SVM) em dados da distribuição da pressão plantar dinâmica, em indivíduos diabéticos, conseguiram prever, com acurácia de 94,6%, a probabilidade de um paciente diabético vir a ter úlceras de pressão. Apesar de bons resultados e grande potencial clínico, uma das limitações é que o estudo avaliou apenas um modelo de AM, não comparando com outros modelos possíveis. Diferentemente de Corpin *et al.* (2019) que utilizaram diversos algoritmos de AM no intuito de criar um sistema que analisasse dados da pressão plantar a fim de detectar DPN. Os modelos SVM e perceptron multicamadas (MLP) tiveram os melhores desempenhos de classificação dos pacientes. No entanto, o estudo não detalhou o número amostral de cada grupo estudado, não utilizou técnicas de balanceamento entre os grupos e não relatou como lidaram com os dados perdidos (*missing data*) ao longo das coletas.

Logo, foi observado a falta de aplicações de modelos de AM, as quais integrem dados clínicos e de execução da marcha, que possam classificar indivíduos diabéticos de não diabéticos. E a partir disso possam fornecer uma análise direcionada sobre as complicações clínicas da diabetes que sejam capazes de serem evidenciadas na marcha. Aplicações que permitam avaliar e diagnosticar o padrão de marcha prevendo futuras complicações clínicas para que assim possam direcionar terapias específicas antes que essas complicações se instalem.

O modelo preditivo proposto permitirá que o mesmo seja aplicado no desenvolvimento de novas tecnologias, ou seja, aplicados no funcionamento de dispositivos inteligentes, os que serão importantes para identificação precoce de complicações da diabetes. Tecnologias que servirão de parâmetros para identificar os potenciais pacientes diabéticos que estão propensos a apresentar quadros mais graves da doença. Essas tecnologias poderão auxiliar na promoção, prevenção e reabilitação do paciente.

O prognóstico de futuras complicações e constante acompanhamento do paciente poderá traçar medidas efetivas que auxiliem o tratamento. Por conseguinte, poderá beneficiar o Sistema Único de Saúde (SUS) em termos de redução de custos no tratamento de diabetes (tratamentos de úlceras, amputações e internações). Assim, esse trabalho pode apresentar um impacto nacional e internacionalmente, em termos de ajudar os profissionais da saúde na prática clínica para que possam antecipar condutas antes que complicações da doença se instalem no paciente.

3 Objetivos

3.1 Objetivo Geral

Investigar modelos de AM sobre dados de avaliação da marcha de diabéticos, tipo 2, para analisar e identificar os padrões de execução de marcha a fim de prever complicações clínicas da diabetes.

3.2 Objetivos Específicos

- Verificar evidências na literatura sobre os métodos preditivos usados no padrão de marcha de diabéticos e quais variáveis objetivas da marcha são as mais empregadas na implementação desses métodos;
- Caracterizar e verificar se padrões de execução de marcha diferem entre diabéticos e não diabéticos;
- Verificar se modelos de AM conseguem classificar diabéticos de não diabéticos a partir de dados de execução da marcha e identificar características de execução da marcha que influenciam essa classificação;
- Verificar se modelos de AM conseguem classificar complicações da diabetes que possam ser evidenciadas na execução da marcha e identificar características de execução da marcha que influenciam essa classificação.

4 Materiais e Métodos

4.1 Apectos Éticos

O presente estudo foi realizado mediante banco de dados fornecidos pela parceria com o Prof. Dr. Edgar Ramos Vieira do Departamento de Fisioterapia da *Florida International University* (FIU). O estudo inicial do Prof. Dr. Vieira foi realizado dentro das normas do Comitê de Ética em Pesquisa da FIU (IRB-19–0037) (VIEIRA *et al.*, 2021). Logo, no atual estudo não houve intervenção ou contato com nenhum dos pacientes do estudo inicial.

4.2 Delineamento do estudo

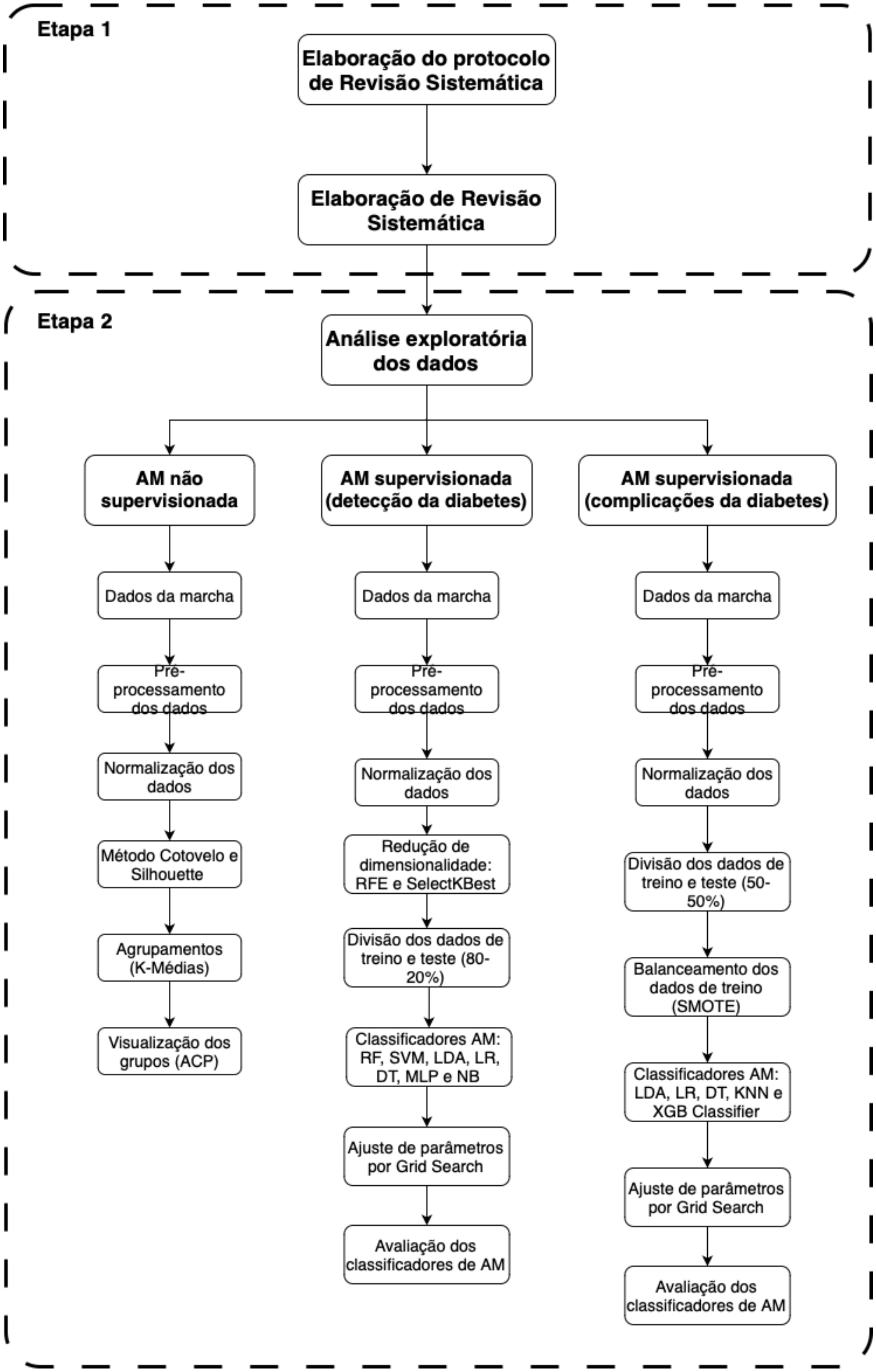
O projeto de pesquisa foi composto por duas etapas integradas (Figura 4.1): 1) Elaboração de protocolo e Revisão Sistemática da literatura; 2) Análise exploratória do banco de dados fornecidos pela FIU e aplicação dos modelos de AM.

4.3 Revisão Sistemática

Inicialmente foi conduzido um protocolo seguido de revisão sistemática da literatura conforme as recomendações do Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A revisão visou verificar sistematicamente na literatura quais métodos preditivos estão sendo aplicados para realizar a análise da marcha em pacientes com diabetes tipo 2. Além disso, verificou entre a ampla variedade de dados, captados pelas ferramentas de análise de marcha, quais características (variáveis) da marcha são mais usadas na implementação desses modelos preditivos. Foram incluídos na revisão estudos que descreveram o desenvolvimento e/ou validaram um modelo preditivo para avaliar a marcha de adultos (>18 anos) com diabetes tipo 2, em qualquer estágio da doença, sem amputações ou uso de dispositivos auxiliares durante a execução da marcha.

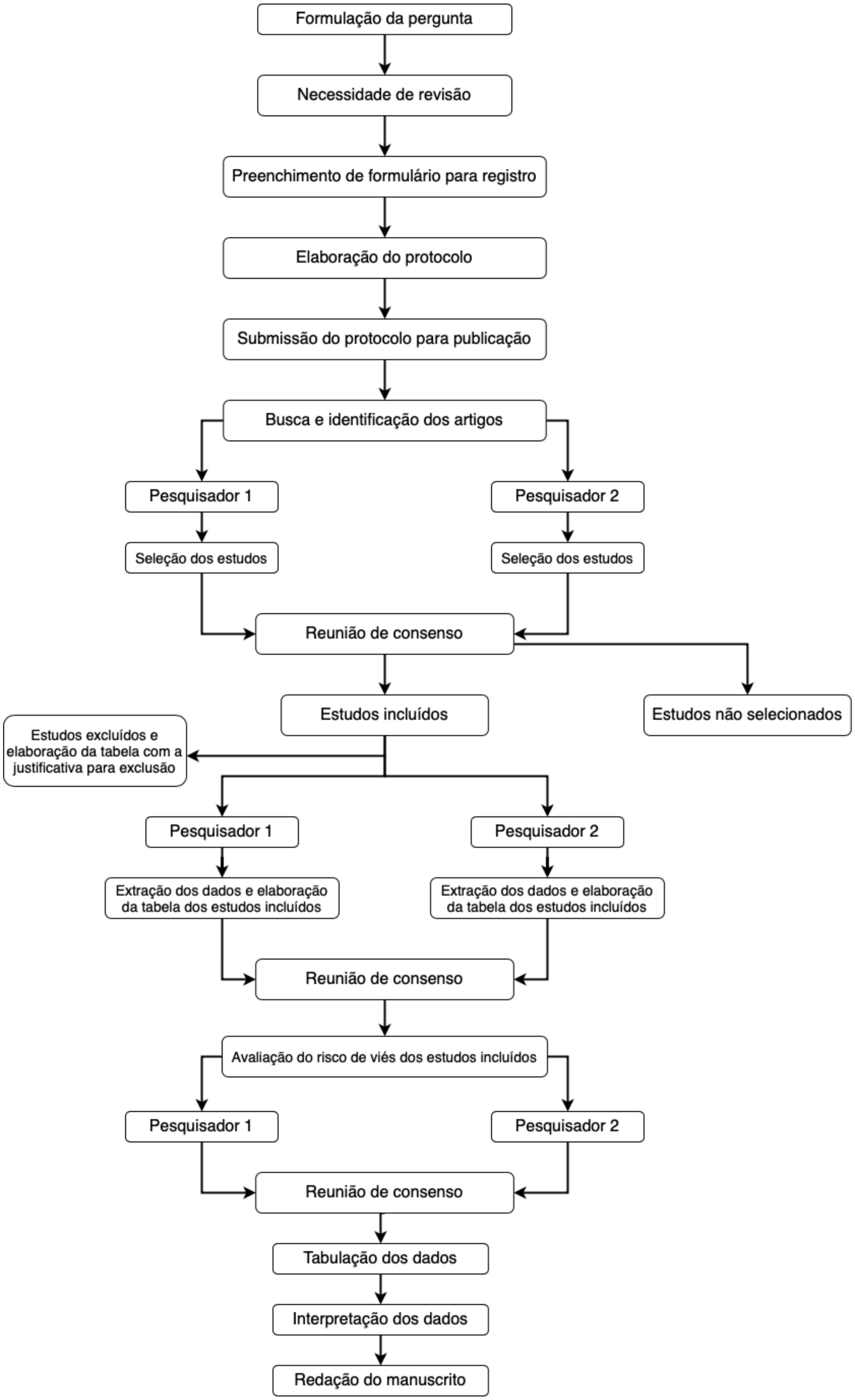
O protocolo encontra-se registrado no PROSPERO (CRD42020199495). A descrição detalhada da estrutura metodológica e de como foi conduzida o protocolo e a revisão sistemática encontra-se nas seções 5.1 e 5.2 desta tese e resumido na Figura 4.2.

Figura 4.1 – Fluxograma do delineamento do estudo.



Fonte: Elaborado pela autora.

Figura 4.2 – Processo de desenvolvimento da revisão sistemática.



Fonte: Elaborado pela autora.

4.4 Análise exploratória do banco de dados fornecidos pela FIU

Os dados quantitativos deste estudo foram fornecidos pela parceria científica estabelecida com o Prof. Dr. Edgar Ramos Vieira, do Departamento de Fisioterapia da FIU. Os dados são referentes ao projeto intitulado “Intervenções na dieta e no exercício de idosos hispânicos com diabetes” (VIEIRA *et al.*, 2021), coordenado pelo Prof. Dr. Vieira e executado em parceria com colaboradores. Um dos colaboradores do estudo foi a Prof. Dra. Fabrícia A. C. Cavalcanti durante período de pós doutorado como professora visitante júnior na FIU, entre setembro de 2019 e março de 2020, pelo Edital CAPES/PRINT n. 41/2017. Essa parceria também resultou no doutorado sanduíche da discente (Edital n. 02/2020 – CAPES/PRINT) entre setembro de 2021 e junho de 2022. Os dados coletados pela discente encontram-se no banco de dados do equipamento GAITRite do laboratório de desempenho humano do Departamento de Fisioterapia da FIU.

O presente estudo consistiu na coleta de dados de 38 idosos ($\geq$ 65 anos) não diabéticos e 38 idosos hispânicos ($\geq$ 65 anos) com diagnóstico clínico de diabetes tipo 2, sem quadro de demência ($>$ 3/5 pontos no teste Mini Cog – ANEXO A), residentes em Miami, Flórida. Os dados compreenderam valores quantitativos e qualitativos obtidos durante a avaliação dos idosos, como índices glicêmicos, tempo de diagnóstico da doença, dados antropométricos e execução da marcha. A seleção dos 38 idosos não diabéticos foi realizada mediante pareamento dos índices glicêmicos e dados antropométricos de acordo com os dados dos 38 idosos diabéticos (Tabela 4.1).

Tabela 4.1 – Características demográficas e clínicas (médias ± desvios padrão) dos participantes do estudo.

	T2DM	**Non-T2DM**
M/F (n)	9/29	9/29
Idade (anos)	78.5 (± 6.64)	74 (± 5.46)
IMC (kg/m^2)	30.52 (± 5.68)	28.23 (± 5.30)
HbA1c	6.93 (± 0.83)	-
Tempo de diagnóstico (anos)	17 (± 12.91)	-

M: masculino; F: feminimo; IMC: índice de massa corporal.

Os índices glicêmicos foram os valores referentes a porcentagem de hemoglobina glicada (HbA1c) e os níveis de glicose dos participantes (mg/dL) a partir de coleta de sangue venoso após oito horas de jejum noturno, tendo como valores de referência a Tabela 4.2. Os dados antropométricos consistiram nos valores obtidos de altura e peso (balança SECA com estadiômetro, Seca Corp, Columbia, MD), índice de massa corporal (IMC) (kg/altura em m^2).

Tabela 4.2 – Valores de referência recomendados para os índices glicêmicos de acordo com *American Diabetes Association.*

Índices glicêmicos	**Valores de referência**
Hemoglobina glicada (HbA1c)	Ideal = < 6,5 - 7,0%
Níveis de glicose ideal no jejum	80–130 mg/dL

Fonte: Adaptado de Association *et al.* (2018).

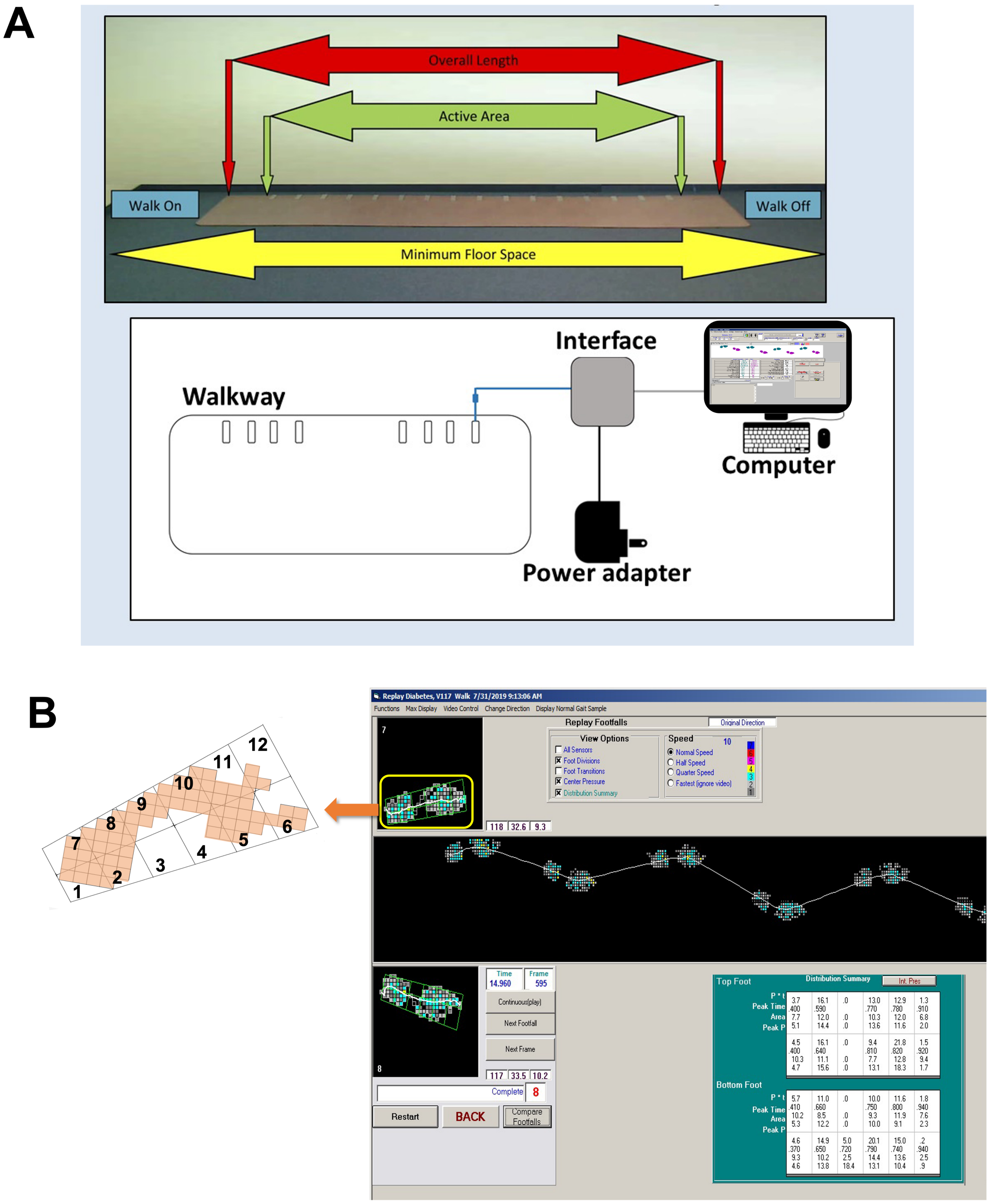
Os dados de execução da marcha foram adquiridos pelo sistema GAITRite (Q209, CIR Systems Inc.). O GAITRite consiste em um tapete (61 X 366 cm) com sensores de 1,27 cm centralizados e organizados em padrão de grade, os quais são acionados mediante pressão mecânica. Esses sensores captam a pressão plantar ao longo de cada passo e a partir disso traçam as informações espaço-temporais e de distribuição da pressão plantar da marcha (dados extraídos na Tabela 4.3) enviando os resultados para seu próprio *software* (MCDONOUGH *et al.*, 2001). Na avaliação da marcha com o GAITRite, os participantes precisaram andar livremente em sua velocidade preferida, sem nenhum tipo de dispositivo que pudesse interferir na execução da marcha e coleta dos dados. A Figura 4.3 exemplifica a coleta de dados feita pelo GAITRite.

Tabela 4.3 – Parâmetros espaço-temporais e de distribuição da pressão plantar de execução da marcha coletados pelo GAITRite.

Parâmetro espaço-temporal	
Velocidade	Velocidade de caminhada em cm/s calculada pela distância percorrida dividida pelo tempo caminhado.
Cadência	Número de passos por minuto.
Número de passos	Número de passos executados.
Comprimento do passo	Distância entre o centro do calcanhar de um pé e o centro do calcanhar do pé contralateral durante o apoio duplo da marcha.
Largura do passo	Distância entre o centro de um pé e o centro do pé contralateral durante o apoio duplo da marcha (é o distanciamento entre os pés durante a marcha).
Tempos de balanço e apoio	Tempo das fases de balanço (tempo que o pé está na fase de balanço, entre o toque final da saída do hálux no solo ao toque inicial do calcanhar ao solo) e das fases de apoio da marcha (tempo em que o pé está na fase de apoio, entre o toque inicial do calcanhar no solo até a saída do hálux).
Tempos de apoio simples e duplo	Simples: tempo em que um dos pés está sozinho no apoio. Duplo: tempo em que os dois pés estão no apoio.
Tempo do ciclo da marcha	Tempo de execução média do momento em que o calcanhar toca o tapete e volta a tocar novamente completando um ciclo de marcha.
Ângulo de progressão do pé	Rotações internas ou externas do pé ao longo da execução da marcha.
Distribuição da pressão plantar	
P*T	Pressão ao longo do tempo em porcentagem (%).
Peak Time	Tempo de pico de pressão em segundos.
Area	A soma da área dos sensores ativos da respectiva zona em cm^2
Peak	Pico de pressão em porcentagem (%).

Fonte: Adaptado de Prakash *et al.* (2018) e Leyh e Feipel (2022)

Figura 4.3 – Esquema de representação do tapete do GAITRite e sua interface com o computador (A). Janela do *software* do GAITRite da representação da distribuição da pressão plantar (B) em que a cada passo 12 zonas são criadas pelo sistema (6 zonas na região medial do pé e 6 na região lateral).



Fonte: Adaptado de GAITRite (2013).

Os dados brutos dos participantes diabéticos e não diabéticos foram salvos em formato .csv e importados para o *software* de código aberto Python^{TM} (versão 3.9.15). A etapa de preparação e pré-processamento dos dados corresponde a 80% do tempo gasto em aplicações bem-sucedidas em AM (WUJEK *et al.*, 2016). Esses dados foram então pré-processados e analisados de três maneiras distintas de acordo com cada aplicação de AM (seções 4.4.1, 4.4.2, 4.4.3).

As técnicas de pré-processamento utilizadas foram baseadas em Raschka (2015) e em Phinyomark *et al.* (2018). Essas incluem:

- Eliminar manualmente atributos que não contribuem para o resultado do problema em questão, como a identificação do paciente;
- Organizar e padronizar os dados quantitativos ou qualitativos que representam uma característica ajustando, por exemplo, dados categóricos em forma de algoritmos de AM;
- Remover e atribuir valores ausentes em uma categoria de conjunto de dado;
- Lidar com dados desbalanceados e *outliers*;
- Aplicar alguma técnica para selecionar adequadamente as variáveis a serem empregadas nos modelos de AM, por exemplo, uma técnica de redução de dimensionalidade;
- Selecionar recursos relevantes para a construção do modelo de AM.

4.4.1 AM não supervisionada na caracterização dos padrões de execução de marcha dos pacientes diabéticos

O estudo de caracterização dos padrões de marcha dos pacientes diabéticos foi realizado mediante análise exploratória, utilizando AM não supervisionada, dos dados de 76 participantes (38 diabéticos e 38 não diabéticos) fornecidos pela parceria estabelecida com a FIU.

As análises foram realizadas no Jupyter Notebook (versão 3.9.15) utilizando-se a linguagem de código aberto Python^{TM}. As bibliotecas empregadas foram Pandas (<https://pandas.pydata.org>), NumPy (<https://numpy.org>), Sci-kit learn (<https://scikit-learn.org/stable/index.html>), Matplotlib (<https://matplotlib.org>) e Plotly (<https://plotly.com>). Na etapa de pré-processamento foi utilizado *one-hot encoding* nas variáveis categoricas. Essa técnica favorece que as variáveis categoricas sejam representadas de forma binária (DAHOUDA; JOE, 2021). A correlação de Pearson foi utilizada para evitar viés na implementação da AM não supervisionada. Correlações entre variáveis acima de 0,8, eliminou-se uma das variáveis. As variáveis finais após aplicação da correlação de Pearson foram normalizadas utilizando o método *StandardScaler* (THARA *et al.*, 2019).

Após o pré-processamento dos dados, o Método Cotovelo (do inglês *Elbow Method*) foi utilizado para encontrar o número ideal de agrupamentos dos dados (LIU; DENG, 2020). Para reforçar os achados do Método Cotovelo, também foi realizada a análise de *Silhouette* (SHUTAYWI; KACHOUIE, 2021). Uma vez encontrado o número ideal de agrupamentos, a AM não supervisionada K-Médias foi implementada. K-Médias é um algoritmo de agrupamento interativo que particiona um conjunto de dados em grupos separados a partir de um número predeterminado de agrupamentos (k) (LIU; DENG, 2020). Depois de aplicar o K-Médias, para facilitar a visualização dos grupos, aplicamos a análise de componentes principais (ACP). A ACP facilita a visualização e a compreensão dos agrupamentos em um espaço de menor dimensão (JIANG *et al.*, 2022).

Uma vez realizada a análise exploratória com os dados de execução da marcha entre os participantes diabéticos e não diabéticos, repetimos as mesmas análises, acrescentando os dados clínicos, apenas com os participantes diabéticos. Mais detalhes sobre esse estudo encontram-se na seção 5.3 dessa tese.

4.4.2 AM supervisionada para análise e classificação de pacientes diabéticos de não diabéticos

Nesse estudo os dados dos 38 pacientes diabéticos e 38 não diabéticos foram analisados por meio do *software* Python^{TM} (versão 3.9.15). Os pacotes de biblioteca usados foram scikit learn para os algoritmos de AM supervisionados, NumPy e pandas para operações de dados e cálculos matemáticos, e matplotlib e seaborn (<https://seaborn.pydata.org>) para plotagem de gráficos. Foram utilizados os valores de cada passo de execução dos parâmetros espaço-temporais e de distribuição plantar da marcha citados na Tabela 4.3.

A etapa de pré-processamento consistiu em lidar com dados ausentes (valores nulos). Esses dados foram substituídos pela média da variável. Além disso, as variáveis com todos os valores iguais a zero foram removidas do conjunto de dados. Após o processo de limpeza inicial, os dados foram divididos aleatoriamente em 80-20% como conjuntos de treinamento e teste, respectivamente. Os recursos selecionados do conjunto de dados de treinamento foram usados como entradas para os algoritmos de classificação de AM, seguidos pela normalização de recursos usando o *StandardScaler*.

Nesse estudo, após esse pré-processamento inicial obtivemos 377 variáveis com dados antropométricos e execução de marcha de 77 participantes. Assim, foram implementadas duas técnicas de redução de dimensionalidade no conjunto de treinamento. A primeira foi realizada com base na eliminação de características recursivas (RFE). O RFE é um método *wrapper* que remove variáveis redundantes e menos relevantes de acordo com uma métrica de desempenho, buscando melhorar a previsão do recurso de destino (ARTUR, 2021). A técnica RFE com a Floresta Aleatória, do inglês *Random Forest* (RF), foi usada para selecionar o número ideal de variáveis. A segunda foi realizada com base na seleção univariada que considera cada variável individualmente; porém, não captura redundância entre as variáveis (GHIMATGAR *et al.*, 2018). O método SelectKBest seleciona um número fixo k de variáveis que, com base no teste f_classif, a seleção de variáveis usando ANOVA-F mede um limite e descarta o maior valor p (SIDHAWARA *et al.*, 2020). Em ambos os métodos, fixamos um número de variáveis baseados em um quarto, um terço, metade, dois terços e três quartos do número total de variáveis do conjunto de dados. Assim, aplicamos os modelos de AM nesses cinco subconjuntos e com base nas métricas avaliadas de análise de dados, selecionamos o número ideal de variáveis para cada tipo de modelo de AM.

Os algoritmos de AM de classificação selecionados para esse estudo foram determinados mediante uso do módulo *Lazy Predict*. Esse módulo compara o desempenho de modelos distintos e ajuda a entender qual deles funciona melhor sem nenhum ajuste de parâmetro (documentação: https://lazypredict.readthedocs.io/en/latest/index.html). Os algoritmos de AM selecionados após a aplicação do *Lazy Predict*: Random Forest (RF), Support Vector Machine (SVM), Linear Discriminant Analysis (LDA), Logistic Regression (LR), Decision Tree (DT), Multilayer Perceptron (MLP) e Naïve Bayes (NB).

Antes de aplicar cada um desses modelos de AM, realizamos o ajuste de parâmetro para cada algoritmo classificador usando *Grid Search*. Este método pode examinar o melhor parâmetro para cada algoritmo classificador (BUTTAN *et al.*, 2021). Após um método de validação cruzada de 10 vezes, obtivemos os parâmetros ideais de ajuste para cada algoritmo de AM. Assim, os modelos de AM foram empregados para diferenciar os pacientes diabéticos dos não diabéticos. Foi utilizada a Floresta Aleatória (RF) para identificar as variáveis mais importantes na classificação entre pacientes diabéticos e não diabéticos. Mais detalhes sobre esse estudo encontram-se na seção 5.4 dessa tese.

4.4.3 AM supervisionada para análise e classificação das complicações da diabetes que possam ser evidenciadas na marcha

Nesse estudo os 38 adultos ($\geq$ 65 anos) diabéticos e 10 adultos não diabéticos pareados pela idade foram considerados. Esses participantes foram classificados em três grupos conforme as diretrizes da *American Diabetes Association* (ADA) (ASSOCIATION *et al.*, 2018) para os níveis de hemoglobina glicada (HbA1C): grupo não diabético (HbA1C $<$ 5,7), grupo pré-diabetes (5,7 $\geq$ HbA1C $\leq$ 6,4) e Grupo diabetes (HbA1C $\geq$ 6,5). Foram utilizados a média de execução dos parâmetros espaço-temporais (velocidade, cadência, comprimento e largura do passo, tempos de apoio e balanço) e de distribuição plantar da marcha (descritos na Tabela 4.3).

O estudo foi conduzido no ambiente Jupyter Notebook (versão 3.9.15) utilizando a linguagem de programação Python. Usamos as seguintes bibliotecas: NumPy, pandas, sci-kit, seaborn e matplotlib. Foram removidas todas as variáveis que apresentaram grande quantidade de valores nulos que poderiam interferir na aplicação dos modelos AM, como o pico de pressão plantar. As variáveis com alguns dados ausentes foram tratadas pela imputação de sua respectiva média.

A técnica de redução de dimensionalidade implementada nesse estudo foi mediante a análise entre as variáveis pelo coeficiente de correlação de Spearman. Nas correlações acima de 0,8, uma das variáveis foi removida. Depois do pré-processamento, dividimos, aleatoriamente, 50-50% em conjuntos de treinamento e teste para garantir que a proporção das classes seja a mesma. Em seguida, realizamos a normalização usando o método de dimensionamento de recursos chamado *StandardScaler*.

Os algoritmos de AM supervisionada foram escolhidos após a aplicação do módulo *"Lazy Predict"*, conforme utilizado no estudo anterior (seção 4.4.2). Assim, os classificadores empregados foram: Linear Discriminant Analysis (LDA), Logistic Regression (LR), Decision Tree (DT), K-Nearest Neighbor (KNN) e Extreme Gradient Boost Classifier (XGB Classifier).

O conjunto final de dados foi composto por 48 indivíduos divididos em três grupos diferentes de HbA1C, a distribuição de instâncias nas três classes não foi igual. Logo, o conjunto de treinamento ficou ligeiramente desbalanceado. Assim, com o intuito de balancear os dados, empregamos o *Synthetic Minority Oversampling Technique* (SMOTE). Esse método pode equilibrar o conjunto de treinamento selecionando aleatoriamente as k amostras vizinhas mais próximas às categorias com menores valores para que apresentem o mesmo número das categorias com maiores valores (CHANG *et al.*, 2022).

Ao final, conforme etapa já mencionada no item 4.4.2, antes de implementar os modelos de AM, buscamos os melhores valores de hiperparâmetros para cada classificador usando o método *Grid Search*. A *Grid Search* foi realizada com validação cruzada de 10 vezes para encontrar os hiperparâmetros apropriados. Também foi empregado RF para analisar quais as dez principais variáveis utilizadas foram decisivas na classificação dos três grupos. Mais detalhes sobre esse estudo encontram-se na seção 5.5 dessa tese.

4.5 Análise dos dados

4.5.1 Avaliação dos modelos de AM não supervisionada

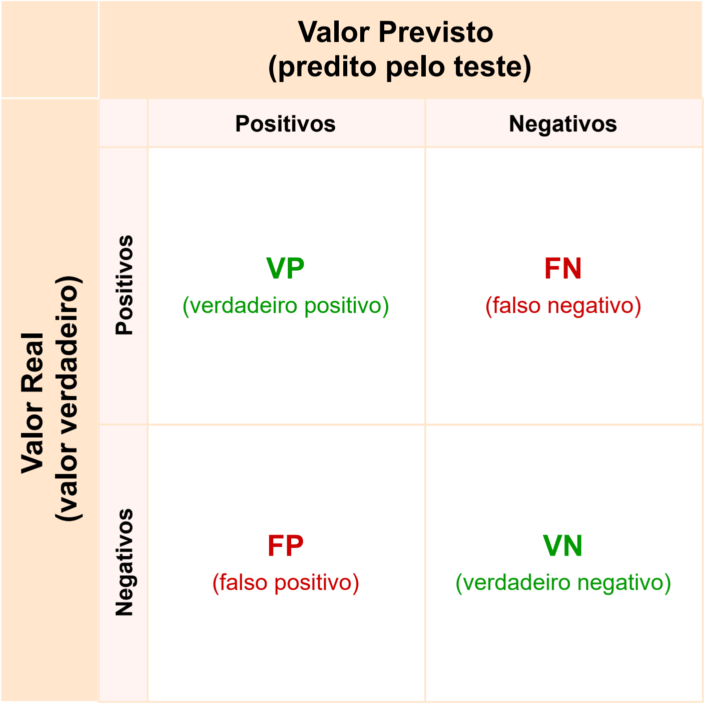
Para avaliar a qualidade do algoritmo de agrupamento K-Médias utilizamos o escore da análise de *Silhouette*. Após a identificação dos grupos, suas diferenças estatísticas foram analisadas por meio do *software* JASP (0.16.2; University of Amsterdam). As variáveis contínuas foram expressas com média e desvio padrão e as variáveis categóricas como porcentagem (%). Após o teste de Shapiro-Wilk, as diferenças entre os grupos foram analisadas por meio do teste t ou Mann-Whitney. O nível de significância estabelecido foi $p < 0,05$ para todas as análises estatísticas.

4.5.2 Avaliação dos modelos de AM supervisionada

Após implementação dos modelos de AM supervisionada, o desempenho de cada um dos modelos foi avaliado com o intuito de observar qual modelo se adaptou melhor ao estudo. Essas análises serviram para distinguir qual modelo de AM utilizado apresentou melhor eficiência e capacidade de generalização na classificação.

A avaliação de cada modelo foi realizada por meio da análise de diversas métricas. As métricas usadas nos modelos de classificação de AM supervisionada foram: acurácia, precisão, *recall*, F1 *score* e a área sobre a curva característica de operação do receptor (AUC), as quais se baseiam na matriz de confusão (Figura 4.4).

Figura 4.4 – Modelo da matriz de confusão em que as linhas representam a classe real e as colunas a classe prevista.



		Valor Previsto (predito pelo teste)	
		Positivos	**Negativos**
Valor Real (valor verdadeiro)	**Positivos**	**VP** (verdadeiro positivo)	**FN** (falso negativo)
	Negativos	**FP** (falso positivo)	**VN** (verdadeiro negativo)

Fonte: Adaptado de Dangeti (2017).

Baseada na matriz de confusão, a acurácia diz respeito ao número de previsões corretas (verdadeiros positivos e verdadeiros negativos) dividido pelo número total de previsões positivas e negativas (4.1). Ela quantifica de forma geral o desempenho de um modelo de AM (RASCHKA, 2015).

$$Acurácia = \frac{VP + VN}{VP + VN + FP + FN} \tag{4.1}$$

A precisão é o número de previsões corretas (VP) dividido pelo número total de previsões dessa classe (4.2). É a frequência das previsões positivas (DANGETI, 2017; GÉRON, 2019).

$$Precisão = \frac{VP}{VP + FP} \tag{4.2}$$

O *recall* ou revocação é uma métrica usada junto com a precisão, ele representa a divisão do número de previsões corretas (VP) pelo número total real (4.3). É a proporção de frequências positivas que são detectadas corretamente pelo classificador (GÉRON, 2019).

$$Recall = \frac{VP}{VP + FN} \tag{4.3}$$

O F1 *score* é uma métrica estatística que faz a combinação entre o *recall* e a precisão em uma única métrica (4.4). O resultado do F1 *score* é a média harmônica do *recall* e da precisão (GÉRON, 2019). Ele indica a qualidade geral do modelo, quanto mais próximo de 1, melhor o modelo (MÜLLER; GUIDO, 2016).

$$F1score = \frac{2 \times precisão \times recall}{precisão + recall} \tag{4.4}$$

A curva de Característica de Operação do Receptor, conhecida como curva ROC também poderá ser realizada. A curva ROC é outra ferramenta comumente usada em problemas de classificação. Ela representa a sensibilidade (o *recall*) sendo a taxa de verdadeiros positivos (4.5) e a especificidade que é a taxa de verdadeiros negativos (4.6) (GÉRON, 2019).

$$Sensibilidade = \frac{VP}{VP + FN} \tag{4.5}$$

$$Especificidade = \frac{VN}{VN + FP} \tag{4.6}$$

A curva ROC é uma medida usada para avaliar e estimar o poder preditivo dos modelos de AM fazendo a relação entre taxa de sensibilidade versus a taxa de especificidade (GÉRON, 2019). A AUC é a área sobre a curva ROC, considera-se que quanto mais próximo de 1, melhor o classificador (GÉRON, 2019).

Mediante o uso dessas métricas, os resultados de desempenho dos modelos de AM foram avaliados. O modelo final escolhido de cada estudo de classificação foi o que apresentou os melhores desempenhos e capacidade de generalização em torno do problema em questão.

5 Resultados e Discussão

A sessão de resultados será apresentada por meio de 05 artigos científicos elaborados a partir do embasamento teórico e da análise do banco de dados avaliado nesta pesquisa.

Artigo 01: ***Existing predictive methods applied to gait analysis of patients with diabetes: study protocol for a systematic review***

Este artigo foi elaborado seguindo as recomendações de protocolos de revisão sistemática *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA-P), sob o registro no PROSPERO de número CRD4202019949.

O protocolo de revisão sistemática está publicado na revista *"BMJ Open"* (doi: http://dx.doi.org/10.1136/bmjopen-2021-051981) que atualmente possui Qualis A2 segundo a nova classificação da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), com fator de impacto 3,007.

O objetivo desse estudo foi elaborar as etapas de uma revisão sistemática da literatura com o intuito de observar as evidências na literatura acerca dos métodos preditivos existentes usados nos padrões de marcha de pacientes com diabetes. Além disso, identificar quais variáveis da marcha são comumente utilizadas na implementação desses métodos preditivos.

Artigo 02: ***A systematic review of existing predictive methods applied to gait analysis of patients with diabetes***

Este artigo foi elaborado seguindo as recomendações de revisão sistemática *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA), baseado no protocolo já publicado (seção 5.1) e citado anteriormente.

A revisão encontra-se em apreciação na revista *"Diabetes and Metabolic Syndrome: Clinical Research and Reviews"* que atualmente possui Qualis A1 segundo a nova classificação da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), com fator de impacto estimado de 8,376.

Os objetivos desta revisão foi analisar as evidências na literatura relacionadas aos métodos preditivos que estão sendo implementados utilizando dados de execução de marcha de pacientes com diabetes tipo 2. Também, visou analisar quais as variáveis da marcha são as mais utilizadas para implementar os métodos preditivos. Até onde sabemos, nenhuma pesquisa resumiu sistematicamente os algoritmos preditivos usados para avaliar a marcha em pacientes com diabetes tipo 2. Diante disso, os achados desta revisão sistemática mostrou que pouquíssimos estudos utilizaram AM na avaliação da marcha de pacientes diabéticos. Assim, nos incentivando a realizar diversas análises implementando modelos de AM em busca de *insights* que possam ser evidenciados na execução da marcha dessa população.

Artigo 03: ***Clusters of patients with diabetes type 2: an exploratory unsupervised machine learning approach based on gait parameters***

Após a apreciação da banca examinadora, este artigo será submetido para a revista *"International Journal of Medical Informatics"* que atualmente possui Qualis A2 segundo a nova classificação da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), com fator de impacto 4,73.

Este estudo teve como objetivo caracterizar os padrões de execução de marcha de diabéticos por meio de análise exploratória utilizando AM não supervisionada. Também objetivou-se entender quais características do desempenho da marcha pode ser um bom preditor para identificar e distinguir indivíduos com diabetes. Nos resultados foi observado diferenças estatísticas ($p < 0{,}05$) nos padrões de velocidade, comprimento do passo e na distribuição de pressão plantar entre diabéticos e não diabéticos. Além disso, diferenças estatísticas ($p < 0{,}05$) também foram observadas nos padrões de distribuição de pressão plantar e nos valores glicêmicos entre os diabéticos.

Artigo 04: ***Machine learning-based on type 2 diabetes detection using spatiotemporal and pressure distribution gait parameters***

Após a apreciação da banca examinadora, este artigo será submetido para a revista *"Gait and Posture"* que atualmente possui Qualis A2 segundo a nova classificação da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), com fator de impacto 2,746.

O objetivo principal deste artigo foi utilizar modelos de AM para classificar diabéticos de não diabéticos mediante dados antropométricos e de execução da marcha. Além disso, identificar quais variáveis da marcha são as mais relevantes para realizar essa classificação. Os resultados mostraram que os dois melhores modelos de AM foram a regressão logística (LR) e a árvore de decisão (DT). Observou-se também que diabéticos apresentaram maior pico de pressão plantar na região do calcanhar; sendo uma variável importante a ser analisada nessa população a fim de que seja evitado complicações futuras da doença.

Artigo 05: *Machine learning models for identifying diabetes complications based on gait parameters*

O artigo encontra-se em fase de revisão pelos autores e após as considerações da banca examinadora, será submetido para a revista *“Journal of Diabetes Science and Technology”* que atualmente possui Qualis A2 segundo a nova classificação da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), com fator de impacto estimado de 3,12.

Este estudo visou utilizar AM para classificar as complicações da diabetes (pelos níveis de HbA1c), baseando-se em dados antropométricos e de execução da marcha dos participantes. O intuito foi observar também quais variáveis da marcha são evidenciadas nessas complicações. O classificador XGB Classifier superou os demais modelos de AM utilizados. Observou-se também que as três variáveis da marcha mais relevantes para prever complicações na diabetes são as alterações na base de suporte, na média de distribuição da pressão plantar pelo tempo nas regiões distais dos metatarsos I-III e na média da área ativa de pressão plantar na região das falanges III-IV.

5.1 Artigo 01: Existing predictive methods applied to gait analysis of patients with diabetes: study protocol for a systematic review

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ABSTRACT

Introduction Type 2 diabetes can lead to gait abnormalities, including a longer stance phase, shorter steps and improper foot pressure distribution. Quantitative data from objective methods for evaluating gait patterns are accurate and cost-effective. In addition, it can also help predictive methods to forecast complications and develop early strategies to guide treatments. To date, no research has systematically summarised the predictive methods used to assess type 2 diabetic gait. Therefore, this protocol aims to identify which predictive methods have been employed to assess the diabetic gait. **Methods and analysis** This protocol will follow the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) statement. Electronic searches of articles from inception to January 2022 will be performed, from May 2021 to 31 January 2022, in the Web of Science, MEDLINE, Embase, IEEE Xplore Digital Library, Scopus, CINAHL, Google Scholar, APA PsycInfo, the Cochrane Library and in references of key articles and grey literature without language restrictions. We will include studies that examined the development and/or validation of predictive methods to assess type 2 diabetic gait in adults aged >18 years without amputations, use of assistive devices, ulcers or neuropathic pain. Two independent reviewers will screen the included studies and extract the data using a customised charting form. A third reviewer will resolve any disagreements. A narrative synthesis will be performed for the included studies. Risk of bias and quality of evidence will be assessed using the Prediction Model Risk of Bias Assessment Tool and the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis. **Ethics and dissemination** Ethical approval is not required because only available secondary published data will be analysed. The findings will be disseminated through peer-reviewed journals and/or presentations at relevant conferences and other media platforms. **PROSPERO registration number** CDR42020199495.

Strengths and limitations of this study

- This study will be the first systematic review to comprehensively analyse the existing predictive methods for gait analysis in patients with type 2 diabetes.
- This systematic review will focus on the predictive method's performance (surrogate outcomes) rather than on patient-reported outcome measures.
- Abroad search strategy and robust quality assessment criteria (Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis) will be used to appraise and examine the existing literature.
- Two independent reviewers will be responsible for conducting the study selection, data extraction and quality assessment.
- A limitation could be the potential lack of studies that meet the established inclusion criteria.

INTRODUCTION

Diabetes mellitus is a worldwide health concern, with a prevalence of 8.8% in 2017.[1] With type 2 diabetes mellitus being the most common,[2] this condition is related to a dysfunction either in the pancreatic β-cells' ability to secrete insulin, insulin resistance in target organs or a combination of both, resulting in hyperglycaemia.[1,3] Patients can also present with blood vessel degeneration [4,5] that can evolve into neuropathy and damage sensory and motor nerve fibres.[4,5] Diabetes also alters physical function and mobility.[6] Both can lead to motor abnormalities such as longer stance time (ie, greater support base) and shorter steps, which may exhibit as slower gait speeds and increased cadence.[7,8] In addition, changes in the sensibility of the plantar surface of the foot can worsen plantar pressure distribution, balance and gait.[5,7]

Boosting insight into diabetic gait pattern alterations can be important for preventing complications caused by diabetes and developing strategies to guide treatments. [6,9] In clinical practice, while there is a high prevalence of observational methods,[10,11] this may be unreliable in assessing and diagnosing gait patterns. Observational methods are subjective and can generate inaccuracies during the assessment and diagnosis of the patient's movements due to different interpretations between examiners. In addition, these differences can impair decision-making to address a specific treatment.[12-14] On the contrary, objective methods are reliable, accurate, quicker and cost-effective owing to quantitative metric results. [8]

Objective gait analysis methods require data collected from patients wearing sensors or performing gait in specific devices, such as inertial measurement units (IMUs), electromyography (EMG), optoelectronic systems or force platforms.[10] Data from quantitative gait measures can be analysed using various methods. One of these is the use of predictive analytics that combine the collected data and estimate probabilities that can assist clinicians and potentially influence their decision to manage treatments to restore gait.[15–18] Predictive methods are mathematical equations (from statistics or machine learning (ML) approaches) that can combine information from a set of data, resulting in a response forecasting the probability of a particular outcome.[19–20]

Emerging predictive methods include ML algorithms. ML can be used for automatic gait recognition to predict possible complications such as the risk of falls and pressure ulcers. [21] Newer methods have opened new perspectives for the early diagnosis of gait disorders. This is essential in preventing potential future complications and to draw on personalised gait training[15] by quantifying the treatment progress and follow-ups. [22]

To our knowledge, no research has systematically summarised predictive algorithms used to assess gait in patients with type 2 diabetes. Based on this, we raise an important question about the existence of predictive methods used to evaluate the gait of patients with type 2 diabetes. Therefore, the purpose of this study is to conduct a systematic review of the literature to summarise the evidence regarding existing predictive methods used in the gait patterns of patients with diabetes.In addition,we intend to describe the characteristics of the studies identified among the variety of gait data collected regarding which input features are the most commonly used to implement a predictive method.

METHODS AND ANALYSES

Study design

This systematic review protocol was prepared using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P). [23]

Study registration

This protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO). Available from:<https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020199495>.

Eligibility criteria

Types of study

Articles will be eligible for review when they describe the development and/or validation of a predictive method to assess gait in human type 2 diabetes. Furthermore, all published and unpublished studies (eg, dissertations and theses), conference proceedings that deal with diabetic gait analysis, independent of the parameters measured, will be included if developed and/or validated as a predictive method. There will be no geographical or language restrictions. Wherever necessary, relevant articles will be arranged for translation.

Participants

We will include clinical data from adult participants (>18 years old) who had type 2 diabetes diagnosed at any disease stage without lower limb amputations or the use of gait assistive devices. In addition, data with participants with ulcers or neuropathic pain (that could have interfered in the gait execution) will be excluded. There will be no restrictions on gender or race.

Outcome measures

The primary outcome will comprise all predictive methods (eg, ML models) applied to analyse gait in patients with type 2 diabetes. The secondary outcome will include gait data input features (eg, spatiotemporal, angular gait parameters, EMG data, force data and plantar pressure data) most commonly used to implement a predictive model.

Search strategy for the identification of relevant studies

The search strategy will be guided by the PRISMA extension for searching (PRISMA-S).[24] The following electronic databases will be searched: Web of Science (Clarivate Analytics), MEDLINE (PubMed), Embase (Elsevier), IEEE Xplore Digital Library (IEEE), Scopus (Elsevier), CINAHL (EBSCOhost), Google Scholar (Google), APA PsycInfo (APA PsycNet) and the Cochrane Library (Wiley) from May 2021 to 31 January 2022. The time range of the published studies was from inception to January 2022. We will manually search the reference list of the studies included in the review. Grey literature involving published and unpublished studies (eg, dissertations and theses) and conference proceedings will also be searched without language restrictions, but this must be limited to human participants.

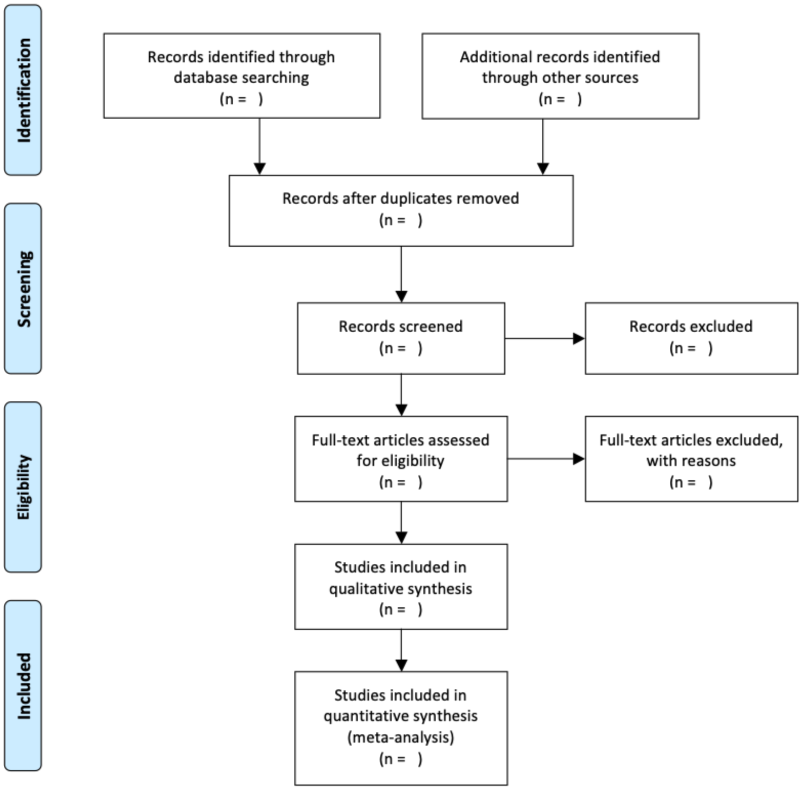
The articles will be searched using a combination of free keywords and the terminology registered in the Medical Subject Headings of the US National Library of Medicine. The terms that will be used are related to diabetes (eg, 'Type 2 Diabetes', 'Diabetes, Type 2', 'Diabetes Mellitus, Type 2'), gait (eg, 'Gait', 'Gait Analysis', 'Kinematic', 'Kinetic', 'Range of Motion') and prediction (eg, 'Artificial Intelligence', 'Machine Learning', 'Statistical- learning', 'Predictive Value of Tests', 'Support Vector Machine', 'Neural Networks, Computer'). The search strategy was pilot tested and finalised in MEDLINE (PubMed) before being translated for use in other databases. Details of the search strategies are provided in online supplemental appendix 1.

Screening of the studies

Based on the previously described inclusion criteria, two independent reviewers (PMMdS, ABOB) will screen titles and abstracts identified during electronic and manual searches to determine its eligibility. Study record information, including title and abstract from the searched online database, will be imported into the Rayyan systematic review software.[25] This platform will guide the reviewers in conducting the literature review process through its ability to explore and filter searched studies. Duplicate studies will be removed. If the title or abstract does not provide enough information for inclusion, the full text will be obtained for a full review. The same two reviewers (PMMdS, ABOB) will independently screen the full-text articles to identify studies for inclusion and record the reasons for exclusion for ineligible studies. Any disagreements that arise will be resolved initially by a discussion between the two reviewers, or, if necessary, with assistance from a third reviewer (FAdCC).

All reasons for the exclusion of ineligible studies will be recorded. The results of the screening process will be provided in detail using the PRISMA information flow chart (figure 5.1).

Figura 5.1 – Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram for the identification, screening and eligibility of included articles.



Data extraction

A data extraction form was developed through a discussion among all authors and adapted from the critical appraisal and data extraction for systematic reviews of prediction modelling studies (CHARMS) checklist. [26] The included studies will go forward to the data extraction and quality assessment stages of the review. Two independent reviewers (PMMdS, ABOB) will extract the outcome data from the included studies. If necessary, disagreements in data extraction will be discussed between the two reviewers and judged by a third reviewer (FAdCC).

The data collection form will aim to extract the key features of the review. Hence, we will divide the items within the data collection form into four blocks: (1) study information including publication year, author information, funding or sponsorship information, type of study, journal name and population, intervention, control and outcome (PICO elements); (2) database information including name, sample size, host organisation and sponsorship; (3) patient demographic information including gender, age, race and disease severity and (4) predictive methodological information including the type of gait assessment, comparisons with gold standard devices, type of predictive algorithm used (including its statistical or ML model name), format of input feature, optimisation algorithm, objective function, feature extraction methods, type of extraction feature and computational efficiency, and cost. Table 5.1 presents an example of the data extraction form. These data will be presented in the 'Characteristics of included studies' table.

Missing data may include missing outcomes, missing summary data or missing individual results. The authors will consider the reasons for the missing data. Where possible, we will contact the original investigators to obtain any missing data. However, in the case of contact difficulty, we will present the findings according to the statistical information available in each review, and this will be clearly stated in the final overview.

Quality of evidence

The quality of the predictive model used on the eligible studies will be assessed based on Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) checklist.[27] The TRIPOD Statement is a checklist of 22 items for the appropriate reporting of studies developing or validating multivariable prediction models.19 Each item will be scored as 0, 1 and 2, ranked as 'no report', 'inadequate report' and 'adequate report', respectively.

Risk of bias

The preselected articles will be evaluated and scored for methodological quality using the Prediction Model Risk of Bias Assessment Tool (PROBAST)[20] by two independent revi-

Tabela 5.1 – Example of the data extraction form for all included studies

Study information	
Study year	Year of the study publication
Author information	Last name of the author, whether clinical practitioners participated in the study
Type of study	Source of data (eg, cohort, case-control, randomised trial participants or registry data)
Journal name	Journal name
PICO elements	PICO elements in summary
Database information	
Database name	Name of the database used for modelling
Host organisation	Name of the hosting organisation of the database
Sponsorship	The funding or sponsorship information
Sample size	Sample size used for building the model
Source or data	From which source the database was used (eg, electronic health records, clinical registry, administrative data, cohort study, clinical trial)
Patient demographic information	
Gender	Sex of adults (male, female, alternative gender)
Age	Age and/or year of birth
Country	Country or countries in which study was based
Diabetes severity	Disease severity
Predictive methodological information	
Predictors	Timing of predictor measurement (eg, at patient presentation, at diagnosis, at treatment initiation)
Number of features	Number of features for building the model
Selected features	Did the study reported the importance of selected features?
Type of extracted feature	Which features the algorithm uses (eg, pressure, gait velocity, cadence, step width, pixel feature, action unit)
Tool used for gait assessment	Quantitative tool used to assess gait kinetic or kinematic (eg, IMU, force platform, optoelectronic, EMG)
Used highly rated standard devices	Quantitative tool used to assess gait kinetic or kinematic was a device considered as gold standard (eg, force platform, optoelectronic)
Predictive method used	Type of predictive method used to assess gait (eg, which machine learning techniques were used)
Model name	The name of the predictive model used. The underlying mathematical model used (eg, linear regression, support vector machine)
Missing data	Number of participants with missing data for each predictor and the process handled with missing data (eg, complete- case analysis, imputation or other methods)
Format of input feature (predictor or variables)	Which input gait data were used (eg, plantar pressure, frame, sequence or image)
Model performance/ validation	Performance metrics and scores of how accurate the model used is predicting (eg, accuracy, average errors, R-squared, confusion matrix)
Model evaluation	Method used for testing model performance: development dataset only (random split of data, resampling methods, eg, bootstrap or cross-validation) or separate external validation (eg, temporal, geographical, different setting, different investigators)
Computational efficiency and cost	Computational efficiency (speed, cloud space, etc) and cost related to the algorithm (eg, require GPU resources, large cluster)

EMG, electromyography; GPU, graphics processing unit; IMU, inertial measurement unit; PICO, population, intervention (exposure), control, outcome.

ewers (PMMdS, ABOB). In cases of opinion divergence, a third reviewer (FAdCC) will decide the score. The questionnaire consists of 20 items with four domains (participants, predictors, outcome and analysis). Based on the questionnaire ratings, the risk of bias for each domain will be ranked as 'low risk', 'high risk' or 'too unclear for judgement'. PROBAST will be used to categorise the included studies regarding their methodological quality, but these studies will not be excluded based solely on this evaluation.

Strategy for data synthesis

A narrative synthesis will be conducted with the information presented in the text and table to summarise and explain the characteristics and findings of the included studies. Data will be summarised using descriptive statistics and visual plots. Categorical data about the reporting, methodological conduct and risks of bias will be described using numbers and percentages. The distribution of continuous data, such as sample sizes and the number of features, will be described using measures of central tendency such as mean and SD for normally distributed data and median and percentiles (25th and 75th) for non-normally distributed data.

The risk of bias assessment will be summarised and graphically presented for each PROBAST domain and the overall risk of bias judgement. The results will be stratified by prevalent predictive techniques and study design (development with internal validation and/or external validation). The quality of evidence based on TRIPOD will also be summarised and graphically presented for each included study and its respective score rank.

Analyses of subgroups or subsets

We plan to conduct subgroup analyses using predictive model types (eg, regression models vs classification models, neural networks vs traditional ML models) and gait input parameters (eg, kinematic vs kinetic data features, IMUs vs EMG data features). In addition, we plan to classify participants according to their anthropometric subgroup (eg, age, body index mass, height, weight, gait measurements and diabetes vitals). More exploratory subgroup analyses will be decided during the data extraction and analysis process.

ETHICS AND DISSEMINATION

To the best of our knowledge, this systematic review is the first that will synthesise existing evidence regarding the types of predictive methods used to assess gait in patients with type 2 diabetes. Predictive methods are increasingly being appraised and recommended for formal risk assessment in treatment decision-making and clinical guidelines. The proposed systematic review may inform future research and clinicians. For instance, it may help researchers in designing customisable prediction tools to be used in diabetic care, and thus allow physiotherapists to better conduct rehabilitative gait treatments in the patients with type 2 diabetes.

Because we will be using secondary data sources, ethical approval is not required for this systematic review study. Our findings will be disseminated through peer-reviewed publications, presentations at conferences and clinical and patient networks.

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Competing interests None declared.

Patient consent for publication Not required. Ethics approval This study does not involve human participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. The study is a protocol for a systematic review. Thus, no data are available.

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Supplementary Appendix 1. The search terms across databases

Database	**Search terms**
MEDLINE (PubMed)	("Diabetes"[tiab]) OR ("Diabetes Mellitus/analysis"[Mesh] OR "Diabetes Mellitus/classification"[Mesh] OR "Diabetes Mellitus/rehabilitation"[Mesh] OR "Diabetes Mellitus/therapy"[Mesh] OR "Diabetes Mellitus, Type 2"[Mesh]) OR ("Diabetic"[tiab]) OR ("Diabetic Neuropathies/classification"[Mesh] OR "Diabetic Neuropathies/diagnosis"[Mesh] OR "Diabetic Neuropathies/diagnostic imaging"[Mesh] OR "Diabetic Neuropathies/physiopathology"[Mesh] OR "Diabetic Neuropathies/rehabilitation"[Mesh] OR "Diabetic Neuropathies/statistics AND numerical data"[Mesh] OR "Diabetes Complications"[Mesh]) OR "Type 2 Diabetes" [tw] OR "Diabetes, Type 2" [tw] AND ("Gait"[tiab]) OR ("Gait Analysis"[tiab]) OR ("Gait/classification"[Mesh] OR "Gait/instrumentation"[Mesh] OR "Gait/methods"[Mesh] OR "Gait/organization and administration"[Mesh] OR "Gait/physiology"[Mesh] OR "Gait/standards"[Mesh] OR "Gait/statistics and numerical data"[Mesh] OR "Gait/trends"[Mesh]) OR ("Gait Disorders, Neurologic"[Mesh]) OR ("Walking Speed"[Mesh] OR "Walking"[tiab]) OR ("Locomotion"[tiab]) OR "Locomotion"[tiab] OR "Gait Kinetic*"[tw] OR "Gait Kinematic*"[tw] OR "range of motion"[tw] AND "Artificial Intelligence"[Mesh] OR Machine Learning[MeSH] OR Deep learning[MeSH] OR "Neural Networks, Computer"[Mesh] OR data mining[MeSH] OR machine[tiab] AND (learn* OR model*) OR (statistical[tiab] OR "statistical-learning"[tiab]) AND (strateg*[tiab]) OR multilayer perceptron*[tiab] OR random forest*[tiab] OR bayes* network*[tiab] OR support vector machine*[tiab] OR nearest neighbor*[tiab] OR k nearest neighbor*[tiab] OR elastic net[tiab] OR naive bayes*[tiab] OR (classification[tiab] OR regression[tiab] OR estimation[tiab] OR decision[tiab]) AND tree[tiab] OR ridge[tiab] OR kernel[tiab] OR ensemble[tiab] OR bagging[tiab] OR bagged[tiab] OR boosting[tiab] OR boosted[tiab] OR fuzzy[tiab] OR ("Predictive Value of Tests"[Mesh] OR "Probability Learning"[Mesh] OR "Forecasting"[Mesh] OR "Computing Methodologies"[Mesh] OR "Cluster Analysis"[Mesh]) OR (Validat* OR Predict* OR Rule*) OR (Predict* AND Outcome* OR Risk* OR Model*) OR (History OR Variable* OR Criteria OR Scor* OR Characteristic* OR Finding* OR Factor*) AND (Predict* OR Model* OR Decision* OR Identif* OR Prognos*) OR (Decision* AND Model* OR Clinical*) OR (Prognostic AND History OR Variable* OR Criteria OR Scor* OR Charcteristic* OR Finding* OR Factor* OR Model*) OR (discrimination[tiab] OR discriminative[tiab] OR discriminatory[tiab]) AND (accuracy[tiab] OR ability[tiab] OR performance[tiab] OR value[tiab] OR model[tiab] OR models[tiab] OR power[tiab] OR efficiency[tiab]) OR "Generalized linear models"[tw] NOT "review"[pt]
CINAHL (EBSCOhost)	TI (("Diabetes") OR ("Diabetes Mellitus/analysis" OR "Diabetes Mellitus/classification" OR "Diabetes Mellitus/rehabilitation" OR "Diabetes Mellitus/therapy" OR "Diabetes Mellitus, Type 2") OR ("Diabetic") OR ("Diabetic Neuropathies/classification" OR "Diabetic Neuropathies/diagnosis"

	OR "Diabetic Neuropathies/diagnostic imaging" OR "Diabetic Neuropathies/physiopathology" OR "Diabetic Neuropathies/rehabilitation" OR "Diabetic Neuropathies/statistics AND numerical data" OR "Diabetes Complications" OR "Type 2 Diabetes" OR "Diabetes, Type 2")) AND TI (("Gait") OR ("Gait Analysis") OR ("Gait/classification" OR "Gait/instrumentation" OR "Gait/methods" OR "Gait/organization and administration" OR "Gait/physiology" OR "Gait/standards" OR "Gait/statistics and numerical data" OR "Gait/trends") OR ("Gait Disorders, Neurologic") OR ("Walking Speed" OR "Walking") OR ("Locomotion") OR "Gait Kinetic*" OR "Gait Kinematic*" OR "range of motion") AND ("Artificial Intelligence" OR Machine Learning OR Deep learning OR "Neural Networks, Computer" OR data mining OR machine AND (learn* OR model*) OR (statistical OR "statistical-learning") AND (strateg*) OR multilayer perceptron* OR random forest* OR bayes* network* OR support vector machine* OR nearest neighbor* OR k nearest neighbor* OR elastic net OR naive bayes* OR (classification OR regression OR estimation OR decision) AND tree OR ridge OR kernel OR ensemble OR bagging OR bagged OR boosting OR boosted OR fuzzy OR ("Predictive Value of Tests" OR "Probability Learning" OR "Forecasting" OR "Computing Methodologies" OR "Cluster Analysis") OR (Validat* OR Predict* OR Rule*) OR (Predict* AND Outcome* OR Risk* OR Model*) OR (History OR Variable* OR Criteria OR Scor* OR Characteristic* OR Finding* OR Factor*) AND (Predict* OR Model* OR Decision* OR Identif* OR Prognos*) OR (Decision* AND Model* OR Clinical*) OR (Prognostic AND History OR Variable* OR Criteria OR Scor* OR Charcteristic* OR Finding* OR Factor* OR Model*) OR (discrimination OR discriminative OR discriminatory) AND (accuracy OR ability OR performance OR value OR model OR models OR power OR efficiency) OR "Generalized linear models") NOT review
The Cochrane Library (Wiley)	("Diabetes") OR ("Diabetes Mellitus/analysis" OR "Diabetes Mellitus/classification" OR "Diabetes Mellitus/rehabilitation" OR "Diabetes Mellitus/therapy" OR "Diabetes Mellitus, Type 2") OR ("Diabetic") OR ("Diabetic Neuropathies/classification" OR "Diabetic Neuropathies/diagnosis" OR "Diabetic Neuropathies/diagnostic imaging" OR "Diabetic Neuropathies/physiopathology" OR "Diabetic Neuropathies/rehabilitation" OR "Diabetic Neuropathies/statistics AND numerical data" OR "Diabetes Complications") OR "Type 2 Diabetes" OR "Diabetes, Type 2" in Title Abstract Keyword AND ("Gait") OR ("Gait Analysis") OR ("Gait/classification" OR "Gait/instrumentation" OR "Gait/methods" OR "Gait/organization and administration" OR "Gait/physiology" OR "Gait/standards" OR "Gait/statistics and numerical data" OR "Gait/trends") OR ("Gait Disorders, Neurologic") OR ("Walking Speed" OR "Walking") OR ("Locomotion") OR "Gait Kinetic*" OR "Gait Kinematic*" OR "range of motion" in Title Abstract Keyword AND "Artificial Intelligence" OR Machine Learning OR Deep learning OR "Neural Networks, Computer" OR data mining OR machine AND (learn* OR model*) OR (statistical OR "statistical-learning") AND (strateg*) OR multilayer perceptron* OR random forest* OR bayes* network* OR support vector machine* OR nearest neighbor* OR k nearest neighbor* OR elastic net OR naive bayes* OR (classification OR regression OR estimation OR decision) AND tree OR ridge OR kernel OR ensemble OR bagging OR bagged OR boosting OR boosted OR fuzzy OR ("Predictive Value of Tests" OR "Probability

	Learning" OR "Forecasting" OR "Computing Methodologies" OR "Cluster Analysis") OR (Validat* OR Predict* OR Rule*) OR (Predict* AND Outcome* OR Risk* OR Model*) OR (History OR Variable* OR Criteria OR Scor* OR Characteristic* OR Finding* OR Factor*) AND (Predict* OR Model* OR Decision* OR Identif* OR Prognos*) OR (Decision* AND Model* OR Clinical*) OR (Prognostic AND History OR Variable* OR Criteria OR Scor* OR Charcteristic* OR Finding* OR Factor* OR Model*) OR (discrimination OR discriminative OR discriminatory) AND (accuracy OR ability OR performance OR value OR model OR models OR power OR efficiency) OR "Generalized linear models" OR "Random Forest" in Title Abstract Keyword NOT "review"
Embase (Elsevier)	('diabetes' OR 'diabetes mellitus/analysis' OR 'diabetes mellitus/classification' OR 'diabetes mellitus/rehabilitation' OR 'diabetes mellitus/therapy' OR 'diabetes mellitus, type 2' OR 'diabetic' OR (('diabetic neuropathies/classification':ti,ab,kw OR 'diabetic neuropathies/diagnosis':ti,ab,kw OR 'diabetic neuropathies/diagnostic imaging':ti,ab,kw OR 'diabetic neuropathies/physiopathology':ti,ab,kw OR 'diabetic neuropathies/rehabilitation':ti,ab,kw OR 'diabetic neuropathies/statistics':ti,ab,kw) AND 'numerical data':ti,ab,kw) OR 'diabetic complication':ti,ab,kw OR 'non insulin dependent diabetes mellitus':ti,ab,kw) AND ('gait':ti,ab,kw OR 'gait analysis':ti,ab,kw OR 'gait/classification':ti,ab,kw OR 'gait/instrumentation':ti,ab,kw OR 'gait/methods':ti,ab,kw OR 'gait/organization':ti,ab,kw AND administration:ti,ab,kw OR 'gait/physiology':ti,ab,kw OR 'gait/standards':ti,ab,kw OR 'gait/statistics':ti,ab,kw) AND ('numerical data':ti,ab,kw OR 'gait/trends':ti,ab,kw OR 'gait disorders, neurologic':ti,ab,kw OR 'walking speed':ti,ab,kw OR 'walking':ti,ab,kw OR 'locomotion':ti,ab,kw OR 'gait kinetic*':ti,ab,kw OR 'gait kinematic*':ti,ab,kw OR 'range of motion':ti,ab,kw) AND ('artificial intelligence' OR 'machine learning' OR 'deep learning' OR 'neural networks, computer' OR 'data mining' OR 'machine') AND ('learn*' OR 'model*') OR 'statistical' OR 'statistical-learning' AND 'strateg*' OR 'multilayer perceptron*' OR 'random forest*' OR 'bayes* network*' OR 'support vector machine*' OR 'nearest neighbor*' OR 'k nearest neighbor*' OR 'elastic net' OR 'naive bayes*' OR 'classification' OR 'regression' OR 'estimation' OR 'decision' AND 'tree' OR 'ridge' OR 'kernel' OR 'ensemble' OR 'bagging' OR 'bagged' OR 'boosting' OR 'boosted' OR 'fuzzy' OR 'predictive value of tests' OR 'probability learning' OR 'forecasting' OR 'computing methodologies' OR 'cluster analysis' OR 'validat*' OR 'predict*' OR 'rule*' OR ('predict*' AND 'outcome*') OR 'risk*' OR 'model*' OR 'history' OR 'variable*' OR 'criteria' OR 'scor*' OR 'characteristic*' OR 'finding*' OR 'factor*') AND ('predict*' OR 'model*'OR 'decision*' OR 'identif*' OR 'prognos*') OR ('decision*' AND 'model*') OR 'clinical*' OR ('prognostic' AND 'history') OR 'variable*' OR 'criteria' OR 'scor*' OR 'charcteristic*'OR 'finding*' OR 'factor*' OR 'model*' OR 'discrimination' OR 'discriminative' OR 'discriminatory') AND ('accuracy' OR 'ability' OR 'performance' OR 'value' OR 'model' OR 'models' OR 'power' OR 'efficiency') OR 'generalized linear models') NOT review:ab,ti
APA PsycInfo (APA PsycNet)	(Any Field: "Diabetes" [tiab]) *OR* (Any Field: "Diabetes Mellitus/analysis" [Mesh] *OR* Any Field: "Diabetes Mellitus/classification" [Mesh] *OR* Any Field: "Diabetes

	Mellitus/rehabilitation" [Mesh] *OR* Any Field: "Diabetes Mellitus/therapy" [Mesh] *OR* Any Field: "Diabetes Mellitus, Type 2" [Mesh]) *OR* (Any Field: "Diabetic" [tiab]) *OR* (Any Field: "Diabetic Neuropathies/classification" [Mesh] *OR* Any Field: "Diabetic Neuropathies/diagnosis" [Mesh] *OR* Any Field: "Diabetic Neuropathies/diagnostic imaging" [Mesh] *OR* Any Field: "Diabetic Neuropathies/physiopathology" [Mesh] *OR* Any Field: "Diabetic Neuropathies/rehabilitation" [Mesh] *OR* Any Field: "Diabetic Neuropathies/statistics AND numerical data" [Mesh] *OR* Any Field: "Diabetes Complications" [Mesh]) *OR* Any Field: "Type 2 Diabetes" [tw] *OR* Any Field: "Diabetes, Type 2" [tw]*AND* (Any Field: "Gait" [tiab]) *OR* (Any Field: "Gait Analysis" [tiab]) *OR* (Any Field: "Gait/classification" [Mesh] *OR* Any Field: "Gait/instrumentation" [Mesh] *OR*Any Field: "Gait/methods" [Mesh] *OR* Any Field: "Gait/organization and administration" [Mesh] *OR* Any Field: "Gait/physiology" [Mesh] *OR* Any Field: "Gait/standards" [Mesh] *OR* Any Field: "Gait/statistics and numerical data" [Mesh] *OR* Any Field: "Gait/trends" [Mesh]) *OR* (Any Field: "Gait Disorders, Neurologic" [Mesh]) *OR* (Any Field: "Walking Speed" [Mesh] *OR* Any Field: "Walking" [tiab]) *OR* (Any Field: "Locomotion" [tiab]) *OR* Any Field: "Locomotion" [tiab]*OR* Any Field: "Gait Kinetic*" [tw] *OR* Any Field: "Gait Kinematic*" [tw] *OR* Any Field: "range of motion" [tw]*AND* Any Field: "Artificial Intelligence" [Mesh] *OR* Any Field: Machine Learning[MeSH] *OR* Any Field: Deep learning[MeSH] *OR* Any Field: "Neural Networks, Computer" [Mesh] *OR* Any Field: data mining[MeSH]*OR* Any Field: machine[tiab] *AND* (Any Field: learn* *OR* Any Field: model*) *OR* (Any Field: statistical[tiab]*OR* Any Field: "statistical-learning" [tiab]) *AND* (Any Field: strateg*[tiab]) *OR* Any Field: multilayer perceptron*[tiab] *OR* Any Field: random forest*[tiab]*OR* Any Field: bayes* network*[tiab] *OR* Any Field: support vector machine*[tiab] *OR* Any Field: nearest neighbor*[tiab] *OR* Any Field: k nearest neighbor*[tiab]*OR* Any Field: elastic net[tiab] *OR* Any Field: naive bayes*[tiab] *OR* (Any Field: classification[tiab] *OR* Any Field: regression[tiab] *OR* Any Field: estimation[tiab]*OR* Any Field: decision[tiab]) *AND* Any Field: tree[tiab]*OR* Any Field: ridge[tiab] *OR* Any Field: kernel[tiab] *OR*Any Field: ensemble[tiab] *OR* Any Field: bagging[tiab]*OR* Any Field: bagged[tiab] *OR* Any Field: boosting[tiab] *OR* Any Field: boosted[tiab] *OR* Any Field: fuzzy[tiab] *OR* (Any Field: "Predictive Value of Tests" [Mesh] *OR* Any Field: "Probability Learning" [Mesh] *OR* Any Field: "Forecasting" [Mesh] *OR* Any Field: "Computing Methodologies" [Mesh] *OR* Any Field: "Cluster Analysis" [Mesh]) *OR* (Any Field: Validat* *OR* Any Field: Predict* *OR* Any Field: Rule*) *OR* (Any Field: Predict* *AND* Any Field: Outcome* *OR*Any Field: Risk* *OR* Any Field: Model*) *OR* (Any Field: History *OR* Any Field: Variable* *OR* Any Field: Criteria *OR* Any Field: Scor* *OR* Any Field: Characteristic* *OR* Any Field: Finding* *OR* Any Field: Factor*) *AND* (Any Field: Predict* *OR* Any Field: Model*

	OR Any Field: Decision* OR Any Field: Identif*OR Any Field: Prognos*) OR (Any Field: Decision*AND Any Field: Model* OR Any Field: Clinical*) OR(Any Field: Prognostic AND Any Field: History OR Any Field: Variable* OR Any Field: Criteria OR Any Field: Scor* OR Any Field: Charcteristic* OR Any Field: Finding* OR Any Field: Factor* OR Any Field: Model*) OR (Any Field: discrimination[tiab] OR Any Field: discriminative[tiab] OR Any Field: discriminatory[tiab]) AND (Any Field: accuracy[tiab] OR Any Field: ability[tiab] OR Any Field: performance[tiab] OR Any Field: value[tiab] OR Any Field: model[tiab] OR Any Field: models[tiab] OR Any Field: power[tiab] OR Any Field: efficiency[tiab]) OR Any Field: "Generalized linear models" [tw] NOT "review" [pt]
Google Scholar	Diabetes AND Gait "Artificial Intelligence" OR machine OR AND OR learning OR deep OR AND OR learning OR "Neural Networks" OR data OR AND OR mining OR "Predictive Value of Tests" OR "Cluster Analysis" -review
IEEE Xplore Digital Library (IEEE)	("All Metadata":"Type 2 Diabetes" OR "All Metadata":"Diabetes" OR "All Metadata":"Diabetic Neuropathies") AND ("All Metadata":"Gait" OR "All Metadata":"Gait Analysis" OR "All Metadata":"Range of Motion" OR "All Metadata":"Walking" OR "All Metadata":"Locomotion") AND ("All Metadata":"Artificial Intelligence" OR "All Metadata":"Machine learning" OR "All Metadata":"Predictive Value of Tests")
Scopus (Elsevier)	ALL (("Diabetes") OR ("Diabetes Mellitus/analysis" OR "Diabetes Mellitus/classification" OR "Diabetes Mellitus/rehabilitation" OR "Diabetes Mellitus/therapy" OR "Diabetes Mellitus, Type 2") OR ("Diabetic") OR ("Diabetic Neuropathies/classification" OR "Diabetic Neuropathies/diagnosis" OR "Diabetic Neuropathies/diagnostic imaging" OR "Diabetic Neuropathies/physiopathology" OR "Diabetic Neuropathies/rehabilitation" OR "Diabetic Neuropathies/statistics AND numerical data" OR "Diabetes Complications" OR "Type 2 Diabetes")) AND ALL (("Gait") OR ("Gait Analysis") OR ("Gait Disorders, Neurologic") OR ("Walking Speed" OR "Walking") OR ("Locomotion") OR "Gait Kinetic*" OR "Gait Kinematic*" OR "range of motion") AND ALL ("Artificial Intelligence" OR machine AND learning OR deep AND learning OR "Neural Networks" OR data AND mining OR "predictive value off tests" OR "Classification" OR "Cluster Analysis" OR "support vector machine" OR "Random Forest" OR "Naive Bayes" OR "Generalized linear models" OR "nearest neighbor*" OR "k nearest neighbor*") AND NOT "Review"
Web of Science (Clarivate Analytics)	(((TS=(("Diabetes") OR ("Diabetes Mellitus/analysis" OR "Diabetes Mellitus/classification" OR "Diabetes Mellitus/rehabilitation" OR "Diabetes Mellitus/therapy" OR "Diabetes Mellitus, Type 2") OR ("Diabetic") OR ("Diabetic Neuropathies/classification" OR "Diabetic Neuropathies/diagnosis" OR "Diabetic Neuropathies/diagnostic imaging" OR "Diabetic Neuropathies/physiopathology" OR "Diabetic Neuropathies/rehabilitation" OR "Diabetic Neuropathies/statistics and numerical data" OR "Diabetes Complications" OR "Type 2 Diabetes" OR "Diabetes, Type 2"))) AND

	TS=(("Gait") OR ("Gait Analysis") OR ("Gait/classification" OR "Gait/instrumentation" OR "Gait/methods" OR "Gait/organization and administration" OR "Gait/physiology" OR "Gait/standards" OR "Gait/statistics and numerical data" OR "Gait/trends") OR ("Gait Disorders, Neurologic") OR ("Walking Speed" OR "Walking") OR ("Locomotion") OR "Gait Kinetic*" OR "Gait Kinematic*" OR "range of motion")) AND TS=("Artificial Intelligence" OR Machine Learning OR Deep learning OR "Neural Networks, Computer" OR data mining OR (machine AND (learn* OR model*)) OR (statistical OR ”statistical-learning”) AND (strateg*) OR multilayer perceptron* OR random forest* OR bayes* network* OR support vector machine* OR nearest neighbor* OR k nearest neighbor* OR elastic net OR naive bayes* OR (classification OR regression OR estimation OR decision) AND tree OR ridge OR kernel OR ensemble OR bagging OR bagged OR boosting OR boosted OR fuzzy OR ("Predictive Value of Tests" OR "Probability Learning" OR "Forecasting" OR “Computing Methodologies” OR “Cluster Analysis”) OR (Validat* OR Predict* OR Rule*) OR (Predict* AND Outcome* OR Risk* OR Model*) OR (History OR Variable* OR Criteria OR Scor* OR Characteristic* OR Finding* OR Factor*) AND (Predict* OR Model* OR Decision* OR Identif* OR Prognos*) OR (Decision* AND Model* OR Clinical*) OR (Prognostic AND History OR Variable* OR Criteria OR Scor* OR Charcteristic* OR Finding* OR Factor* OR Model*) OR (discrimination OR discriminative OR discriminatory) AND (accuracy OR ability OR performance OR value OR model OR models OR power OR efficiency) OR "Generalized linear models")) NOT TS=(Review)

5.2 Artigo 02: A systematic review of existing predictive methods applied to gait analysis of patients with diabetes

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ABSTRACT

Background and aims: Type 2 diabetes mellitus (T2DM) damage sensory and motor nerve fibres leading to gait abnormalities. Quantitative data from objective gait assessment tools are reliable and accurate in improving decision-making to address specific treatments. We aimed to review the literature about the existing predictive methods to assess gait in T2DM patients. Furthermore, to check which input features are the most used to implement a predictive method.

Methods: Following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. Electronic searches from inception to January 2022 were performed, May 2021 to January 2022, in scientific databases and references of key articles without language restrictions. We included studies that examined the development and/or validation of predictive methods to assess T2DM gait in adults (>18 years) without amputations, use of assistive devices, ulcers, or neuropathic pain. Risk of bias (RoB) and quality of evidence assessed using the Prediction Model Risk of Bias Assessment Tool and the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD).

Results: Four studies (208 participants) included. Two used Machine Learning (ML) techniques. One conventional statistic based on stepwise multiple regression and one uncertainty method through a Fuzzy classifier. Nineteen TRIPOD items reached at least 75% of the adequate report. Three included studies classified as high RoB.

Conclusions: While much progress has been identified still is a newly emerging subject of study. Therefore, further studies are necessary to develop and improve new predictive tools to forecast and prevent potential T2DM complications.

Keywords: Diabetes, Gait Analysis, Predictive Value of Tests.

1. Introduction

Type 2 Diabetes Mellitus (T2DM) is a global health concern and the most common type of diabetes [1,2]. It is characterized by blood vessel degeneration that can damage sensory and motor nerve fibers [3] and lead to changes in mobility and physical function, particularly in dynamic balance tasks such as gait movement [4,5,6]. T2DM complications can lead to reduced velocity, an increased time during support base, and inconsistent plantar pressure distribution [4,5,6,7]. Preventive treatment strategies can be an effective tool [5,8] to avoid more serious problems.

The use of objective gait assessment tools can improve the accuracy and reliability of treatment planning strategies for T2DM [7,8,9]. These tools include a variety of input data, such as inertial measurement units, force platforms, and plantar pressure data [10], which can be analyzed using predictive methods such as machine learning [11,12]. Predictive methods have been used for a variety of purposes, including forecasting unknown events, and verifying relationships among input data features [13]. In the context of T2DM, predictive methods offer new perspectives for early detection and personalized treatment to prevent complications [14].

Although other studies summarised predictive methods to evaluate gait [13,15,16]. Our primary aim was to systematically review the literature about the existing predictive methods (e.g., ML models, statistical algorithms) applied to assess gait in patients with T2DM. Further, our secondary aim was to identify the most commonly input features data (e.g., spatiotemporal, EMG data, and plantar pressure data) used to implement a gait predictive model.

2. Method

The protocol for this systematic review has been published [17]. We followed the pre-planned methods described in the review protocol [17] and summarised them below. We previously registered in the PROSPERO (CRD42020199495) and followed the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. No ethical approval was needed for this study.

2.2 Study eligibility criteria

As planned in the review protocol [17], inclusion criteria for studies encompassed both published and unpublished studies in any language that involved the development or validation of a predictive method to assess gait in individuals with T2DM ($>$ over 18 years old); with no lower limb amputations or use assistive devices for walking. Exclusion criteria were set for participants who have ulcers or neuropathic pain that could impact gait movement. There were no restrictions based on gender or race.

2.3 Search strategy

Planned in the review protocol [17], we searched for trials in all languages, limited to human participants, and translated relevant articles when necessary.

We searched the following electronic bibliographic databases from May 2021 to 31 January 2022:

- Web of Science (Clarivate Analytics) (from 1945 to January 2022).
- MEDLINE (PubMed), Embase (Elsevier) (from 1948 to January 2022).
- IEEE Xplore Digital Library (IEEE) (from 1952 to January 2022).
- Scopus (Elsevier) (from 1788 to January 2022).
- CINAHL (EBSCOhost) (from 1937 to January 2022).
- Google Scholar (Google) (searched May to December 2021 and January 2022).
- APA PsycInfo (APA PsycNet) (from 1800 to January 2022).
- Cochrane Library (Wiley) (from 1996 to January 2022).

The search for articles was conducted using a blend of free keywords and the medical terminology listed in the Medical Subject Headings of the US National Library of Medicine. General search terms used include: ‘Diabetes, Type 2’, ‘Type 2 Diabetes’, ‘Gait Analysis’, ‘Gait’, ‘Kinematic’, ‘Kinetic’, ‘Statistical-learning’, ‘Predictive Value of Tests’, ‘Artificial Intelligence’, ‘Machine Learning’. We developed the MEDLINE search strategy and adapted it for the other databases (Appendix I).

To identify further published, unpublished studies and conference proceedings we:

1. screened reference lists of all relevant articles.
2. used Science Citation Index Cited Reference search for forwarding tracking of important articles.

3. contacted experts and researchers in our field of study.
4. searched for PhD and MSc theses.

Using Rayyan systematic review software [19], the duplicates were removed, followed by the screening of titles and abstracts. Full-text reviews were done on potentially eligible titles and abstracts identified by two independent review authors (PMMS, ABOB). We recorded reasons for excluding studies in the PRISMA flowchart.

2.3 Data extraction and management

Two review authors (PMMS, ABOB) independently extracted the data from each eligible study using a data extraction form specified in [18] that included:

1. Study information: publication year, author information, type of study, and PICO elements.
2. Database information: sample size, host organisation/sponsorship.
3. Patient demographic information.
4. Predictive methodological information: type of gait assessment, compared with gold standard devices, type of predictive algorithm used, input feature format, use optimisation algorithm, feature extraction methods.

One review author entered all extracted data (PMMS), and two other reviewers (ABOB, LBAF) independently verified the accuracy of the data. Any missing data were pursued by contacting the original investigators. In case of contact difficulty, the findings were presented based on the available statistical information from each study.

2.4 Risk of bias assessment, quality of evidence and data synthesis

According to the review protocol [18], the risk of bias (RoB) of the included studies was carried out using the Prediction Model Risk of Bias Assessment Tool (PROBAST) [20]. Two review authors (PMMS and ABOB) independently assessed the RoB and addressed any discrepancies. If needed, another reviewer (FACC) was consulted to reach a conclusion.

The quality of evidence was evaluated using the Transparent Reporting of a multivariable prediction model for the Individual Prognosis or Diagnosis (TRIPOD) checklist [21]. Each item was scored as follows:

- Zero: ‘no report’.

- One: : ‘inadequate report’.
- Two: ‘adequate report’.

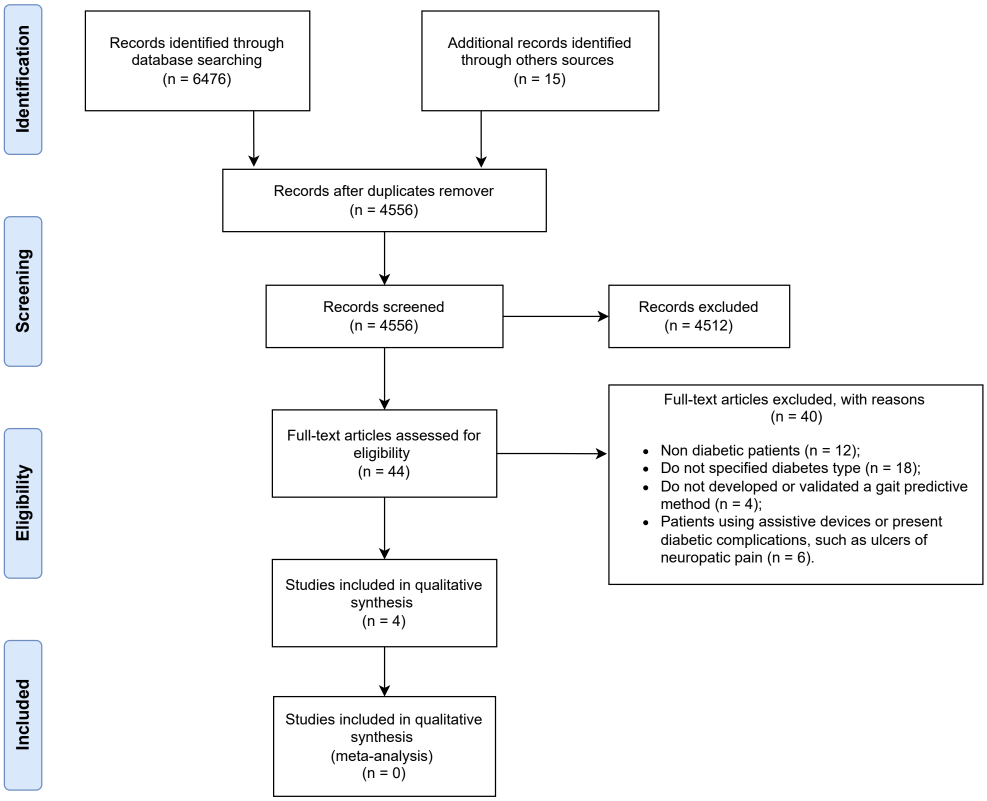
A summary of the information presented, characterizing, and explaining the findings of the included studies, was created through a narrative synthesis. In the review protocol [18], we planned to conduct different subgroup analyses; however, it was not possible due to the heterogeneity in age, body index mass (BMI), predictive methods used and gait input parameters of the included studies.

3. Results

3.1 Results of the search

A flow diagram of the study selection process is shown in Fig. 1. A total of 6476 publications were identified, with the number from each database as follows: Web of Science (717), PubMed (989), Embase (554), IEEE Xplore Digital Library (84), Scopus (222), CINAHL (1379), Google Scholar (2548), The Cochrane Library (160), and 15 articles from other databases.

Figura 5.2 – Study flow diagram.



3.2 Included studies

This review includes four studies with a total of 208 participants. Two used ML techniques. One developed a system to map plantar pressure data to detect diabetic peripheral neuropathy (DPN) using ML-supervised algorithms [21]. Another validated the clinical efficacy of a plantar pressure classification system developed using an ML unsupervised algorithm [22]. One study developed energy expenditure prediction equations using conventional statistics based on stepwise multiple regression based on accelerometers [23]. The last one used uncertainty methods through a Fuzzy classifier to develop an automated system to classify normal subjects, TD2M with and without neuropathy [24]. Details of the studies are presented in the Summary characteristics of selected studies (Table 5.2).

Tabela 5.2 – Summary characteristics of selected studies.

Study, year	**Location**	**Description**	**Sample**	**Age**	**BMI**	**Source of data**	**Tool used to assess gait**	**Gait input features**	**Model used**	**Model performance**	**Results**
Deschamps et al., 2016	Belgium	Study using classification models to see patterns of plantar pressure distribution in patients with type 1 and 2 DM. Also, aimed to determine clinical efficacy of these classification models.	78	63.38 ±9.69	28.95 ± 5.55	Electronic health records, clinical registry	Footscan plate and force plate	Plantar pressure, spatiotemporal parameters	Kmeans clustering	Cross-validation	Pixel-level comparisons between groups showed regional differences in the plantar pressure areas. Majority of the ulcers regions detected by classification methods were in foot regions with highest forces. Classification recognition rate around 90% or highest, sensitivity and specificity in the groups around 0.7 and 0.8, respectively in all cross-validation subsets.
Caron et al., 2020	France	Predictive method equations developed based on acceleration to analyse energy expenditure in middle-aged healthy adults and patients with T2DM, based on static and gait performance.	40	57.5 ± 8.0	25.43 ± 0.35	Voluntary recruitment	IMUs	Three-dimensional accelerations of the lower limbs center of mass	Stepwise multiple regression	Monte Carlo cross-validation	Three linear prediction equations to estimate energy expenditure showed in cross-validation coefficients of determination between 0.81 to 0.85.

Acharya et al., 2012	Singapore	ML technique used to classify normal individuals and patients with type 2 diabetes with and without neuropathy.	91	57 ± 7.87	26.19 ± 1.69	Clinical registry	F-Scan® in-shoe system (pedobarograph)	Plantar pressure image	Fuzzy classifier	Six-Fold stratified cross-validation	The proposed ML method showed accuracy of 93.7%, 100% sensitivity, and 83.3% specificity. The use of eigenvalues helped to differentiate normal from diabetic subjects.
Corpin et al., 2019	Philippines	ML techniques applied to detect DPN through plantar pressure data in patients with T2D.	36	54.48 ± 8.62	27.29 ± 1.04	Clinical registry	F-Scan® in-shoe system and Tekscan Medical Sensor 3000E	Plantar pressure	Support Vector Machine (SVM), Random Forest, Multilayer Perceptron (MLP), K-Nearest Neighbor (KNN), and Gaussian Process (GP)	10-Fold cross-validation	ML classification algorithms applied showed the SVM and MLP methods results in highest accuracy, 92.91% and 91.74%, respectively.

BMI: Body Index Mass; IMUs: Inertial Measurement Units.

3.2.1 Participants

All studies divided participants into healthy controls and patients with T2DM. Deschamps et al. [22] study also presented patients with type 1 DM; however, these participants were discriminated from patients with T2DM. Ascrarya et al. [24] also divided in three groups, patients with T2DM were divided according to present or not neuropathy.

3.2.2 Intervention

Plantar pressure data were gathered during walking in a natural gait cadence. One study used this method to find regional differences in plantar areas to avoid pressure ulcers [22]. Another study tried to find the differences between healthy to non-neuropathic participants; and neuropathic participants with T2DM [21].

Foot images were another type of data used to identify neuropathic and non-neuropathic patients with T2DM [24]. In contrast, one of the studies developed prediction equations for estimating energy expenditure through walking and static conditions from patients with T2DM and healthy [23].

3.2.3 Outcomes

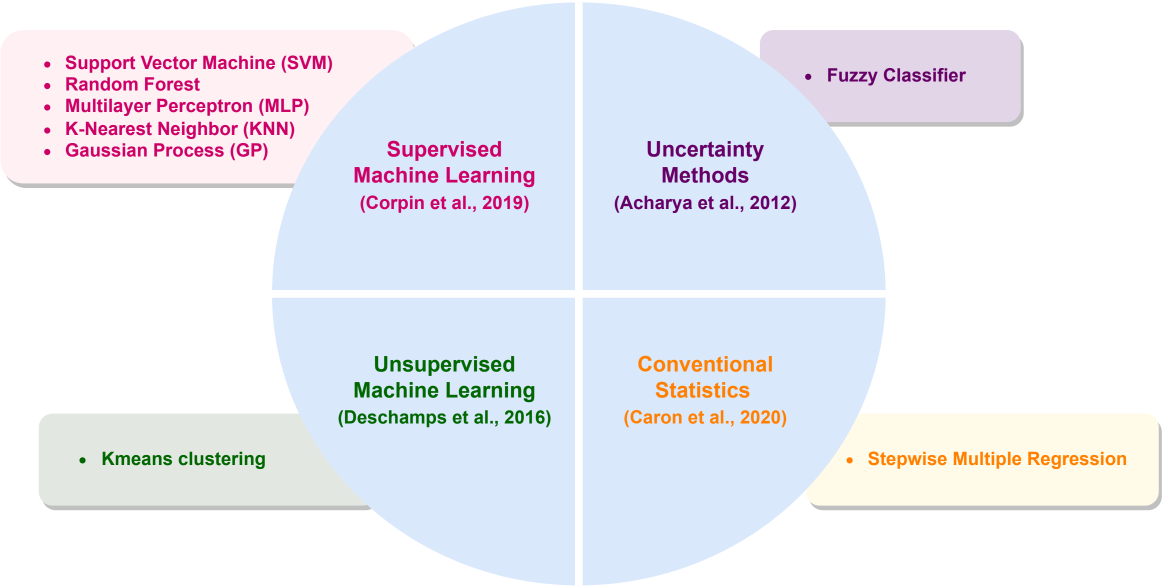
Predictive methods used to analyse plantar pressure data showed that most ulcers in patients with T2DM appeared in regions with the highest forces as medial M1, central, T1-M1 and lateral M4-M5 patterns [22]. The patients presented lateral M4-M5 an atypical pattern suggestive of a lack of plantar distribution under the hallux and first metatarsal region. Whereas pressure peaks among metatarsals two and five. Healthy participants presented plantar pressure similarities to non-neuropathic patients with T2DM, such as maximum plantar pressure force (

Dynamic plantar pressure analysed by images can predict and differentiate healthy participants from T2DM neuropathic or non-neuropathic patients better than analysing static plantar pressure [24]. Moreover, wearables, such as accelerometers to predict energy expenditure by regression equations, might be useful during walking prescriptions for patients with T2DM [23].

3.3 Predictive methods

Different predictive methods were used in the selected studies. Artificial intelligence methods, like ML and computational intelligence, were implemented (Fig. 5.3). ML methods were the most popular by the papers included.

Figura 5.3 – Distribution of the different predictive methods included in this systematic review.



Supervised classification ML methods included support vector machine (SVM), Random Forest (RF), Multilayer Perceptron (MLP), K-Nearest Neighbour (KNN) and Gaussian Progress (GP). Among these methods, SVM and MLP showed the highest accuracy in predicting diabetic neuropathy through plantar pressure data in patients with T2DM [21]. Unsupervised ML methods covered by K-means clustering were able to make pixel-level comparisons between groups showing regional plantar pressure differences to predict pressure ulcers [22].

Uncertainty computational intelligence methods implemented fuzzy classifiers that classified healthy participants from patients with T2DM with or without neuropathy. The authors used eigenvalues that helped the classification [24]. One of the studies utilised conventional statistics methods applying stepwise multiple regression to evaluate the variables analysed and reach the goals of the study, which was related to linear prediction equations to estimate energy expenditure based on static and gait performance [23].

3.4 Quality of evidence

Nineteen TRIPOD items reached at least 75% of the adequate report (sections: background, source of data, participants, outcomes, predictors, statistical analysis methods, model specification, model performance, and funding), whilst 7 TRIPOD items were 25% (Fig. 5.4). Results for the overall TRIPOD item stratified by study type are shown in Appendix II.

3.4.1 Title and abstract (items 1 and 2)

Only one study completely adhered to the title recommendations. Half the selected studies (50%) poorly reported the description of identifying the study as developing and/or validating. Although the outcome to be predicted was well addressed. Three studies did not fully report item 2, abstract, lacking primarily information about participants and sample size (75%).

3.4.2 Introduction (item 3)

Background and objectives sections were often reported items. Only one of the included studies did not describe the development or validation of the model, although implicit development information.

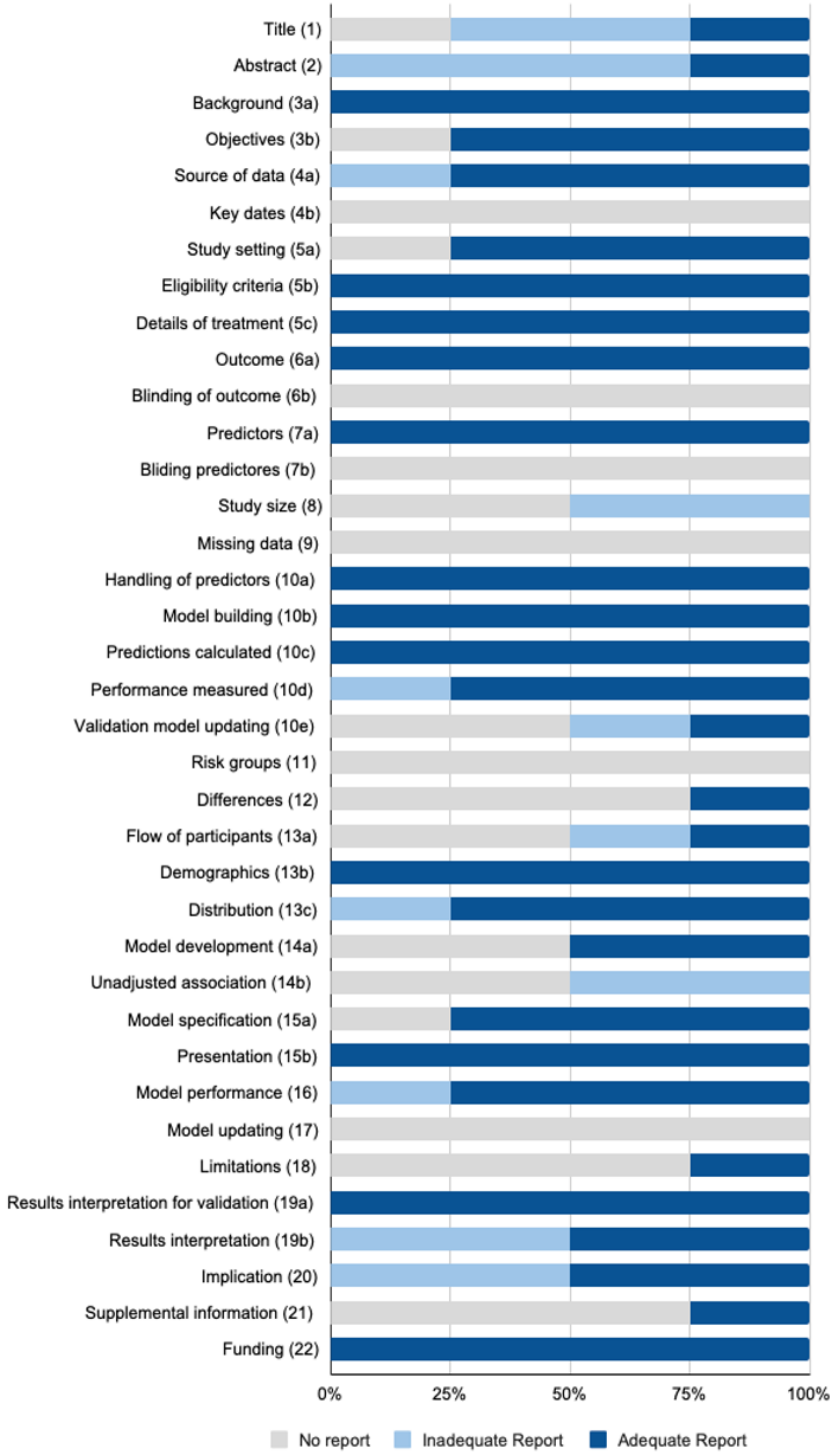
3.4.3 Methods (items 4-12)

Statistical analysis methods were the most often reported item in the methods section and across all TRIPOD items (10), followed by participants (items 5). The source of data was adequately reported in 3/4 studies. However, no study specified the key study dates, including the start, end, or follow-up periods that gathered the data. The outcome (item 6) was adequately reported in all studies, while none reported actions to blind assessment of the outcome to be predicted. The same pattern occurred in the predictors' section (item 7). Half of the studies inadequately explained how the sample size arrived (item 8), and none described how missing data were handled (item 9).

3.4.4 Results (items 13-17)

One study described the flow of participants. Characteristics of study participants were reported in all studies (item 13b). Basic demographics (at least age, gender, BMI, and diabetes type), clinical features, and predictors used; were provided. Validation (item 13c) showing comparisons with the development data of the variable distribution was reported in 75% of the studies. However, one of them needed a way to outline these comparisons. In the model development section (item 14), half of the included studies specified the number of participants and outcome events in each analysis; this half did not report the unadjusted

Figura 5.4 – Overall results per TRIPOD item in all studies included.



association between each candidate predictor and outcome. Model development (item 5) and model performance (item 16) were often reported in most studies (75%), except one that did not describe the full prediction model to allow predictions for individuals. Also, one of them inadequately reported performance measures of the prediction model. None of the studies reported on model updating (item 17).

3.4.5 Discussion (items 18-20)

The overall interpretation of results (item 19) was reported in all studies. Although, two studies mislead these interpretations, considering the objectives of their studies, limitations, and other relevant evidence. Only one study discussed the limitation (item 18). Half of the studies adequately discussed the potential clinical use of the model and its implications (item 20) for future research.

3.4.6 Other information (items 21 and 22)

Only one study mentioned the supplementary resources (item 21). All included studies reported the funding information (item 22).

3.5 Risk of bias in included studies

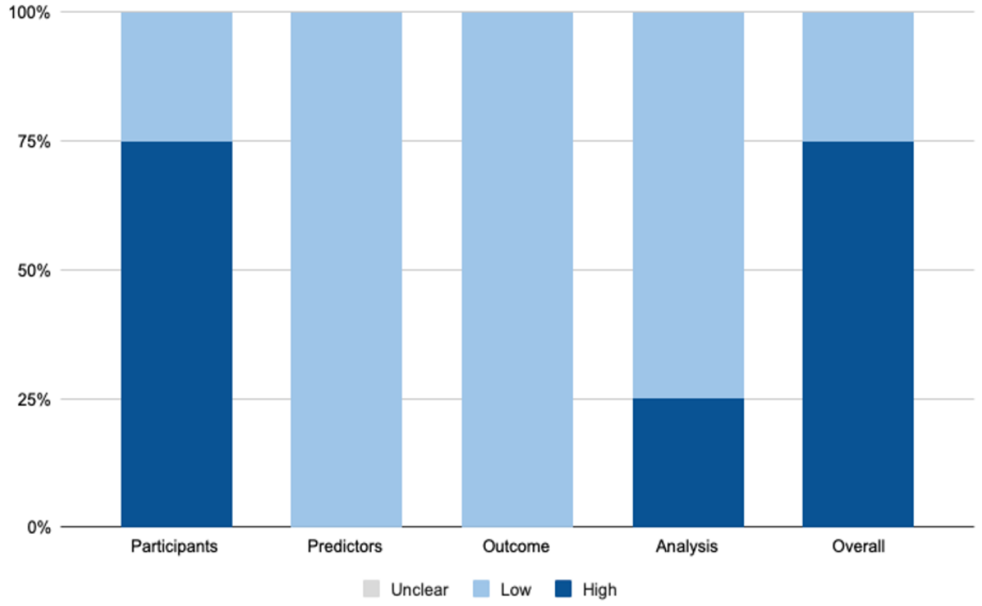
Using PROBAST criteria, we assessed all included studies. The overall risk of bias (RoB) was classified as high in three out of the four included studies (Appendix III). High RoB (Fig. 5.5) most often originated in the domains ‘participants’ (item 1.1 were appropriate data sources used?) and ‘analysis’ (item 4.3 Were all enrolled participants included in the analysis?).

3.6 Analyses of subgroups or subsets

Due to the heterogeneity of the included studies, the subgroup analysis planned in the protocol [18] was not possible. One of the factors could be a variety of model performances by choice of statistical method, sample size and the number of predictors within studies. All models assessed discrimination using a type of cross-validation method. Most of these were k-fold cross-validation (50% of all models; 2 studies), a resampling method, which involves testing a model on each of k independent partitions of a dataset, every time training on the remaining k-1 folds. In half of all models, sensitivity and specificity were the classification metrics applied, and one showed the properly confusion matrix metrics.

Regarding gait input features, plantar pressure was the most used in the studies (75% of all studies; 3 studies). Two, used only plantar pressure images, and one associated with a force plate (assessing spatiotemporal parameters as well). One used IMUs as input features, assessing gait movement by three-dimensional parameters.

Figura 5.5 – Percentage risk of bias (RoB) according to the domain of assessment for all included studies; assessed using PROBAST.



4. Discussion

As previously presented, predictive methods have been used to determine different gait disorders. Our main goal was to comprise all predictive methods applied to analyse gait in patients with T2DM. Additionally, we intended to check which gait input features are the most used to implement a predictive method.

The four-phase reviewing process yielded four studies that met our inclusion criteria (a total of 208 participants), and each study used a different predictive method. Even though three studies used plantar pressure as a gait input feature, the experimental designs varied considerably, leading to distinct outcomes. For this reason, subgroup analysis became inappropriate, which was one of our original purposes [17]. All studies were of a single intervention, except one that enhanced data features with electronic health records from another study.

Regarding data acquisition, most of the included studies used methods different from gold-standard methods to obtain gait data, which may contribute to inaccurate outcomes and high RoB. Whereas the lack of standardisation of predictive variables. Plantar pressure distribution was often applied either as input to the systems or the predicted measure. Thus, we highlight its versatility and relevance for gait analysis.

In general, we observed that no standard methodology for predicting T2DM gait data exists. ML techniques were the most applied predictive method among the included studies. One study [22] used unsupervised ML model K-means clustering. This technique is the most widely used; it can categorise and classify gait data based on common features [11]. Another study used different techniques of ML [21]. Amongst the models used, Support Vector Machine (SVM) and Multilayer Perceptron (MLP) presented the best performance metrics. SVM is a supervised machine learning technique that is commonly used for classification or regression tasks. It finds a hyperplane that maximizes the distance from the nearest training data points of each class in an n-dimensional space [25,26]. MLP, or Multi-Layer Perceptron, is a popular deep learning technique that uses multiple interconnected processing elements to solve a problem [25,26,27]. It is modelled after the human brain and consists of an input layer, one or more hidden layers, and an output layer [26,27].

A successful ML model depends on either the data used and the performance of the learning algorithm. Most studies on ML-based prediction models show a poor methodological quality that resulted in high RoB. Factors contributing to this include lack of describing participants selection, small study size and poor handling of missing data. A lack of information can impose significant bias that may affect estimated model performance [27] and the quality of evidence.

Regarding the quality of evidence, in the literature, few predictive studies use the Transparent Reporting of a multivariable prediction model for the Individual Prognosis or Diagnosis (TRIPOD) checklist [20]. The TRIPOD Statement is a checklist to guide predictive studies to appropriate reports. Efforts to improve the design, conduct, reporting, and validation of such studies are necessary to boost the prediction approaches in clinical practice.

In general, existing predictive models for gait analysis in T2DM patients yielded several limitations. We now describe these limitations and identify several opportunities to improve predictive models for gait analysis of T2DM patients. One possible source of bias could be the adopted search strategy, in which we used diverse terms. Thus, even though we found studies applied exclusively to T2DM patients, the sample of papers could be likely biased toward other disorders. Additionally, the diversified methodologies of the papers prevented us from performing subgroup analysis.

The outcomes of this systematic review showed a lack of standardization in reporting the methodology using predictive methods. For example, most studies delved insufficiently into describing how were handled missing data and the absence of rigour concerning data acquisition. These inconsistencies and the fact of predictive methods are a new subject of study; the readers should consider such findings cautiously.

5. Conclusions

Throughout the reviewing process, we observed that there exists no standard methodology for predicting the gait analysis of patients with diabetes, probably because it is a new subject of study. ML algorithms were the most applied predictive algorithm among the included studies. Another highlight from this systematic review is the plantar pressure as the most common gait input feature. Thus, our results encourage further studies necessary to develop and improve new predictive tools to forecast and prevent diabetes complications.

Conflicts of interest

The authors declare no conflict of interest.

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Supplementary Appendix I. The search terms across databases

Database	Search terms
MEDLINE (PubMed)	("Diabetes"[tiab]) OR ("Diabetes Mellitus/analysis"[Mesh] OR "Diabetes Mellitus/classification"[Mesh] OR "Diabetes Mellitus/rehabilitation"[Mesh] OR "Diabetes Mellitus/therapy"[Mesh] OR "Diabetes Mellitus, Type 2"[Mesh]) OR ("Diabetic"[tiab]) OR ("Diabetic Neuropathies/classification"[Mesh] OR "Diabetic Neuropathies/diagnosis"[Mesh] OR "Diabetic Neuropathies/diagnostic imaging"[Mesh] OR "Diabetic Neuropathies/physiopathology"[Mesh] OR "Diabetic Neuropathies/rehabilitation"[Mesh] OR "Diabetic Neuropathies/statistics AND numerical data"[Mesh] OR "Diabetes Complications"[Mesh]) OR "Type 2 Diabetes" [tw] OR "Diabetes, Type 2" [tw] AND ("Gait"[tiab]) OR ("Gait Analysis"[tiab]) OR ("Gait/classification"[Mesh] OR "Gait/instrumentation"[Mesh] OR "Gait/methods"[Mesh] OR "Gait/organization and administration"[Mesh] OR "Gait/physiology"[Mesh] OR "Gait/standards"[Mesh] OR "Gait/statistics and numerical data"[Mesh] OR "Gait/trends"[Mesh]) OR ("Gait Disorders, Neurologic"[Mesh]) OR ("Walking Speed"[Mesh] OR "Walking"[tiab]) OR ("Locomotion"[tiab]) OR "Locomotion"[tiab] OR "Gait Kinetic*"[tw] OR "Gait Kinematic*"[tw] OR "range of motion"[tw] AND "Artificial Intelligence"[Mesh] OR Machine Learning[MeSH] OR Deep learning[MeSH] OR "Neural Networks, Computer"[Mesh] OR data mining[MeSH] OR machine[tiab] AND (learn* OR model*) OR (statistical[tiab] OR "statistical-learning"[tiab]) AND (strateg*[tiab]) OR multilayer perceptron*[tiab] OR random forest*[tiab] OR bayes* network*[tiab] OR support vector machine*[tiab] OR nearest neighbor*[tiab] OR k nearest neighbor*[tiab] OR elastic net[tiab] OR naive bayes*[tiab] OR (classification[tiab] OR regression[tiab] OR estimation[tiab] OR decision[tiab]) AND tree[tiab] OR ridge[tiab] OR kernel[tiab] OR ensemble[tiab] OR bagging[tiab] OR bagged[tiab] OR boosting[tiab] OR boosted[tiab] OR fuzzy[tiab] OR ("Predictive Value of Tests"[Mesh] OR "Probability Learning"[Mesh] OR "Forecasting"[Mesh] OR "Computing Methodologies"[Mesh] OR "Cluster Analysis"[Mesh]) OR (Validat* OR Predict* OR Rule*) OR (Predict* AND Outcome* OR Risk* OR Model*) OR (History OR Variable* OR Criteria OR Scor* OR Characteristic* OR Finding* OR Factor*) AND (Predict* OR Model* OR Decision* OR Identif* OR Prognos*) OR (Decision* AND Model* OR Clinical*) OR (Prognostic AND History OR Variable* OR Criteria OR Scor* OR Chracteristic* OR Finding* OR Factor* OR Model*) OR (discrimination[tiab] OR discriminative[tiab] OR discriminatory[tiab]) AND (accuracy[tiab] OR ability[tiab] OR performance[tiab] OR value[tiab] OR model[tiab] OR models[tiab] OR power[tiab] OR efficiency[tiab]) OR "Generalized linear models"[tw] NOT "review"[pt]
CINAHL (EBSCOhost)	TI (("Diabetes") OR ("Diabetes Mellitus/analysis" OR "Diabetes Mellitus/classification" OR "Diabetes Mellitus/rehabilitation" OR "Diabetes Mellitus/therapy" OR "Diabetes Mellitus, Type 2") OR ("Diabetic") OR ("Diabetic Neuropathies/classification" OR "Diabetic Neuropathies/diagnosis"

	OR "Diabetic Neuropathies/diagnostic imaging" OR "Diabetic Neuropathies/physiopathology" OR "Diabetic Neuropathies/rehabilitation" OR "Diabetic Neuropathies/statistics AND numerical data" OR "Diabetes Complications" OR "Type 2 Diabetes" OR "Diabetes, Type 2")) AND TI (("Gait") OR ("Gait Analysis") OR ("Gait/classification" OR "Gait/instrumentation" OR "Gait/methods" OR "Gait/organization and administration" OR "Gait/physiology" OR "Gait/standards" OR "Gait/statistics and numerical data" OR "Gait/trends") OR ("Gait Disorders, Neurologic") OR ("Walking Speed" OR "Walking") OR ("Locomotion") OR "Gait Kinetic*" OR "Gait Kinematic*" OR "range of motion") AND ("Artificial Intelligence" OR Machine Learning OR Deep learning OR "Neural Networks, Computer" OR data mining OR machine AND (learn* OR model*) OR (statistical OR "statistical-learning") AND (strateg*) OR multilayer perceptron* OR random forest* OR bayes* network* OR support vector machine* OR nearest neighbor* OR k nearest neighbor* OR elastic net OR naive bayes* OR (classification OR regression OR estimation OR decision) AND tree OR ridge OR kernel OR ensemble OR bagging OR bagged OR boosting OR boosted OR fuzzy OR ("Predictive Value of Tests" OR "Probability Learning" OR "Forecasting" OR "Computing Methodologies" OR "Cluster Analysis") OR (Validat* OR Predict* OR Rule*) OR (Predict* AND Outcome* OR Risk* OR Model*) OR (History OR Variable* OR Criteria OR Scor* OR Characteristic* OR Finding* OR Factor*) AND (Predict* OR Model* OR Decision* OR Identif* OR Prognos*) OR (Decision* AND Model* OR Clinical*) OR (Prognostic AND History OR Variable* OR Criteria OR Scor* OR Charcteristic* OR Finding* OR Factor* OR Model*) OR (discrimination OR discriminative OR discriminatory) AND (accuracy OR ability OR performance OR value OR model OR models OR power OR efficiency) OR "Generalized linear models") NOT review
The Cochrane Library (Wiley)	("Diabetes") OR ("Diabetes Mellitus/analysis" OR "Diabetes Mellitus/classification" OR "Diabetes Mellitus/rehabilitation" OR "Diabetes Mellitus/therapy" OR "Diabetes Mellitus, Type 2") OR ("Diabetic") OR ("Diabetic Neuropathies/classification" OR "Diabetic Neuropathies/diagnosis" OR "Diabetic Neuropathies/diagnostic imaging" OR "Diabetic Neuropathies/physiopathology" OR "Diabetic Neuropathies/rehabilitation" OR "Diabetic Neuropathies/statistics AND numerical data" OR "Diabetes Complications") OR "Type 2 Diabetes" OR "Diabetes, Type 2" in Title Abstract Keyword AND ("Gait") OR ("Gait Analysis") OR ("Gait/classification" OR "Gait/instrumentation" OR "Gait/methods" OR "Gait/organization and administration" OR "Gait/physiology" OR "Gait/standards" OR "Gait/statistics and numerical data" OR "Gait/trends") OR ("Gait Disorders, Neurologic") OR ("Walking Speed" OR "Walking") OR ("Locomotion") OR "Gait Kinetic*" OR "Gait Kinematic*" OR "range of motion" in Title Abstract Keyword AND "Artificial Intelligence" OR Machine Learning OR Deep learning OR "Neural Networks, Computer" OR data mining OR machine AND (learn* OR model*) OR (statistical OR "statistical-learning") AND (strateg*) OR multilayer perceptron* OR random forest* OR bayes* network* OR support vector machine* OR nearest neighbor* OR k nearest neighbor* OR elastic net OR naive bayes* OR (classification OR regression OR estimation OR decision) AND tree OR ridge OR kernel OR ensemble OR bagging OR bagged OR boosting OR boosted OR fuzzy OR ("Predictive Value of Tests" OR "Probability

	Learning" OR "Forecasting" OR "Computing Methodologies" OR "Cluster Analysis") OR (Validat* OR Predict* OR Rule*) OR (Predict* AND Outcome* OR Risk* OR Model*) OR (History OR Variable* OR Criteria OR Scor* OR Characteristic* OR Finding* OR Factor*) AND (Predict* OR Model* OR Decision* OR Identif* OR Prognos*) OR (Decision* AND Model* OR Clinical*) OR (Prognostic AND History OR Variable* OR Criteria OR Scor* OR Charcteristic* OR Finding* OR Factor* OR Model*) OR (discrimination OR discriminative OR discriminatory) AND (accuracy OR ability OR performance OR value OR model OR models OR power OR efficiency) OR "Generalized linear models" OR "Random Forest" in Title Abstract Keyword NOT "review"
Embase (Elsevier)	('diabetes' OR 'diabetes mellitus/analysis' OR 'diabetes mellitus/classification' OR 'diabetes mellitus/rehabilitation' OR 'diabetes mellitus/therapy' OR 'diabetes mellitus, type 2' OR 'diabetic' OR (('diabetic neuropathies/classification':ti,ab,kw OR 'diabetic neuropathies/diagnosis':ti,ab,kw OR 'diabetic neuropathies/diagnostic imaging':ti,ab,kw OR 'diabetic neuropathies/physiopathology':ti,ab,kw OR 'diabetic neuropathies/rehabilitation':ti,ab,kw OR 'diabetic neuropathies/statistics':ti,ab,kw) AND 'numerical data':ti,ab,kw) OR 'diabetic complication':ti,ab,kw OR 'non insulin dependent diabetes mellitus':ti,ab,kw) AND ('gait':ti,ab,kw OR 'gait analysis':ti,ab,kw OR 'gait/classification':ti,ab,kw OR 'gait/instrumentation':ti,ab,kw OR 'gait/methods':ti,ab,kw OR 'gait/organization':ti,ab,kw AND administration:ti,ab,kw OR 'gait/physiology':ti,ab,kw OR 'gait/standards':ti,ab,kw OR 'gait/statistics':ti,ab,kw) AND ('numerical data':ti,ab,kw OR 'gait/trends':ti,ab,kw OR 'gait disorders, neurologic':ti,ab,kw OR 'walking speed':ti,ab,kw OR 'walking':ti,ab,kw OR 'locomotion':ti,ab,kw OR 'gait kinetic*':ti,ab,kw OR 'gait kinematic*':ti,ab,kw OR 'range of motion':ti,ab,kw) AND ('artificial intelligence' OR 'machine learning' OR 'deep learning' OR 'neural networks, computer' OR 'data mining' OR 'machine') AND ('learn*' OR 'model*') OR 'statistical' OR 'statistical-learning' AND 'strateg*' OR 'multilayer perceptron*' OR 'random forest*' OR 'bayes* network*' OR 'support vector machine*' OR 'nearest neighbor*' OR 'k nearest neighbor*' OR 'elastic net' OR 'naive bayes*' OR 'classification' OR 'regression' OR 'estimation' OR 'decision' AND 'tree' OR 'ridge' OR 'kernel' OR 'ensemble' OR 'bagging' OR 'bagged' OR 'boosting' OR 'boosted' OR 'fuzzy' OR 'predictive value of tests' OR 'probability learning' OR 'forecasting' OR 'computing methodologies' OR 'cluster analysis' OR 'validat*' OR 'predict*' OR 'rule*' OR ('predict*' AND 'outcome*') OR 'risk*' OR 'model*' OR 'history' OR 'variable*' OR 'criteria' OR 'scor*' OR 'characteristic*' OR 'finding*' OR 'factor*') AND ('predict*' OR 'model*'OR 'decision*' OR 'identif*' OR 'prognos*') OR ('decision*' AND 'model*') OR 'clinical*' OR ('prognostic' AND 'history') OR 'variable*' OR 'criteria' OR 'scor*' OR 'charcteristic*'OR 'finding*' OR 'factor*' OR 'model*' OR 'discrimination' OR 'discriminative' OR 'discriminatory') AND ('accuracy' OR 'ability' OR 'performance' OR 'value' OR 'model' OR 'models' OR 'power' OR 'efficiency') OR 'generalized linear models') NOT review:ab,ti
APA PsycInfo (APA PsycNet)	(Any Field: "Diabetes" [tiab]) *OR* (Any Field: "Diabetes Mellitus/analysis" [Mesh] *OR* Any Field: "Diabetes Mellitus/classification" [Mesh] *OR* Any Field: "Diabetes

	Mellitus/rehabilitation" [Mesh] *OR* Any Field: "Diabetes Mellitus/therapy" [Mesh] *OR* Any Field: "Diabetes Mellitus, Type 2" [Mesh]) *OR* (Any Field: "Diabetic" [tiab]) *OR* (Any Field: "Diabetic Neuropathies/classification" [Mesh] *OR* Any Field: "Diabetic Neuropathies/diagnosis" [Mesh] *OR* Any Field: "Diabetic Neuropathies/diagnostic imaging" [Mesh] *OR* Any Field: "Diabetic Neuropathies/physiopathology" [Mesh] *OR* Any Field: "Diabetic Neuropathies/rehabilitation" [Mesh] *OR* Any Field: "Diabetic Neuropathies/statistics AND numerical data" [Mesh] *OR* Any Field: "Diabetes Complications" [Mesh]) *OR* Any Field: "Type 2 Diabetes" [tw] *OR* Any Field: "Diabetes, Type 2" [tw]*AND* (Any Field: "Gait" [tiab]) *OR* (Any Field: "Gait Analysis" [tiab]) *OR* (Any Field: "Gait/classification" [Mesh] *OR* Any Field: "Gait/instrumentation" [Mesh] *OR*Any Field: "Gait/methods" [Mesh] *OR* Any Field: "Gait/organization and administration" [Mesh] *OR* Any Field: "Gait/physiology" [Mesh] *OR* Any Field: "Gait/standards" [Mesh] *OR* Any Field: "Gait/statistics and numerical data" [Mesh] *OR* Any Field: "Gait/trends" [Mesh]) *OR* (Any Field: "Gait Disorders, Neurologic" [Mesh]) *OR* (Any Field: "Walking Speed" [Mesh] *OR* Any Field: "Walking" [tiab]) *OR* (Any Field: "Locomotion" [tiab]) *OR* Any Field: "Locomotion" [tiab]*OR* Any Field: "Gait Kinetic*" [tw] *OR* Any Field: "Gait Kinematic*" [tw] *OR* Any Field: "range of motion" [tw]*AND* Any Field: "Artificial Intelligence" [Mesh] *OR* Any Field: Machine Learning[MeSH] *OR* Any Field: Deep learning[MeSH] *OR* Any Field: "Neural Networks, Computer" [Mesh] *OR* Any Field: data mining[MeSH]*OR* Any Field: machine[tiab] *AND* (Any Field: learn**OR* Any Field: model*) *OR* (Any Field: statistical[tiab]*OR* Any Field: "statistical-learning" [tiab]) *AND* (Any Field: strateg*[tiab]) *OR* Any Field: multilayer perceptron*[tiab] *OR* Any Field: random forest*[tiab]*OR* Any Field: bayes* network*[tiab] *OR* Any Field: support vector machine*[tiab] *OR* Any Field: nearest neighbor*[tiab] *OR* Any Field: k nearest neighbor*[tiab]*OR* Any Field: elastic net[tiab] *OR* Any Field: naive bayes*[tiab] *OR* (Any Field: classification[tiab] *OR* Any Field: regression[tiab] *OR* Any Field: estimation[tiab]*OR* Any Field: decision[tiab]) *AND* Any Field: tree[tiab]*OR* Any Field: ridge[tiab] *OR* Any Field: kernel[tiab] *OR*Any Field: ensemble[tiab] *OR* Any Field: bagging[tiab]*OR* Any Field: bagged[tiab] *OR* Any Field: boosting[tiab] *OR* Any Field: boosted[tiab] *OR* Any Field: fuzzy[tiab] *OR* (Any Field: "Predictive Value of Tests" [Mesh] *OR* Any Field: "Probability Learning" [Mesh] *OR* Any Field: "Forecasting" [Mesh] *OR* Any Field: "Computing Methodologies" [Mesh] *OR* Any Field: "Cluster Analysis" [Mesh]) *OR* (Any Field: Validat* *OR* Any Field: Predict* *OR* Any Field: Rule*) *OR* (Any Field: Predict* *AND* Any Field: Outcome* *OR*Any Field: Risk* *OR* Any Field: Model*) *OR* (Any Field: History *OR* Any Field: Variable* *OR* Any Field: Criteria *OR* Any Field: Scor* *OR* Any Field: Characteristic* *OR* Any Field: Finding* *OR* Any Field: Factor*) *AND* (Any Field: Predict* *OR* Any Field: Model*

	_OR_ Any Field: Decision* _OR_ Any Field: Identif*_OR_ Any Field: Prognos*) _OR_ (Any Field: Decision*_AND_ Any Field: Model* _OR_ Any Field: Clinical*) _OR_(Any Field: Prognostic _AND_ Any Field: History _OR_ Any Field: Variable* _OR_ Any Field: Criteria _OR_ Any Field: Scor* _OR_ Any Field: Charcteristic* _OR_ Any Field: Finding* _OR_ Any Field: Factor* _OR_ Any Field: Model*) _OR_ (Any Field: discrimination[tiab] _OR_ Any Field: discriminative[tiab] _OR_ Any Field: discriminatory[tiab]) _AND_ (Any Field: accuracy[tiab] _OR_ Any Field: ability[tiab] _OR_ Any Field: performance[tiab] _OR_ Any Field: value[tiab] _OR_ Any Field: model[tiab] _OR_ Any Field: models[tiab] _OR_ Any Field: power[tiab] _OR_ Any Field: efficiency[tiab]) _OR_ Any Field: "Generalized linear models" [tw] NOT "review" [pt]
Google Scholar	Diabetes AND Gait "Artificial Intelligence" OR machine OR AND OR learning OR deep OR AND OR learning OR "Neural Networks" OR data OR AND OR mining OR "Predictive Value of Tests" OR "Cluster Analysis" -review
IEEE Xplore Digital Library (IEEE)	("All Metadata":"Type 2 Diabetes" OR "All Metadata":"Diabetes" OR "All Metadata":"Diabetic Neuropathies") AND ("All Metadata":"Gait" OR "All Metadata":"Gait Analysis" OR "All Metadata":"Range of Motion" OR "All Metadata":"Walking" OR "All Metadata":"Locomotion") AND ("All Metadata":"Artificial Intelligence" OR "All Metadata":"Machine learning" OR "All Metadata":"Predictive Value of Tests")
Scopus (Elsevier)	ALL (("Diabetes") OR ("Diabetes Mellitus/analysis" OR "Diabetes Mellitus/classification" OR "Diabetes Mellitus/rehabilitation" OR "Diabetes Mellitus/therapy" OR "Diabetes Mellitus, Type 2") OR ("Diabetic") OR ("Diabetic Neuropathies/classification" OR "Diabetic Neuropathies/diagnosis" OR "Diabetic Neuropathies/diagnostic imaging" OR "Diabetic Neuropathies/physiopathology" OR "Diabetic Neuropathies/rehabilitation" OR "Diabetic Neuropathies/statistics AND numerical data" OR "Diabetes Complications" OR "Type 2 Diabetes")) AND ALL (("Gait") OR ("Gait Analysis") OR ("Gait Disorders, Neurologic") OR ("Walking Speed" OR "Walking") OR ("Locomotion") OR "Gait Kinetic*" OR "Gait Kinematic*" OR "range of motion") AND ALL ("Artificial Intelligence" OR machine AND learning OR deep AND learning OR "Neural Networks" OR data AND mining OR "predictive value off tests" OR "Classification" OR "Cluster Analysis" OR "support vector machine" OR "Random Forest" OR "Naive Bayes" OR "Generalized linear models" OR "nearest neighbor*" OR "k nearest neighbor*") AND NOT "Review"
Web of Science (Clarivate Analytics)	(((TS=(("Diabetes") OR ("Diabetes Mellitus/analysis" OR "Diabetes Mellitus/classification" OR "Diabetes Mellitus/rehabilitation" OR "Diabetes Mellitus/therapy" OR "Diabetes Mellitus, Type 2") OR ("Diabetic") OR ("Diabetic Neuropathies/classification" OR "Diabetic Neuropathies/diagnosis" OR "Diabetic Neuropathies/diagnostic imaging" OR "Diabetic Neuropathies/physiopathology" OR "Diabetic Neuropathies/rehabilitation" OR "Diabetic Neuropathies/statistics and numerical data" OR "Diabetes Complications" OR "Type 2 Diabetes" OR "Diabetes, Type 2"))) AND

	TS=(("Gait") OR ("Gait Analysis") OR ("Gait/classification" OR "Gait/instrumentation" OR "Gait/methods" OR "Gait/organization and administration" OR "Gait/physiology" OR "Gait/standards" OR "Gait/statistics and numerical data" OR "Gait/trends") OR ("Gait Disorders, Neurologic") OR ("Walking Speed" OR "Walking") OR ("Locomotion") OR "Gait Kinetic*" OR "Gait Kinematic*" OR "range of motion")) AND TS=("Artificial Intelligence" OR Machine Learning OR Deep learning OR "Neural Networks, Computer" OR data mining OR (machine AND (learn* OR model*)) OR (statistical OR ”statistical-learning”) AND (strateg*) OR multilayer perceptron* OR random forest* OR bayes* network* OR support vector machine* OR nearest neighbor* OR k nearest neighbor* OR elastic net OR naive bayes* OR (classification OR regression OR estimation OR decision) AND tree OR ridge OR kernel OR ensemble OR bagging OR bagged OR boosting OR boosted OR fuzzy OR ("Predictive Value of Tests" OR "Probability Learning" OR "Forecasting" OR “Computing Methodologies” OR “Cluster Analysis”) OR (Validat* OR Predict* OR Rule*) OR (Predict* AND Outcome* OR Risk* OR Model*) OR (History OR Variable* OR Criteria OR Scor* OR Characteristic* OR Finding* OR Factor*) AND (Predict* OR Model* OR Decision* OR Identif* OR Prognos*) OR (Decision* AND Model* OR Clinical*) OR (Prognostic AND History OR Variable* OR Criteria OR Scor* OR Charcteristic* OR Finding* OR Factor* OR Model*) OR (discrimination OR discriminative OR discriminatory) AND (accuracy OR ability OR performance OR value OR model OR models OR power OR efficiency) OR "Generalized linear models")) NOT TS=(Review)

Supplementay Appendix II. TRIPOD Checklist for Reporting Assessment of included studies.

Section/Topic	Item	Deschamps et al., 2016	Caron et al., 2020	Acharya et al., 2012	Corpin et al., 2019
Title and abstract					
Title	1	1	0	2	1
Abstract	2	1	2	1	1
Introduction					
Background and objectives	3a	2	2	2	2
	3b	2	2	0	2
Methods					
Source of data	4a	2	1	2	2
	4b	0	0	0	0
Participants	5a	2	0	2	2
	5b	2	2	2	2
	5c	2	2	2	2
Outcome	6a	2	2	2	2
	6b	0	0	0	0
Predictors	7a	2	2	2	2
	7b	0	0	0	0
Sample size	8	1	0	0	1
Missing data	9	0	0	0	0
Statistical analysis methods	10a	2	2	2	2
	10b	2	2	2	2
	10c	2	2	2	2
	10d	2	1	2	2
	10e	0	1	0	2
Risk groups	11	0	0	0	0
Development vs. validation	12	0	0	2	0
Results					
Participants	13a	0	0	1	2
	13b	2	2	2	2
	13c	2	1	2	2
Model development	14a	2	0	2	0
	14b	1	0	1	0
Model specification	15a	2	2	2	0
	15b	2	2	2	2
Model performance	16	2	2	1	2
Model-updating	17	0	0	0	0
Discussion					
Limitations	18	0	2	0	0
Interpretation	19a	2	2	2	2
	19b	2	2	1	1
Implications	20	2	2	1	1
Other information					
Supplementary information	21	2	0	0	0
Funding	22	2	2	2	2

Supplementay Appendix III. ROB of included studies.

Study	Overall judgement about risk of bias and applicability of the prediction model evaluation	Overall judgement of applicability	Observations
Deschamps et al., 2016	Low	Low	-
Caron et al., 2020	High	High	Risk of bias introduced by selection of participants and the results are not much clear about what should address the importance of EE for patients with Diabetes type 2.
Acharya et al., 2012	High	Low	Risk of bias introduced by selection of participants and inappropriate data sources used.
Corpin et al., 2019	High	Low	Risk of bias introduced by selection of participants.

5.3 Artigo 03: Clusters of patients with diabetes type 2: an exploratory unsupervised machine learning approach based on gait parameters

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ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) is the most prevalent form of diabetes linked to poor glycemic control and impairments in the nervous system that can affect gait and increase the risk of falling. Unsupervised machine learning (ML) can assist in traditional gait analysis by handling large diabetes datasets and identifying early detection insights, reducing diagnosis time and cost and aiding patient treatment. **Objectives:** This study aimed to use unsupervised ML to analyze gait heterogeneity in individuals with and without T2DM and to clarify if there are significant traits in gait performance that can identify and distinguish T2DM patients. **Methods:** 76 participants (T2DM and non-T2DM) over 65 years old from Human Performance Laboratory GAITRite database at Florida International University (FIU) Physical Therapy Department were analyzed using the K-Means algorithm through principal component analysis (PCA) visualizations. Silhouette score was used to evaluate K-Means performance. The clustering groups were statistically analyzed using JASP software (significance level set at $p<0.05$). **Results:** K-Means separated the dataset into two clusters group (PCA silhouette score = 0.47). Velocity, step length and pressure distribution gait patterns were statistically different ($p < 0.05$) between T2DM and non-T2DM. Also, clusters analyses among T2DM participants shown a statistical significance difference ($p < 0.05$) in the pressure distribution patterns. **Conclusions:** Our exploratory analysis using K-Means clustering was able to differentiate T2DM participants based on spatiotemporal gait parameters and plantar pressure distribution. Plantar pressure differences in T2DM data suggests that higher glucose levels, greater probability to present foot deformities changing gait movement. Future work aims to use other ML algorithms to predict T2DM complications and develop tools to assist healthcare professionals in treatment and rehabilitation.

Keywords: Type 2 Diabetes; Gait; Artificial Intelligence; Unsupervised Machine Learning; Clustering Analysis

Introduction

Diabetes is a metabolic disease that affects the secretion or the body's inability to respond to insulin, a hormone that regulates blood sugar levels (JAISWAL et al., 2021; WOO et al., 2021). It is a considerable public health concern, and the number of people affected by it is increasing worldwide (JAISWAL et al., 2021). Type 2 diabetes mellitus (T2DM) is the most prevalent (JIANG et al., 2022). The principal cause of diabetes is unknown and can be influenced by various factors such as genetics, obesity, high cholesterol, high carbohydrate diet, and lack of physical exercise.

Poor glycemic control in T2DM has been linked to the mechanism of damage to the vestibular, somatic, and autonomic nervous systems (PETROFSKY et al., 2005). These impairments seem to slow reflexes and motor control schemes, which may increase the risk of falling (PETROFSKY et al., 2005) and impair gait execution (TRAMONTI et al., 2022). T2DM commonly present a prolonged double support time, decreased gait velocity, and increased support base (TRAMONTI et al., 2022). These gait characteristics can be indicative of abnormal mechanical foot loading during walking that can be due to the inability of the neuromuscular control system to respond to environmental challenges (SAWACHA et al., 2020; TRAMONTI et al., 2022). Thus, quantitative gait function analysis can be a relevant predictor for detecting T2DM gait abnormalities and recognizing postural instabilities.

Traditional gait analysis methods have been challenged by data complexity. Artificial intelligence (AI) techniques, such as machine learning (ML), can overcome this by handling high dimensional, temporal, and complex data. ML have been used in various fields, such as medical diagnosis and pattern recognition (KHERA AND KUMAR, 2020). Among ML applications, unsupervised learning is a powerful tool that can be used to analyze large datasets in healthcare, particularly electronic health records (EHRs). It can help identify new and potentially valuable insights from EHRs that may not be obvious to human analysts (ALANAZI, 2020). Additionally, used to define new risk domains, stratify patients into subgroups with similar characteristics, and facilitate epidemiological analysis and personalized care (WANG et al., 2020).

Diabetic gait refers to changes in walking pattern and posture that increase the risk of falls, injuries, and other complications (TRAMONTI et al., 2022). Early detection of diabetic gait can help healthcare professionals to identify individuals at risk of developing diabetes complications and intervene with appropriate treatments and interventions (GNANASUNDARAM et al., 2020). This can include foot care, physical therapy, and other interventions that can help to prevent or slow the progression of diabetes-related complications. Automated computational prediction methods using machine learning can assist in the early and accurate detection of diabetes, reducing the time and cost of diagnosis (JAISWAL et al., 2021). The use of AI and soft computing techniques in diabetes prediction are a promising area of research and has the potential to assist patients in self-diagnosis.

ML methods have been widely used in diabetes clinical research (HASAN et al., 2020; MUHAMMAD et al., 2020; SILVA et al., 2020). However, a few studies have focused on exploratory analysis using unsupervised ML to distinguish the gait execution heterogeneity of T2DM and non-T2DM participants. Accordingly, we aimed to use unsupervised ML to analyze T2DM and non-T2DM gait parameters to clarify if T2DM patients presents crucial predictors that can be evidenced on gait performance.

Methods

In this section, we present the dataset description. Subsequently, we explain how we analyzed the dataset in this exploratory analysis.

Dataset

The dataset consisted of older adults Hispanics ($\geq$ 65 years) with T2DM and non-T2DM participants (gender and BMI matched) data, respectively, from Vieira et al. (2021) study approved by the Institutional Review Board (IRB-19–0037) and Human Performance Laboratory GAITRite database at Florida International University (FIU) Physical Therapy Department. As this is an exploratory study, no contact was made with the participants.

The exclusion criteria were data from participants' gait movement using assistive devices, no execution at a preferred gait speed, and incomplete clinical information. Finally, after scanning the Human Performance Laboratory GAITRite database, we included 76 participants.

The data collected were:

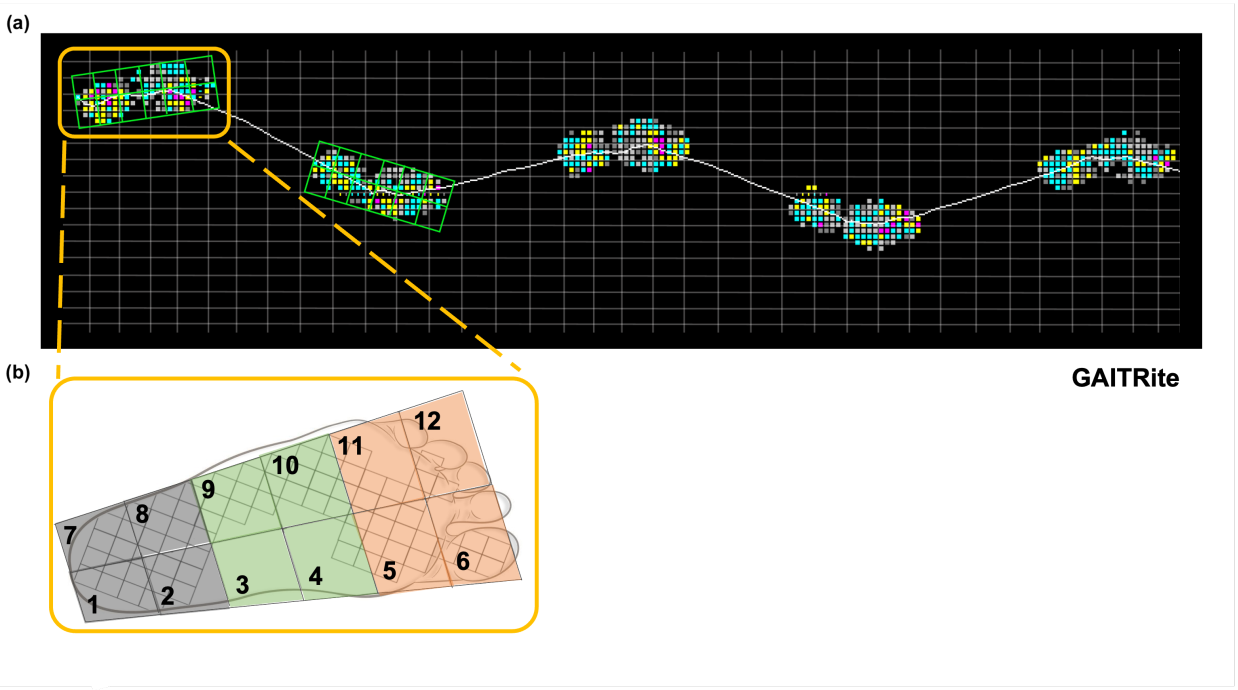
- Anthropometric (i.e., age, gender, and body mass index)
- T2DM participants' clinical information (i.e., glycated hemoglobin, blood glucose, years diagnosed with diabetes, taking the medications, diabetes control)

- Mean spatiotemporal gait parameters (i.e., velocity, cadence, distance, step count, ambulation time, step time and length, laterality differences of step time, step length, and cycle time, stride length, stance time, single and double support time, double support load and unload time)
- Mean plantar pressure distribution (i.e., pressure over time in seconds, pressure peak, time of peak pressure in seconds, the sum of the active sensor's area) of each zone.

GAITRite analysis

Gait data performance was gathered from the mean steps of one preferred gait movement execution on GAITRite. GAITRite is an electronic walkway mat, 4.57 m long, which assesses gait performance from at least three footprints center of heels. The walkway mat consists of grid-arranged 13.824 sensors (1 cm diameter each – active area of 3.66 x 0.61 cm) those can recreate in its software quantitative spatiotemporal parameters and plantar pressure distribution (LEYH AND FEIPEL, 2022). For plantar pressure distribution, once a footprint is detected on the mat, 12 zones are delimited (Figure 5.6) to 4 zones representing the hindfoot, 4 to midfoot, and 4 to the forefoot (Figure 5.6.b).

Figura 5.6 – Plantar pressure distribution detected by GAITRite (a) software and (b) zones of plantar pressure sensors detection, where gray is related to hindfoot (zones 1, 2, 7, and 8), green to midfoot (zones 3, 4, 9, and 10), and orange to forefoot (zones 5, 6, 11, and 12).



Study procedure

Python version 3.9.15 through Jupyter Notebook was used as the programming language in combination with the following libraries: Pandas, NumPy, scikit learn, matplotlib and Plotly. To avoid data bias, the dataset used for this analysis included only anthropometric and gait parameters data.

During the preprocessing step, we observed a different plantar pressure distribution pattern from the side that started to walk on the mat. To overcome this, we flipped the mean pressure distribution of these participants that started from a different side.

We performed pairwise Pearson correlations. The correlation coefficient between two features above 0.8 removed one of the features. Then, the remaining data were normalized using the StandardScaler method. StandardScaler involves rescaling the dataset to all features mean equals zero and standard deviations equal one (THARA et al., 2019).

Once data was normalized, the elbow method developed by Thorndike (IFENTHALER et al., 2023) was applied to find the optimal number of clusters (k) in the dataset (JIANG et al., 2022). The goal of the elbow method is to find the "elbow point" on a graph that represents the trade-off between the number of clusters and the Within Cluster Sum of Squares (WCSS), which measures the similarity of data points within each cluster group. The method is based on the idea that the optimal number of cluster groups is the value of k by finding the inflection point down (YUAN AND YANG, 2019). Overall, the elbow method is a simple and effective technique for determining the optimal number of clusters in a K-Means clustering analysis and is summarized as follows:

Algorithm 1: Elbow Method

```
Input: Gait database after preprocessing step
Output: wcss, $k$
1: wcss = [];
2: for $k = 1$, $k$ in range(1, 10):
3: $d = \sum_{i=1}^{k} \sum dist(x, c_i)^2$
4: return wcss, $k$;
```

After applying the elbow method to ensure the optimal number of clusters (k), we also employed the silhouette score (ROUSSEEUW, 1987). Silhouette score is a less subjective approach that determines the optimal number of cluster groups (YUAN AND YANG, 2019). Once found the optimal number of clusters, we implemented the unsupervised ML algorithm K-Means. K-Means is a clustering algorithm that defines spherical clusters where each cluster is represented by its centroid (mean). The algorithm iteratively assigns each point to the cluster whose centroid is closest and then updates the centroid based on the points assigned to it. The process continues until the assignments no longer change or a maximum number of iterations is reached (LIU AND DENG, 2020). The result is data partition into k clusters, with each cluster group represented by its centroid (Algorithm 2).

Algorithm 2: K-Means clustering algorithm

```
Input: The number of clusters ($k$) and Gait database after preprocessing step
Output: $k$ clusters minimize the squared error criterion
1: An initial clustering centroid (mean) is determined for each cluster;
2: The algorithm iteratively assigns each point to the cluster whose centroid is closest based on the principle of minimum distance;
3: Using the mean of each cluster to update the centroid;
4: Continues step 2 and 3 until the assignments no longer change or a maximum number of iterations is reached;
5: End.
```

The resulting cluster groups can be visualized in a multi-dimensional feature space. To reduce the number of dimensions in the feature space and preserve as many variations in the data as possible, we applied principal component analysis (PCA). PCA makes it easier to visualize the clusters in a lower-dimensional space and understand the underlying structure of the data (JIANG et al., 2022).

We repeated the same exploratory analysis with the T2DM dataset group, including clinical information data. The idea was to observe how unsupervised ML clustering performs among this group. In this analysis, the only difference was that before Pearson's correlations, we applied a one-hot encoding technique in all categorical data from clinical information, such as taking medications and diabetes control. This technique is used for categorical variables to encode these as one numeric array (DAHOUDA AND JOE, 2021).

Data Analysis

Silhouette score was used to evaluate the quality of the K-Means clustering algorithm. After the cluster group identifications, the following features: anthropometric, clinical, and gait characteristics, were compared among the cluster groups. JASP software version (0.16.2; University of Amsterdam) performed all statistical analyses. Continuous variables are expressed as the mean and standard deviation; categorical variables are presented as numbers (%). After the Shapiro-Wilk test to assess normality, cluster group differences were analyzed through a independent t-test or Mann-Whitney. The significance level was set at $p < 0.05$ for all statistical analyses.

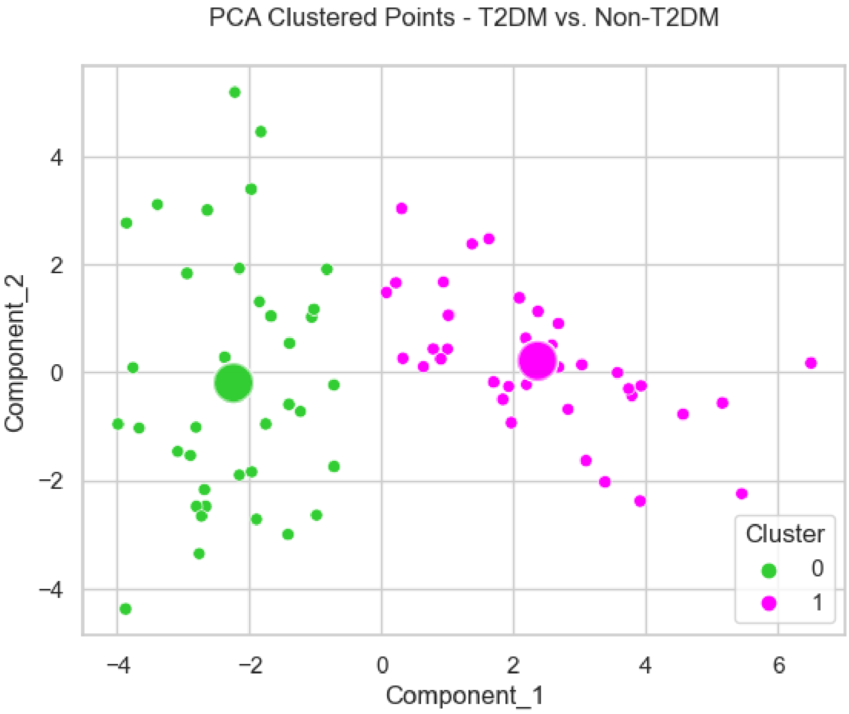
Results

After loading and preprocessing the data, we ended with 76 participants, of which 38 were T2DM (9 males; 78.5 ± 6.64) and 38 non-T2DM (9 males; 74 ± 5.46).

Cluster analysis of the dataset

The elbow method searches to find the number k, assigned 2 clusters, as well as the silhouette score (0.47). These clusters are depicted in the PCA plot in Figure 5.7 where we observed that K-Means algorithms divided the data points according to cluster group 1 (magenta color equals zero) and cluster group 2 (green color equals one).

Figura 5.7 – Cluster groups formed after a principal component analysis (PCA) plot with two principal components. Data points are divided into two clusters, where zero represents cluster group 1 and one cluster group 2.



From 69 parameters (anthropometric, spatiotemporal and pressure distribution) evaluated, the K-Means analysis identified two subgroups named cluster group 1 (n = 37) and cluster group 2 (n = 39). Based on our raw data, we saw that all participants of cluster group 1 present T2DM, and the majority of cluster group 2 participants are non-T2DM (only one T2DM presented in this group). The main characteristics of the participants in the two cluster groups are shown in Table 5.3 and Figure 5.8.

Tabela 5.3 – Comparison of the two cluster characteristics after K-Means applied.

	Cluster 1 - T2DM (n = 37)	**Cluster 2 - non-T2DM** (n = 39)	**P value**
M / F (n)	8 / 29	10 / 29	-
Age (yr)	78.43 (± 6.73)	74.15 (± 5.47)	0.700
BMI (kg/m^2)	30.23 (± 5.46)	28.56 (± 5.63)	0.195
Velocity (cm/s)	80.61 (± 24.10)	99.17 (± 25.45)	0.002*
Step count (n)	9.62 (± 3.81)	7.85 (± 2.43)	0.003*
Step Length (cm)	47.74 (± 9.55)	55.20 (± 9.98)	0.001*
Step time (s)	0.62 (± 0.09)	0.57 (± 0.08)	0.016*
Cycle Time (s)	1.23 (± 0.17)	1.14 (± 0.15)	0.023*
Base of Support Preferred (cm)	11.06 (± 3.57)	10.29 (± 3.96)	0.506
P*t – zone 1 (%)	3.35 (± 2.25)	8.52 (± 10.15)	< 0.001**
P*t – zone 2 (%)	14.06 (± 2.90)	10.57 (± 3.28)	< 0.001**
P*t – zone 3 (%)	11.56 (± 5.20)	4.57 (± 3.93)	< 0.001**
P*t – zone 4 (%)	4.33 (± 3.49)	12.66 (± 5.18)	< 0.001**
P*t – zone 5 (%)	19.70 (± 4.65)	14.36 (± 3.31)	< 0.001**
P*t – zone 6 (%)	14.33 (± 7.12)	3.02 (± 1.64)	< 0.001**
P*t – zone 7 (%)	10.02 (± 5.53)	7.81 (± 3.65)	0.042*
P*t – zone 8 (%)	30.33 (± 5.97)	11.06 (± 3.27)	< 0.001**
P*t – zone 9 (%)	7.80 (± 4.60)	3.54 (± 5.13)	< 0.001**
P*t – zone 10 (%)	2.47 (± 2.27)	7.44 (± 4.91)	< 0.001**
P*t – zone 11 (%)	10.48 (± 2.98)	13.38 (± 3.79)	< 0.001**
P*t – zone 12 (%)	8.84 (± 4.27)	4.88 (± 2.86)	< 0.001**

T2DM: type 2 diabetes mellitus; M: male; F: female; BMI: body mass index; P*t: Pressure over time.
*Indicates that the difference between the two groups is statistically significant with $p < 0.05$.
**Indicates that the difference between the two groups is statistically significant with $p < 0.001$.

Cluster analysis of the T2DM group

According to the elbow method, the optimal number of clusters suggested k were 2. The highest silhouette score (0.35) was also with k equal to 2. PCA plots of these clusters are shown in Figure 5.9.

After correlation, 78 T2DM parameters (anthropometric, clinical information, spatio-temporal and pressure distribution) were evaluated by K-Means analysis. The unsupervised ML divided cluster group 1 (n= 13) and cluster group 2 (n = 25). The main characteristics of the two cluster groups are shown in Table 5.4 and Figure 5.10.

Discussion

This study utilized an unsupervised ML approach to investigate participants with T2DM and those without T2DM, as well as subgroups of T2DM with varying clinical characteristics. Unsupervised ML for clustering does not rely on manual judgement. Unsuper-

Figura 5.8 – Spatiotemporal characteristics of participants among the two clustering groups. (a) boxplot of the gait velocity (cm/s) of each cluster group; (b) boxplot of the step length (cm) of each cluster group; (c) boxplot of the number of steps of each cluster group; (d) boxplot of gait cycle time (s) of each cluster group. (e) Map of statistical differences between clusters group of plantar pressure distribution over time (%) in the 12 zones delimited by GAITRite.

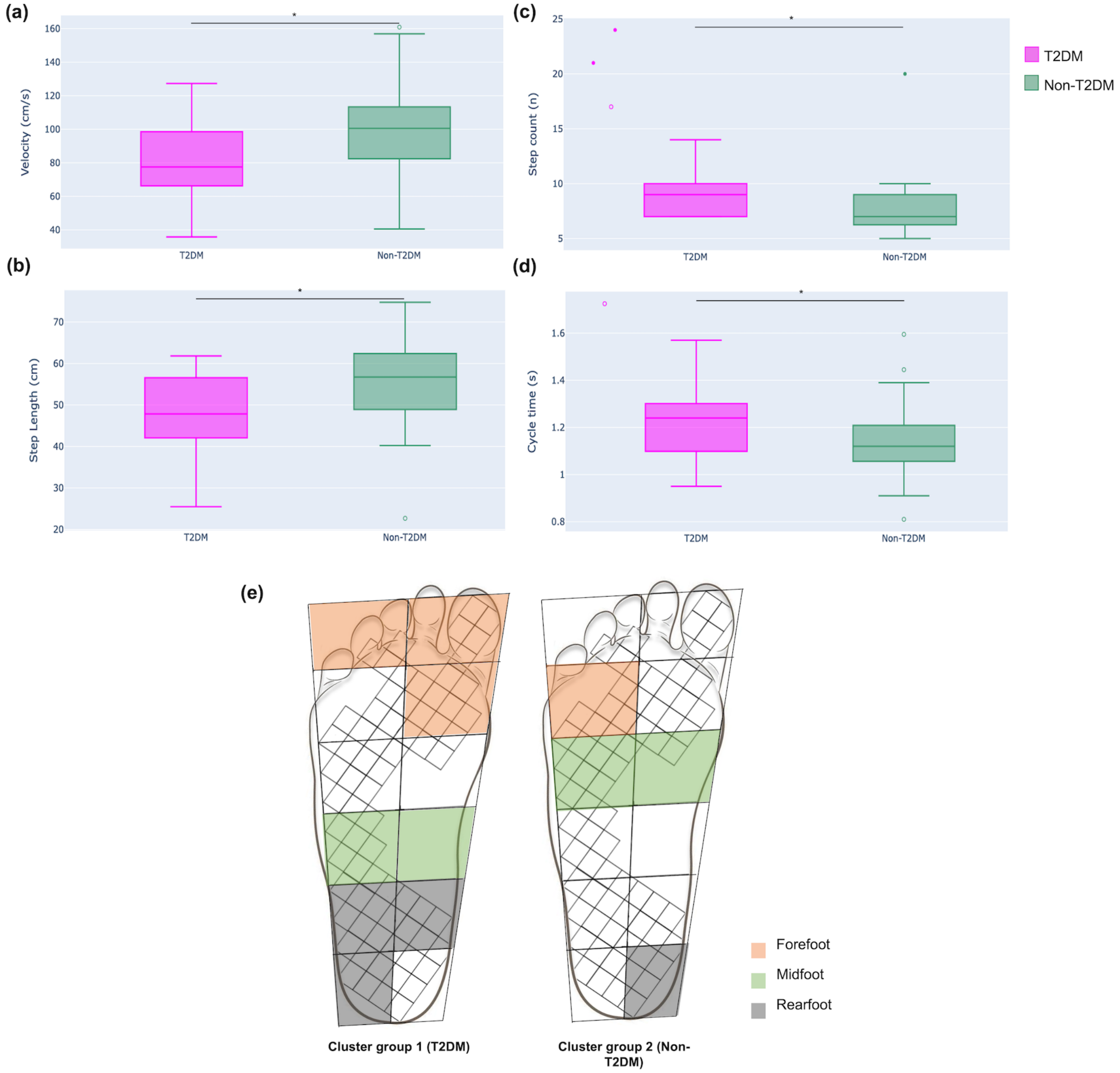


Figura 5.9 – K-Means algorithms divided the data points in cluster group 1 (magenta color equal one) and cluster group 2 (green color equal zero).

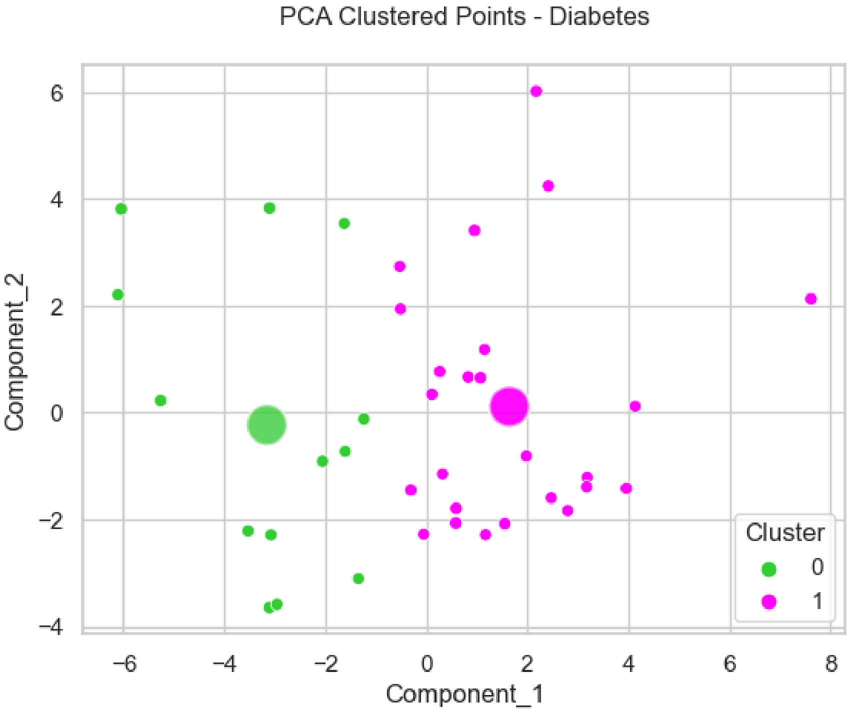


Figura 5.10 – Plantar pressure differences between the two clustering groups of T2DM individuals after statistics analysis. Map of plantar pressure distribution over time (%) of cluster group 1 and cluster group 2.

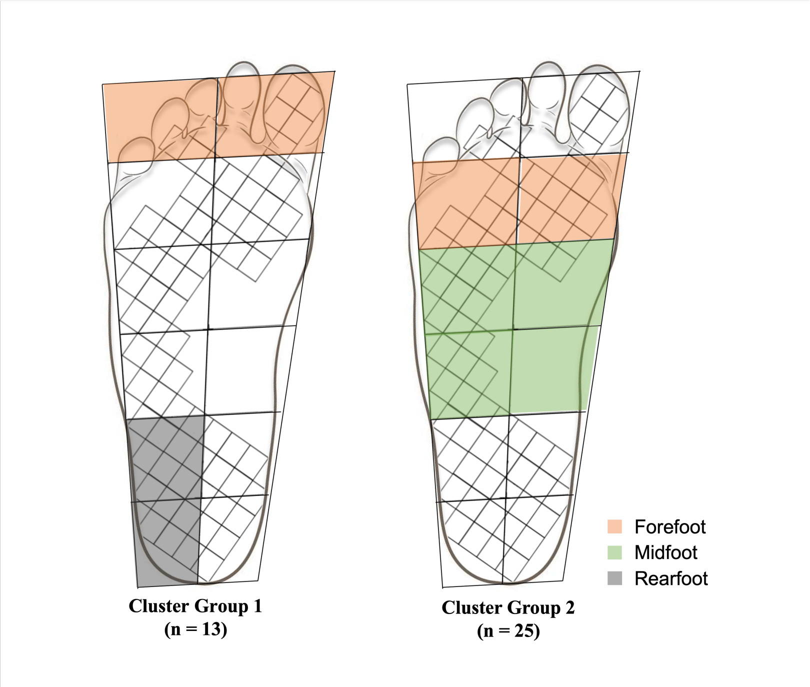


Tabela 5.4 – The two cluster characteristics after K-Means applied in T2DM participants.

	Cluster 1 (n = 13)	**Cluster 2** (n = 25)	**P value**
M / F (n)	0 / 13	9 / 16	-
Age (yr)	79.69 (± 6.38)	77.84 (± 6.81)	0.422
BMI (kg/m^2)	28.92 (± 5.22)	31.35 (± 5.82)	0.214
HbA1c (%)	6.64 (± 0.84)	7.14 (± 0.82)	0.081
Fasting Blood Sugar Test (mg/dL)	110.29 (± 22.92)	153.56 (± 48.52)	0.005*
Time from clinical diagnosis (yr)	11.92 (± 6.20)	19.08 (± 14.85)	0.212
Velocity (cm/s)	73.67 (± 28.53)	84.33 (± 20.51)	0.193
Step count (n)	10.92 (± 4.25)	8.88 (± 3.37)	0.081
Step Length (cm)	43.40 (± 11.93)	50.10 (± 7.07)	0.036*
Cycle Time (s)	1.25 (± 0.21)	1.22 (± 0.16)	0.634
Base of Support Preferred (cm)	10.06 (± 3.52)	11.80 (± 3.61)	0.163
P*t – zone 1 (%)	4.10 (± 2.21)	2.84 (± 2.21)	0.062
P*t – zone 2 (%)	14.99 (± 3.53)	13.32 (± 2.65)	0.109
P*t – zone 3 (%)	8.60 (± 4.23)	13.01 (± 4.98)	0.010*
P*t – zone 4 (%)	2.83 (± 3.01)	5.30 (± 3.54)	0.019*
P*t – zone 5 (%)	17.42 (± 4.29)	20.79 (± 4.39)	0.030*
P*t – zone 6 (%)	19.39 (± 8.55)	11.26 (± 4.53)	< 0.001**
P*t – zone 7 (%)	12.56 (± 5.05)	8.36 (± 5.46)	0.027*
P*t – zone 8 (%)	32.97 (± 6.80)	28.56 (± 5.23)	0.032*
P*t – zone 9 (%)	5.86 (± 4.01)	9.29 (± 5.06)	0.049*
P*t – zone 10 (%)	1.45 (± 1.67)	3.58 (± 3.68)	0.029*
P*t – zone 11 (%)	9.03 (± 1.74)	11.27 (± 3.18)	0.348
P*t – zone 12 (%)	11.98 (± 3.87)	6.98 (± 3.49)	0.002*

T2DM: type 2 diabetes mellitus; M: male; F: female; BMI: body mass index; HbA1c: glycated hemoglobin; P*t: Pressure over time.
*Indicates that the difference between the two groups is statistically significant with $p < 0.05$.
**Indicates that the difference between the two groups is statistically significant with $p < 0.001$.

vised learning allows for the integration of various data sources finding similarities without predetermined specifications (IPARRAGUIRRE-VILLANUEVA et al., 2022; JIANG et al., 2022). Due to this, K-Means clustering method applied could distinguish all participants in two groups, one of them with T2DM clinical gait spatiotemporal and pressure distribution characteristics and other without T2DM characteristics. Repeating the same process only with T2DM data, we could observe two clustering groups majority distinguished by gait plantar pressure distribution. Our results suggest that this method can effectively handle diverse clinical data and has the potential to differentiate subgroups mainly based on gait execution.

In the first part of our study, our main findings showed velocity, step length, step time, step count, and cycle time as the most significant spatiotemporal gait characteristics to distinguish the groups. Following our results, Ko et al. (2011) have already mentioned about slower gait speed of diabetic patients compared to an age-gender-matched group. To them, the slower gait speed in the diabetic group is caused by increasing step time. This cautiousness in the walking pattern may be regulated by adapting spatiotemporal gait variables such as step time, cadence, or increased double support time during gait execution.

Patients with diabetes have been shown to have alterations in their natural walking strategy, including a slower walking speed, and reduced joint range of movement, even before the onset of measurable diabetic peripheral neuropathy (DPN) (REEVES et al., 2021). Flexion reduction of the lower limb joints also diminishes the leverage of the ground reaction force around the specific joint, lowering the joint moment and the muscular forces required to create and control movement at the joint (REEVES et al., 2021; TRAMONTI et al., 2022). This includes a slower self-selected walking speed and shorter step and stride length compared to non-diabetic controls (REEVES et al., 2021). As observed in the literature, our results with unsupervised ML analysis showed that T2DM gait could present remarkable characteristics compared to non-T2DM.

Further, we saw different plantar pressure distribution patterns regarding the two clusters of all participants analyzed. Plantar pressure has long been identified as a risk factor for ulceration in diabetes, but the exact threshold value at which diabetic skin breaks down to form an ulcer is still uncertain (PERREN et al., 2021). Studies have shown an imbalance in pressure distribution between the forefoot and rear foot during walking in persons with diabetes with higher plantar pressure peak in the forefoot (II-IV metatarsal heads), where most skin breakdown occurs (KO et al., 2011; SUTKOWSKA et al., 2019). This is likely due to the considerable mechanical stresses applied to the metatarsal heads and the great toe necessary for generating a propulsive force during a normal gait cycle (KO et al., 2011). Also, the time of illness increases peak plantar pressure at the center of the forefoot before any ulceration is exhibited (PERREN et al., 2021). Endorsed by the literature, in our study, we could see that three out of four sensors' mean pressure over time of the rear and forefoot are statistically higher in the T2DM cluster group.

The changes in the pattern mainly of plantar forefoot pressure distribution may be suggestive feature of diabetics' complications (KO et al., 2011; SUTKOWSKA et al., 2019). As we observed in the second part of our study, clustering analysis among T2DM patients shown a significance difference of pressure over time with highest values among sensors number 5 and 10 (related to I-IV metatarsal heads) in the cluster group 2. This same group presented a highest statically significant fasting blood sugar test value and midfoot pressure over time values (sensors 3, 4, 9, and 10).

Midfoot pressure pattern in diabetic patients was also observed by Ko et al. (2011) and Halawa et al. (2018). According to them, this pattern limits the anterior-posterior excursion for the center of force under the foot from initial contact to toe-off during the stance phase resulting in compensatory musculoskeletal mechanisms altering foot rollover. Thus, changes in foot mechanics may lead to deformities, which is one of the DPN characteristics (SINACORE et al., 2008; JEONG et al., 2021). Based on the literature and our findings, we can infer that even among T2DM participants, there are gait plantar pressure differences. So, early detection of uneven plantar pressure distribution in individuals with T2DM has great clinical significance in the preventive aspect of diabetic neuropathic ulcers (GNANASUNDARAM et al., 2020).

Hospitalization of diabetic patients is more likely to be caused by foot disease than any other complication (PERREN et al., 2021). High plantar pressures have been identified as a key factor in the development of diabetic foot ulceration (KO et al., 2011; PERREN et al., 2021), which is a common complication of diabetes and can lead to lower limb amputation. Our study used ML to analyze gait patterns in T2DM and non-T2DM individuals and those among T2DM. ML algorithms, combined with dynamic plantar pressure analysis, identify patterns in the data that differed from individual normality trends (ALANAZI, 2020; GNANASUNDARAM et al., 2020). This technology shows potential in improving the early detection of diabetic neuropathy and enabling more personalized treatment for diabetic individuals. However, further research is needed to validate and refine this approach before it can be widely used in clinical settings.

Conclusion

Our exploratory analysis has shown that K-Means clustering could distinguish T2DM among distinct participants based on velocity, step length, step time, step count, and cycle time spatiotemporal gait parameters and forefoot and rear foot plantar pressure distribution. Upon analyzing the T2DM data exclusively, we observed differences in plantar pressure distribution, suggesting that higher glucose levels increase the likelihood of foot deformities, which in turn lead to biomechanical changes in gait movement. In future work, we aim to apply other ML algorithms to predict T2DM complications and develop tools to aid healthcare professionals in providing appropriate treatment and rehabilitation.

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5.4 Artigo 04: Machine learning-based on type 2 diabetes detection using spatiotemporal and pressure distribution gait parameters

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ABSTRACT

Introduction: Diabetes is a metabolic disease caused by insulin secretion or action dysfunction resulting in hyperglycemia. Type 2 diabetes mellitus (T2DM) is the most common. Long-term diabetes biomechanics alteration leads to foot ulceration and amputation of the lower limb. New approaches using Machine Learning (ML) have been growing in the literature to predict T2DM. **Objectives:** To identify gait parameters to distinguish T2DM from non-T2DM using ML classifier algorithms. **Methods:** 38 T2DM participants (9 males) aged (78.6 ± 6.67) and 38 aged-matched non-T2DM (9 males) aged (74 ± 5.46) from Human Performance Laboratory GAITRite database at Florida International University (FIU), Physical Therapy Department. The dataset included anthropometric data and spatiotemporal and plantar pressure distribution gait data. Python language, through Jupyter Notebook, was used to implement ML algorithms. Wrapper and univariate feature selection methods were applied. ML performance evaluation metrics were calculated based on the confusion matrix. **Results:** The wrapper method for feature selection showed that the DT classifier achieved the same performance metrics results as RF and LDA but required the least number of features (93). By the univariate method, the LR algorithm outperformed, achieving the highest accuracy (87%), precision (1.0), F1-score (0.82), and AUC (0.85). The most important predictor for detecting T2DM was the heel plantar pressure distribution. **Conclusions:** ML classifiers could detect T2DM from pressure gait distribution on the heel with high sensitivity, but more external validation is needed.

Keywords: Gait; Pressure Distribution; Diabetes; Artificial Intelligence; Machine Learning

1. Introduction

Diabetes is characterized as a metabolic disease generated by a dysfunction in in insulin secretion and/or action, resulting in hyperglycemia (RODEN; SHULMAN, 2019). Diabetes is a worldwide health concern; type 2 diabetes mellitus (T2DM) is the most common (MOURA DA SILVA et al. 2022). In severe cases of T2DM, patients can present blood vessel degeneration that can evolve into neuropathy and damage somatosensory nerve fibers (HUANG et al., 2019).

Diabetic neuropathy alters the physical function and mobility in distal muscles, especially in the lower limbs, interfering the gait performance (HAQUE et al., 2022). Due to the changes in biomechanics during gait, a patient increases support base (i.e., longer gait stance time) and shorter steps, which may exhibit slower gait speeds and increased cadence (KIRKWOOD et al., 2019). In addition, sensibility changes in the foot plantar surface can worsen plantar pressure distribution, kinematic patterns, ground reaction forces, muscle activities, and balance (HUANG et al., 2019; HAQUE et al., 2022). Long-term diabetes biomechanics alteration leads to foot ulceration and, in worsening cases, amputation of the lower limb (HAQUE et al., 2022). Most diabetes foot ulcers are associated with diabetic peripheral neuropathy (DPN) (MOULAEI et al., 2021).

Boosting insight into diabetic mobility alterations such as gait can be important for preventing complications and developing strategies to guide treatments to avoid DPN (TRAMONTI et al., 2022). Despite a significant number of guidelines for preventing T2DM complications (TODAY STUDY GROUP, 2021), the gold standard is still based on clinical evaluation, which includes several subjective factors (MUNDT et al., 2020). Subjective methods can impair decision-making to address a specific treatment (ROBERTS et al., 2017). On the other hand, objective methods are accurate and cost-effective owing to quantitative metric results (MOURA DA SILVA et al., 2022).

In clinical practice, quantitative gait analysis can identify pathologies, track disease progression, and measure the effectiveness of interventions (SLINDEMANN et al., 2020). High-tech gait analysis methods such as 3-D motion capture, electronic walkways, and body-fixed sensors provide a wide range of gait parameters (SLINDEMANN et al., 2020). The choice of which parameters to focus on relies on the clinical or research question, the patient or participant, and the study context. Gait kinematic analysis tools depict spatiotemporal parameters without considering the forces involved in motion (CALDAS et al., 2020) . When movement forces are the focus, like ground reaction force (GRF) is known as gait kinetic analysis (CALDAS et al., 2020). Among different objective gait assessment tools, the GAITRite system is a useful tool; applied to evaluate kinematic and kinetic gait in a clinical setting (LEYH AND FEIPEL, 2022).

Further, new approaches to evaluating objective methods have been growing, one of which is Machine Learning (ML) (JAISWAL et al., 2021). In the literature, most studies using ML in diabetes are related to balance assessment, detection of glucose levels and the presence of retinopathy (REN et al., 2020), with little focus on gait. This ability is pointed out as one of the main factors for preventing falls in diabetic patients, with recovery being an important aspect (ALLET et al., 2008). Characterizing gait executions throughout the progression of the disease using ML becomes a viable alternative since the predictive capacity of ML can direct adequate training before the disease advances to more severe stages, as in DPN.

Therefore, the objective of this work is to contribute to the state-of-the-art focus on the ML-based classification technique through spatiotemporal and plantar pressure distribution data from GAITRite to detect TD2M. As per our knowledge, this is the first ML-based work to classify TD2M patients using GAITRite data during gait. Specifically, we aimed to identify suitable gait parameters that can better i) distinguish TD2M from gender and body mass index (BMI) matched non-T2DM individuals and ii) identify gait features that are important to detect TD2M and possibly forecast complications.

2. Materials and method

2.1. Dataset description

Thirty-eight older Hispanics ($\geq$ 65 years old) with T2DM from Vieira et al. (2021),approved by the Institutional Review Board (IRB-19–0037), were considered in the current study. We used the data from all participants that completed the baseline assessments. In addition to the T2DM cohort, were considered 38 gender- and BMI-matched non-T2DM individuals from Human Performance Laboratory GAITRite database at FIU Physical Therapy Department. The demographic and clinical details of the participants are shown in Table 5.5.

The dataset included anthropometric data, such as age, gender, and body mass index (BMI – kg/m^2). In addition, the year of diabetes onset, blood glucose and glycated hemoglobin (HbA1c) as explained in Vieira et al. (2021) study. In addition, we included data from gait assessment through GAITRite. We excluded data from individuals unable to perform gait movement due to medical issues or physical limitations, to have lower limb amputations or use gait assistive devices. Supplement Material 1 shows the gait features extracted from the dataset.

Tabela 5.5 – Demographic and clinical characteristics (means ± standard deviations) of the study's participants.

	T2DM (n=38)	**Non-T2DM (n=38)**	p-value
M/F (n)	9/29	9/29	1.00
Age (yr)	78.5 (± 6.64)	74 (± 5.46)	0.004*
BMI (kg/m^2)	30.7 (± 5.65)	28.23 (± 5.30)	0.088
HbA1c	6.93 (± 0.83)	-	-
Time from clinical diagnosis (yr)	17 (± 12.91)	-	-

T2DM: type 2 diabetes mellitus; M: male; F: female; BMI: body mass index.
*Indicates that the difference between the two groups is statistically significant with $p < 0.05$.

2.2. Gait analysis

Gait performance data were acquired by the GAITRite system (Q209, CIR Systems Inc.). GAITRite consists of a mat (61 X 366 cm) with centralized 1.27 cm sensors arranged in a grid pattern, activated by mechanical pressure. These sensors capture the plantar pressure along each step and trace the spatiotemporal information of gait execution and send the results to its software (MCDONOUGH et al., 2001). The GAITRite system measures have high concurrent validity (ICC = 0.91–0.99) of speed, cadence, step length, and step time (WEBSTER et al., 2005). GAITRite system also presents reliability of repeated measures of single and double support times (ICC = 0.85-0.93) (BILNEY et al., 2003). The system divides each footprint into 12 zones (6 lateral and 6 medial; totaling 4 zones for hindfoot, 4 for midfoot, and 4 for forefoot) and analyzes the pressure in each zone. The analysis includes the pressure peak (Peak), pressure over time (P*t), time of peak pressure in seconds (PeakTime), and the sum of the active sensor's area (Area).

In our study, all participant's data was from gait at a preferred speed without any assistive device that could interfere with the performance and data collection. To maintain the same number of steps for all participants we used data from the second to the sixth step.

2.3. Machine learning

2.3.1. Feature selection and classification

The studied ML algorithms were implemented using the Python programming language on the Jupyter Notebook environment (3.9.15 version). Jupyter Notebook is multiplatform software that can run and download on several operating systems and software distributions, respectively (ANSELIN AND REY, 2022). The used library packages were scikit-learn for the supervised ML algorithms, NumPy and pandas for data operations and mathematical computations, and matplotlib and seaborn for graph plotting.

The preprocessing step consisted of cleaning the data first. Missing data (null values) was imputed with the feature column's mean. Further, columns that all or majority of values equal to zero were removed from the dataset, such as data from sensors' midfoot pressure distribution (sensors 3, 10, and 11).

Many features may confuse the model adding computational complexity to the ML models. Thus, feature selections allowed further dimensionality reduction, which is the process of finding relevant and independent degrees of freedom in the dataset. We used two methods of feature selection wrapper and univariate. The first step of feature selection on the training set was performed based on Recurse Feature Elimination (RFE). RFE is a wrapper method that removes redundant and least relevant features according to accuracy score seeking to improve target feature prediction (ARTUR, 2021). RFE technique with Random Forest (RF) was used to select the optimal number of features. The univariate selection method considers each feature individually; however, it does not capture redundancy among features (GHIMATGAR et al., 2018). SelectKBest method selects a fixed k number of features that, based on the test f_classif, the feature selection using ANOVA-F measure a threshold and discards higher p-value (SIDHAWARA et al., 2020). In both methods, we fixed the number of features to select a quarter, one-third, one-half, two-thirds, and three-quarters from the total number of features in the dataset. After that, based on their contribution to the classification accuracy, we selected the optimal number. Therefore, we used these five subsets to apply the ML classifier algorithms.

After feature selection process, the data were randomly split into 80–20% as training and testing sets, respectively. The selected features from the training dataset were used as inputs for the ML classification algorithms, followed by feature normalization using StandardScaler. This normalization consists in subtracting the feature value from the mean and then dividing all the values by the standard deviation, making the mean of the distribution approximately zero and the variance equal to 1 (THARA et al., 2019).

The classifier algorithms were selected after applying the Lazy Predict package. Lazy Predict is an MIT-licensed package that compares the performance of distinct algorithm and select the best ones without any parameter tuning (see documentation: <https://lazypredict.readthedocs.io/en/latest/index.html>). Then, the ML algorithms employed were: Random Forest (RF), Support Vector Machine (SVM), Linear Discriminant Analysis (LDA), Logistic Regression (LR), Decision Tree (DT), Multilayer Perceptron (MLP), and Naïve Bayes (NB).

Before the learning process, we set the hyperparameter for each classifier algorithm using grid search. This method can examine the best subset of hyperparameters from a list of parameters determined for each classifier algorithm (BUTTAN et al., 2021). From hyperparameters tuning, after a 10-fold cross-validation method, we obtained the optimum feature numbers for each ML algorithm deriving from the highest performance metric (e.g., accuracy and area under the curve). We also estimated the feature importance using RF classifier. Figure 5.11 illustrates the flowchart of the data preprocessing, feature selection, and ML classifier model performance analysis.

Figura 5.11 – Flow chart of the data preprocessing, feature selection, and ML classifier models performance analysis for T2DM patients' and non-T2DM.

2.3.2. Classification evaluation

The performance metrics of the ML classifier algorithms, employed in this study, were carried out through the analysis of several metrics, such as accuracy, precision, recall, F1-score, and area under the receiver operating characteristic curve (AUC). These metrics are based on the confusion matrix (CM), one of the most used measures in classification problems. It showcases the predicted class versus the actual in the dataset. Our binary classifications problems were described as follows:

- True positive (TP): True T2DM participants diagnosed and defined by Vieira et al. (2021) study.
- True negative (TN): True non-T2DM participants
- False-positive (FP): Non-T2DM participants, classified as T2DM

- False-negative (FN): T2DM participants, classified as a non-T2DM

Accuracy is one of the most used evaluation metrics. It refers to the number of correct predictions (TP and TN) divided by the total number of positive and negative predictions (equation 5.1). It generally quantifies the overall ML model performance regardless of the class (RASCHKA, 2015).

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN} \tag{5.1}$$

Precision is the number of correct predictions (TP) from the total number of predictions in that same class (equation 5.2). It is the frequency of positive predictions (DANGETI, 2017; GÉRON, 2019).

$$Precision = \frac{TP}{TP + FP} \tag{5.2}$$

Recall or sensitivity represents the number of subjects correctly classified as positive (TP) among all that were labelled as positive (equation 5.3). It is the proportion of positive frequencies that are detected correctly by the classifier (LIU et al., 2019; GÉRON, 2019).

$$Recall\ or\ Sensitivity = \frac{TP}{TP + FN} \tag{5.3}$$

F1-score is a statistical metric that measures the harmonic mean between recall and precision values (equation 5.4) (GÉRON, 2019). It considers both recall and precision as equally important measures. F1-score indicates the overall model quality and how balanced the model is between these two metrics (LIU et al., 2019).

$$F1 - score = \frac{2TP}{2TP + FP + FN} \tag{5.4}$$

When comparing ML models, the area under the receiver operating characteristic curve (AUC) indicates the overall performance of a classifier (FERREIRA et al., 2021).

3. Results

The optimized hyperparameters of the studied ML classifier algorithms achieved by grid search are indicated in the Supplemental Material 2. After training seven different ML algorithms (Tabele 5.6), we found in the wrapper method that RF, LDA, and DT classifiers achieved the same performance metric result. However, the later classifier required the least optimum number of features (93) with 83% accuracy, 0.75 precision, 0.9 recall, 0.82 f1-score, and 0.8346 AUC. Although the MLP classifier achieved the same accuracy as DT (83%), it resulted in the highest precision (0.8) and lower recall (0.8), f1-score (0.8), and AUC (0.823).

Using the univariate method for feature selection, we observed that the LR model outperformed (Table 5.6). The LR algorithm performed with the optimum number of features equal to ninety-three, achieving accuracy (87%), precision (1.0), F1-score (0.82), and AUC (0.85). However, this algorithm classifier achieved the lowest recall (0.7) value compared to the other ML algorithms classifiers. Supplementary Material 3 shows the confusion matrix performance values obtained by the studied ML classifier algorithms in terms of TP, FP, FN, and TN.

Figure 5.12 shows the ranked feature importance of the RF classifier in T2DM classification. This classifier chose a total of ten features, and the three most important features were the time of peak pressure distribution over the heel region (zones 1, 2, and 8) during gait movement on the GAITRite mat.

Figura 5.12 – Feature importance. (a) Top-ranked features importance found as to the Random Forest classifier; (b) GAITRite plantar pressure distribution zones graphical map of the three most important features on the heel region (zones 1, 2, and 8 in grey).

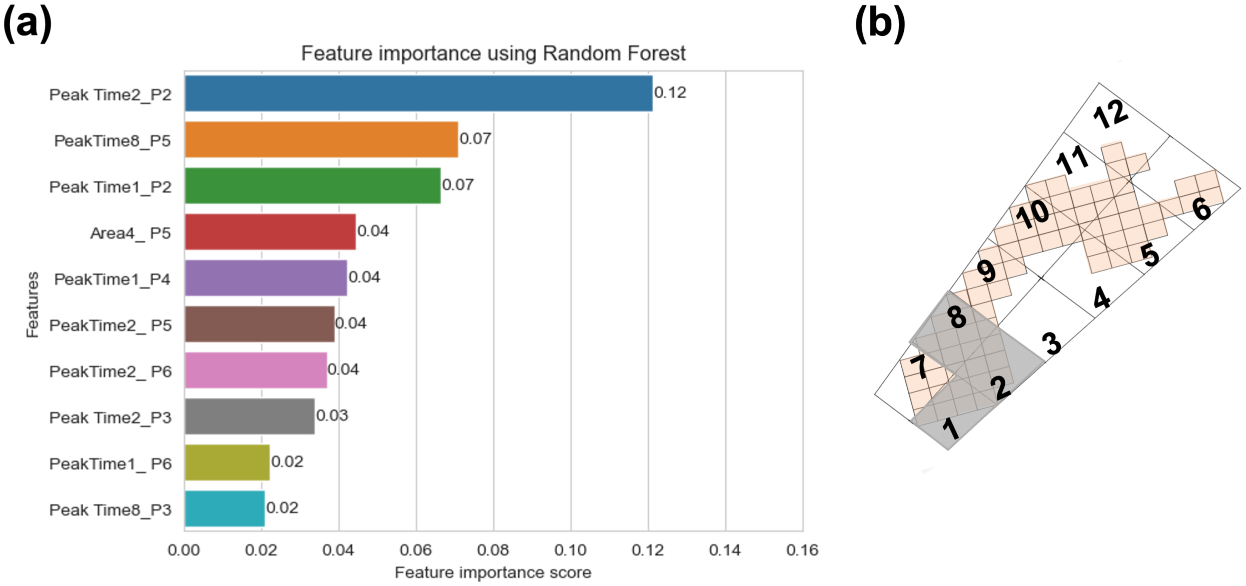

Tabela 5.6 – Performance values obtained by the ML algorithms studied trained on the found optimum number of features. These values are referred to distinguish type 2 diabetes mellitus (T2DM) patients from non-T2DM in the training set.

Algorithms	Feature Selection	Number of features	Accuracy (%)	Precision	Recall	F1-score	AUC
RF	RFE	186	83	0.75	0.9	0.82	0.835
	SelectKBest	93	74	0.64	0.9	0.75	0.758
SVM-RBF	RFE	93	78	0.69	0.9	0.78	0.796
	SelectKBest	93	83	0.75	0.9	0.82	0.835
LDA	RFE	186	83	0.75	0.9	0.82	0.835
	SelectKBest	248	83	0.75	0.9	0.82	0.835
LR	RFE	186	78	0.69	0.9	0.78	0.796
	SelectKBest	93	87	1	0.7	0.82	0.85
DT	RFE	93	83	0.75	0.9	0.82	0.835
	SelectKBest	186	83	0.75	0.9	0.82	0.835
MLP	RFE	93	83	0.8	0.8	0.8	0.823
	SelectKBest	279	83	0.75	0.9	0.82	0.835
NB	RFE	93	78	0.69	0.9	0.78	0.796
	SelectKBest	248	83	0.75	0.9	0.82	0.835

T2DM: Type 2 Diabetes Mellitus; RFE: Recurse Feature Eliminatio; AUC: Area Under the Receiver operating characteristic curve; RF: Random Forest; SVM: Support Vector Machine; RBF: Radial Basis Function Kernel; LDA: Linear Discriminant Analysis; LR: Logistic Regression; DT: Decision Tree; MLP: Multilayer Perceptron; NB: Naïve Bayes.

4. Discussion

In this study, we dealt with two class problems using ML algorithms to classify T2DM patients from non-T2DM individuals using spatiotemporal and plantar pressure distribution gait parameters. We used two different methods of feature selection. Among all seven classifiers analyzed, we observed that T2DM detection could be best achieved by DT using the wrapper method and LR using the univariate method. Overall, we found that hindfoot plantar pressure distribution was an influential feature parameter classify T2DM patients from non-T2DM.

In the literature, the vast majority of studies using ML classifiers in diabetes are related to balance assessment, detection of glucose levels and the presence of retinopathy (REN et al., 2020), with little focus on the execution of the gait. This ability is pointed out as one of the main factors for preventing falls, with recovery being an important aspect (BAKER, 2018). From our results in the performance metrics, the LR classifier achieved the lowest sensitivity amongst the other ML classifiers meaning that it may fail to classify real T2DM participants from non-T2DM. Although overall metrics slightly underperformed, RF, LDA and DT classifiers presented a better sensitivity (90%) metric showing that it may be more efficient in classifying real T2DM patients from non-T2DM. Rehman et al. (2019) reinforced the importance of prioritizing high sensitivity to minimize the risk of misdiagnosis. Different from our results, Brotos et al. (2016) worked with an SVM classifier on dynamic plantar pressure distribution data in insoles and achieved a sensitivity of 96% in classifying diabetic patients from healthy individuals. Despite positive results and great clinical potential, Brotos et al. (2016) performed only one ML classifier in three binary classifications.

Our study has shown impairment in the heel plantar pressure distribution, without any foot deformity, as the most important predictor for detecting T2DM from non-T2DM. Diabetic patients may increase plantar pressure distribution in the heel region due to increased double support phase, bone changes, and reduced plantar arches (GNANASUNDARAM et al., 2020). Under high pressure due to repetitive movement during walking, diabetic skin reduces hyperemic response failing blood flow recovery between footsteps (RATHUR AND BOULTON, 2007). Studies also have noted that foot deformities in T2DM can lead to increased plantar pressure in some areas of the plantar side (JI et al., 2020), where advanced stages demonstrated higher heel loads compared to early stages of diabetes (SACCO et al., 2014).

Nowadays, ML in healthcare systems is used in various biomedical systems for disease classification and detecting complications or diagnosis (HASAN et al., 2020). Thus, as Gnanasundaram et al. (2020) suggest, understanding the complex causes of diabetic foot ulcers (DFU) can help identify risks early and prevent amputation and limb loss. One way is understanding the neurologic mechanism that leads to diabetic gait alterations may help in identifying the risk and preventing diabetic complications. Petrofsky et al. (2005) found that loss in muscle strength and feeling in the feet sole results in slower gait velocity and a wider stance during walking. The study also suggests that gait impairment may appear independent of muscle strength and sensory loss in the foot, potentially due to slower conduction in the peripheral nervous system. Likewise, the literature describes that some gait alterations can precede sensory changes (GNANASUNDARAM et al., 2020).

Ferris et al. (2020) reported that chronic hyperglycemia and loss of insulin signaling lead to inflammatory pathway activation, oxidative stress, and endothelial dysfunction. These microvascular diseases can cause cerebral microvascular lesions, decreasing the activity of primary and secondary motor cortices and the primary somatosensory cortex. So, it is crucial to maintain HbA1c levels below 7% to avoid neurological damage and the risk of complications (PETROFSKY et al., 2005), and ML can be a helpful approach associated with wearable tools that can constantly monitor individuals' movements performance to predict T2DM. Based on this, in the future, our models could be improved by increasing the database to be embedded in a feasible wearable tool to be used in healthcare systems to classify T2DM from non-T2DM, as it includes clinical variables and does not require sophisticated assessments.

As per our knowledge, this is the first study to use spatiotemporal and plantar pressure distribution from GAITRite to classify T2DM and non-T2DM. Thus, a few limitations can be pointed out. Firstly, a small sample size may not accurately represent the population, leading to biased and unreliable results. Secondly, group differences by age can confound the results, as older people often walk differently from younger individuals. This can make it difficult to compare gait patterns across age groups and may limit the generalizability of the findings. Therefore, some caution should be exercised when interpreting the results. Future studies should increase population representation by recruiting a more heterogeneous sample.

Conclusion

In this paper, we applied ML classifier models in spatiotemporal and plantar pressure distribution data to identify T2DM and non-T2DM. The results showed that the ML classifiers, through specific pressure gait distribution on the heel, could present a potential to detect T2DM patients with high sensitivity. Also, bringing out the importance that early detection of gait alterations in T2DM may present great clinical significance in detecting T2DM. However, more external validations are needed.

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Supplemental Material 1: Spatiotemporal gait features extracted from the GaitRite of each foot from the second to the sixth step.

Feature	Meaning
Velocity	Average of gai speed in centimeter per second
Cadence	Number of steps per second
Step count	Number of steps in the mat
Distance	Gait distance during trial
Step time, cycle time, and step length differential	Mean difference of left and right foot of step time, cycle time, and step length
First contact, foot flat, and last contact	Time in seconds of first contact, foot flat and last contact of each step in the mat
Step Length	Step length in centimeter
Preferred base of support	Base of support in centimeter
Step and stance time	Time of each step and stance in seconds
Support time single and double	Time in seconds of single and double base of support
Toe in out	It is the angle between the line of progression and the midline of the footprint (positive, toe-out, when the mid-line of the footprint is outside the line of progression and negative, toe-in, when inside the line of progression)
Step and stride width	Step and stride width in centimeter
Heel on and off	Time in seconds of each step when hindfoot touches the mat and lifts it off
Mid on and off	Time in seconds of each step when midfoot touches the mat and lifts it off
Toe on and off	Time in seconds of each step when forefoot touches the mat and lifts it off
Heel off-on	Time difference, in seconds, between the start of the next step and the end of the previous step
Double support load and unload	Time (in seconds) of double support load and unload
P*T	Pressure over time in percent (%)
Peak Time	Peak pressure time in seconds
Area	The sum of the active sensor's area in cm^2
Peak	Pressure peak in percent (%)

Supplemental material 2. Optimized hyperparameter found by grid search for the studied ML algorithms for T2DM classification.

Algorithm	Feature Selection	Hiperparameter values
RF	RFE	random_state= 0, max_features= 0.25000000000000006, n_estimators= 30
	SelectKBest	random_state= 0, max_features= 0.40000000000000013, n_estimators=5
SVM - RBF	RFE	kernel= 'rbf', random_state= 0, C= 2, gamma= 'scale'
	SelectKBest	kernel= 'rbf', random_state= 0, C= 1, gamma= 'scale'
LDA	RFE	shrinkage= 1, solver= 'lsqr', tol= 0.0001
	SelectKBest	shrinkage= 1, solver= 'lsqr', tol= 0.0001
LR	RFE	max_iter=100, random_state=0, C= 0.1, penalty= 'l1', solver= 'saga'
	SelectKBest	max_iter=100, random_state=0, C= 1, penalty= 'l1', solver= 'liblinear'
DT	RFE	random_state=0, criterion= 'gini', max_depth= 2
	SelectKBest	random_state=0, criterion= 'entropy', max_depth= 2
MLP	RFE	random_state=0, activation= ' tanh', alpha= 10.0, hidden_layer_sizes= (10,), learning_rate= 'constant', solver= 'sgd'
	SelectKBest	random_state=0, activation= 'tanh', alpha= 10.0, hidden_layer_sizes= (50,), learning_rate= 'constant', solver= 'sgd'
NB	RFE	var_smoothing= 0.1
	SelectKBest	var_smoothing= 1e-09

RF: Random Forest**; SVM**: Support Vector Machine; **RBF**: Radial Basis Function kernel; **LDA**: Linear Discriminant Analysis; **LR**: Logistic Regression; **DT**: Decision Tree; **MLP**: Multilayer Perceptron; **NB**: Naïve Bayes.

Supplemental material 3. Performance values obtained after applied all ML classifiers in terms of True Positive (TP), False Positive (FP), True Negative (TN), and False Negative (FN).

Algorithm	**Feature Selection**	**TP**	**FP**	**TN**	**FN**
RF	RFE	9	3	10	1
	SelectKBest	9	5	8	1
SVM - RBF	RFE	9	4	9	1
	SelectKBest	9	3	10	1
LDA	RFE	9	3	10	1
	SelectKBest	9	3	10	1
LR	RFE	9	4	9	1
	SelectKBest	7	0	13	3
DT	RFE	9	3	10	1
	SelectKBest	9	3	10	1
MLP	RFE	8	2	11	2
	SelectKBest	9	3	10	1
NB	RFE	9	4	9	1
	SelectKBest	9	3	10	1

RF: Random Forest**; SVM**: Support Vector Machine; **RBF**: Radial Basis Function kernel; **LDA**: Linear Discriminant Analysis; **LR**: Logistic Regression; **DT**: Decision Tree; **MLP**: Multilayer Perceptron; **NB**: Naïve Bayes.

5.5 Artigo 05: Machine learning models for Diabetes complications based on gait parameters

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ABSTRACT

Introduction: Machine learning (ML) is a branch of artificial intelligence (AI) that uses algorithms to learn from data and make decisions. It is commonly used in medical applications such as diabetes. Type 2 Diabetes Mellitus (T2DM) has become a research focus for ML. The use of ML to understand diabetic gait alterations and how T2DM affects physical function and mobility could be beneficial in early predicting neurologic complications and preventing diabetic complications. **Objectives:** We aimed to apply supervised ML algorithms on spatiotemporal and pressure gait parameters to forecast diabetes complications. **Methods:** 48 participants (12 males), aged 78.89 (± 6.19) years old, from the Human Performance Laboratory of the Physical Therapy Department at Florida International University (FIU), were included. The dataset consisted of anthropometric data, mean spatiotemporal and pressure distribution gait parameters assessed by GAITRite. Participants were divided into three groups by glycated hemoglobin (HbA1C) levels. The study was conducted using the Jupyter Notebook. **Results:** The XGB Classifier outperformed the other studied ML algorithms, reaching an AUC of 0.99, precision of 0.91, recall of 0.90, and f1-score of 0.89. The three most relevant gait features in classifying diabetes complications found were left support base, mean left pressure over time of zone 5 (I-III metatarsals heads region), and mean right of the active sensor's area of zone 12 (III-IV phalanges). **Conclusions:** The proposed framework may help forecast complications before neurological disorders appear. Increasing the dataset is recommended for improved reliability.

Keywords: Gait; Type 2 Diabetes; Supervised Machine Learning

1. Introduction

Machine learning (ML) is an artificial intelligence (AI) growing branch that evolves algorithms capable of making decisions and rules or learning patterns from data (DAGLIATI et al., 2018). It is an area of computer science that learns based on trial-and-error experience without being explicitly programmed contrary to conventional programming algorithms that follow instructions based on if-else statements (MUHAMMAD et al., 2020; JAISWAL et al., 2021). Supervised ML algorithms (i.e., training data labelled) are the most commonly used for disease prediction and diagnosis (MUHAMMAD et al., 2020). Several works have been done with ML, such as in medical image analysis, development of health interventions, epidemic outbreak prediction, drug discovery, and screening of cardiovascular or other diseases (SILVA K. et al., 2020) like Parkinson's and diabetes.

Boosting insight into ML applications, diabetes mellitus (DM) has become a research focus (SILVA K. et al., 2020; JAISWAL et al., 2021). DM is one of the deadliest diseases worldwide (MUHAMMAD et al., 2020). Type 2 (T2DM) is the most common; this condition is related to a dysfunction either in the pancreas to produce insulin or body cells unresponsive to the insulin produced, or both disorders (MUHAMMAD et al., 2020; MOURA DA SILVA et al., 2021). Either case leads to hyperglycemia. ML have been contributing to optimizing T2DM care and predicting neurologic complications.

The process of understanding complex neurologic mechanism which leads to diabetic gait alterations may help in identifying the risk and preventing diabetic complications. Chronic hyperglycemia and loss of insulin signaling generate an inflammatory cascade, oxidative stress, and endothelial dysfunction, resulting in subsequent loss of blood-brain barrier integrity (RICHNER et al., 2019; FERRIS et al., 2020). This allows cerebral microvascular lesions and one of its consequences is the cortical neurodegeneration of sensorimotor areas in the Central Nervous System (CNS) regions (FERRIS et al., 2020). Ferris et al. (2020) suggest that these alterations may not be simply a passive response resulting from the loss of afferent signals from the peripheral nervous system. If so, movement alterations such as gait performance can precede sensory changes, as already mentioned in the literature (WROBEL; NAJAFI, 2010; GNANASUNDARAM et al., 2020).

Understanding how T2DM affects physical function and mobility is crucial (KO et al., 2011). Both can lead to gait abnormalities such as slower gait speed, shorter stride length, longer stance time, and reduced joint moment and range of motion (KO et al., 2011; MOURA DA SILVA et al., 2021). These alterations can be observed in T2DM patients free of peripheral neuropathies (KO et al., 2011; REEVES et al., 2021). Gait evaluation is a helpful tool to be considered during T2DM diagnosis and follow-up, mainly because gait impairment appears at early stages and aggravates during disease progression (REEVES et al., 2021). Spatiotemporal assessment tools are less susceptible to anthropometric paraments like height and age (FERREIRA et al., 2020). They present critical features that could be used to quantify and classify T2DM progression. Thus, early detection of gait alterations in T2DM may present great clinical significance in preventing diabetic complications.

As ML algorithms can learn from experience extracting useful patterns from processed data, they can potentially help to identify T2DM complications. Most ML algorithms employed for T2DM are related to clinical medical record features (TAN et al., 2021), and poor studies applied gait features. Hence, ML algorithms can find hidden patterns in gait parameters that can be crucial to identify T2DM complications. Based on this, we aimed to apply supervised ML algorithms in spatiotemporal and pressure distribution gait parameters to forecast diabetes complications. Specifically, identify, through ML algorithms evaluations, suitable spatiotemporal and plantar pressure distribution gait features that can better distinguish T2DM complications. The proposal of this study could pave new perspectives for ML algorithms use in T2DM as well as determining gait biomarkers that can be a differential in clinical practice to help prevent disease progression.

2. Methods

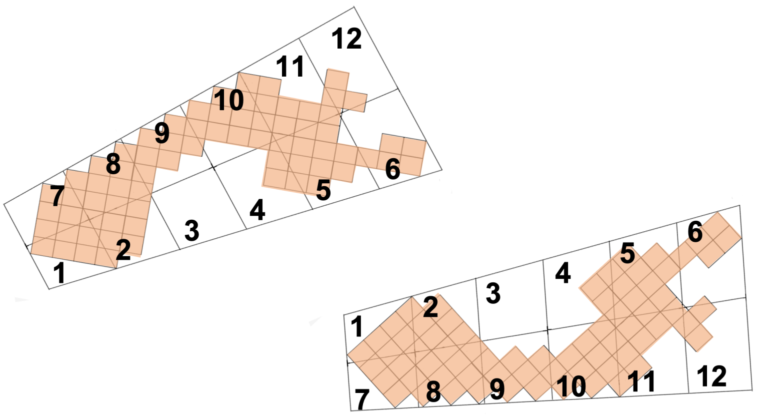
2.1. Dataset description

Old Hispanics adults ($\geq$ 65 years old) diagnosed with T2DM from Vieira et al. (2021) study were considered in the current study, totalizing 38 patients. The study procedures were approved by the Institutional Review Board (IRB-19–0037). Also, ten age- and BMI-matched non-T2DM individuals data from the Human Performance Laboratory GAITRite database at Florida International University (FIU) Physical Therapy Department.

The dataset consisted of anthropometric data (e.g., age, gender, glycated hemoglobin, blood glucose, years diagnosed with diabetes, and body mass index). Further, was assessed spatiotemporal and plantar pressure distribution of gait performance through GAITRite (Q209, CIR Systems Inc) at the preferred velocity. Gait movement recorded without physical limitations (e.g., limb amputations or use of assistive devices) that could interfere with gait performance.

GAITRite consists of an electronic walkway of 4.57 m with grid-arranged sensors (48 $\times$ 288 sensors; 1 cm in diameter each) in an active area of 3.66 x 0.61 m. The geometry of at least three footprints center of heels in 2D dimension is collected from the sensors (activation/deactivation time), giving spatiotemporal as well as dynamic pressure distribution

Figura 5.13 – The twelve zones of plantar pressure distribution detected by GAITRite. Hindfoot represented by zones 1, 2, 7, and 8; Midfoot by zones 3, 4, 9, and 10; and forefoot by zones 5, 6, 11, and 12.



during gait movement (TITIANOVA et al., 2004). Spatiotemporal gait parameters recorded by the system include velocity, cadence, step length, step time, and step count. The pressure distribution of each footprint is evaluated based on 12 zones (six lateral and six medial), four for each foot region (hind-, mid-, and forefoot), created by the system (Figure 5.13). Each pressure zone gives the pressure peak, pressure over time, time of peak pressure in seconds, and the sum of the active sensor's area (LEYH AND FEIPEL, 2022).

2.2. Study procedure

In this study, the participants were classified into three groups according to the American Diabetes Association (ADA) guidelines for glycated hemoglobin (HbA1C) levels: group non-T2DM (HbA1C < 5.7), prediabetes group ($5.7 \geq$ HbA1C ≤ 6.4), and T2DM group (HbA1C ≥ 6.5) (AMERICAN DIABETES ASSOCIATION, 2018).

Once gathered the data, the study was conducted using the Jupyter Notebook environment (3.9.15 version) using Python programming language and the following libraries: NumPy and pandas for spreadsheets data operations; sci-kit learn on ML models applications; and seaborn and matplotlib to plot graphs. We prepared the data by removing all features that presented significant null values that could interfere when applying the ML models, such as Peak Time pressure. Also, we removed features that presented all values equal to zero. Minor missing data were handled by the imputation of its respective feature column mean. Further, a pairwise Spearman's correlation coefficient above 0.8 was removed. Following Akoglu (2018) recommendations, above 0.8 is considered a very strong correlation between features; thus, they are not independent, and one of them should be removed.

After cleaning the data, randomly, we split it 50–50% into training and testing sets to ensure that the ratio of the classes was the same. Then, conducted normalization using the feature scaling method called StandardScaler. StandardScaler normalizes all datasets into standard deviations equal to 1; the mean distribution equals zero, according to the following equation 5.5:

$$z = \frac{x - \mu}{\sigma} \tag{5.5}$$

Where z is the normalized feature, x is the original feature value before normalization, μ is the feature means, and σ is the standard deviation (THARA et al., 2019).

After the dataset cleaning process, the ML classifier algorithms were chosen after applying the Lazy Predict algorithm. Lazy Predict is a licensed MIT package (see documentation: <https://lazypredict.readthedocs.io/en/latest/index.html>) that can analyze the dataset and based on it can suggest different classifier models to be employed. After Lazy Predict, the classifier employed were: Linear Discriminant Analysis (LDA), Logistic Regression (LR), Decision Tree (DT), K-Nearest Neighbor (KNN), and Extreme Gradient Boost Classifier (XGB Classifier).

Before applying the ML classifier models, we searched the best hyperparameter values for each classifier using grid search. Hyperparameter tuning is important to optimize the recognition system. Grid search was performed with 10-fold cross-validation to find the appropriate hyperparameters. As our dataset was composed of 48 individuals divided into three different HbA1C groups, the distribution of instances across the three classes is not equal where the training set was slightly imbalanced. Then, to overcome this, we employed the Synthetic Minority Oversampling Technique (SMOTE), an oversampling method to avoid misjudgment of the classifier during training. SMOTE can balance the training set by generating new synthetic samples using interpolation (Ferreira et al., 2022). It randomly selects the k-nearest neighbor samples to minority categories to present the same number of the majority categories (CHANG et al., 2022). Also, RF classification algorithm was used to rank the importance of features.

2.3. Classification evaluation

All ML algorithms used the same set of data, no ad hoc changes were made to make the dataset suited for a specific ML model. However, each algorithm extract information from the data in a different way. Classification algorithms used to assess the validity of the proposed approach were:

- Linear Discriminant Analysis (LDA): characterize data through linear polynomial separating patterns in two or more classes (ALTILIO et al., 2021).

- Logistic Regression (LR): calculate the probability of the target output belonging to the appropriate category (estimate inclusion probability) (RYMARCZYK, et al., 2019).
- Decision Tree (DT): provides nonlinear sequential analysis starting with a root node comprised of several branches until the end (leaf nodes). The path between the root node and the leaves yields the classification rules (AZAD et al., 2022).
- K-Nearest Neighbor (KNN): a model that computes the k-nearest neighbors to infer the target output (TRIGUERO et al., 2019).
- Extreme Gradient Boost Classifier (XGB Classifier): ensemble learning model that assembles weak classifiers into a stronger classifier by increasing the weight of misclassified classes and making the loss function smoother (CHANG et al., 2022).

All evaluation metrics are derived from the confusion matrix attributes (GAO et al., 2019), which are true positive (TP), false positive (FP), true negative (TN) and false negative (FN). Quantitative evaluation of the classification results performance is summarized in Table 5.7. Macro average values from Table 5.7 metrics were computed through calculations of the arithmetic mean of the metrics for single classes. This method equally weights all classes; no matter what their size (GRANDINI et al., 2020; FERREIRA et al., 2022).

We conducted statistical analyses to examine the differences between the three groups, starting with Shapiro-Wilk tests to assess normality. Differences were analyzed with the ANOVA test when normally distributed data were verified; otherwise, the Kruskal-Wallis test was employed. The alpha significance level was set to $p < 0.05$ for all statistical analyses.

3. Results

The demographic and clinical details of the three groups (non-T2DM, pre-T2DM and T2DM) are shown in Table 5.8. There were no age or BMI differences between the groups.

In the feature selection step, we calculated the Spearman correlation coefficients among 57 features. Supplemental material 1 shows the resulting correlation matrix after removing the highly correlated features ($\rho \geq 0.8$).

The optimized hyperparameters of the studied ML classifier algorithms achieved using the grid search method are shown in Supplemental material 2. After applying five different ML classifier models (Table 5.9), we found that the classifier models improved performance metrics after the training set was balanced using SMOTE method. XGB Classifier outperformed with the highest overall performance metrics AUC (0.99), precision (0.91), recall

Tabela 5.7 – Evaluating performance quantitative metrics used for detecting diabetes complications in the present study.

Name	Formula	Description
Accuracy (correct classification rate – CC)	$\frac{TP+TN}{TP+TN+FP+FN}$	In general, measures the ratio of correct predictions (TP and TN) to the total number of instances evaluated (total number of all positive and negative predictions).
Precision (positive predictive value – PPV)	$\frac{TP}{TP+FP}$	Measure the positive patterns (TP) that are correctly predicted from the total number of predictions in that same class.
Recall (sensitivity or true positive rate – TPR)	$\frac{TP}{TP+FN}$	This metric is used to measure the fraction of positive patterns that are correctly classified (proportion of positive frequencies that are correctly detected by the classifier).
F1-score (F measure)	$\frac{2TP}{2TP+FP+FN}$	It is the harmonic mean of precision and recall.
Area under the receiver operating characteristic curve	$\frac{\frac{TP}{TP+FN}-\frac{FP}{FP+TN}+1}{2}$	In general, measures the ratio of correct predictions (TP and TN) to the total number of instances evaluated (total number of all positive and negative predictions).

TP = True positive; FN = False negative; FP = False positive; TN = True negative.

Tabela 5.8 – Demographic and clinical features (means ± standard deviations) comparisons between non-T2DM, pre-T2DM, and T2DM groups.

	Non-T2DM (n=10)	Pre-T2DM (n=10)	T2DM (n=28)	p-value
Gender (M/F)	3/7	0/10	9/19	0.157
Age (yr)	80.09 (± 3.91)	81.33 (± 5.92)	77.64 (± 6.81)	0.206
BMI (kg/m^2)	27.67 (± 3.44)	29.87 (± 4.44)	30.95 (± 6.05)	0.189
HbA1C	-	6.12 (± 0.21)	7.30 (± 0.73)	$< .001$*
Time from clinical diagnosis (yr)	-	9.78 (± 6.76)	18.75 (± 13.98)	$< .001$*

T2DM: type 2 diabetes mellitus; M: male; F: female; yr: years; BMI: body mass index.
*significance level at 0.05.

(0.90), f1-score (0.89), and accuracy (90%). LDA and LR also presented a good performance metric with a high AUC value (0.98 and 0.97, respectively). KNN presented the lowest performance metrics amongst all ML classifiers. The related confusion matrices of the three best-performing models are shown in Figure 5.14.

Figure 5.15 shows the ranked ten feature importance using RF classifier, the three most gait important features found to classify the individuals into groups are mean left preferred support base (B_Sup_Pref_L), mean left pressure over time (P*T5_TL) of zone 5, and mean right of the active sensor's area (Area12_TR) of zone 12.

4. Discussion

This study aimed to forecast diabetes complications through spatiotemporal and pressure distribution gait parameters in three groups based on HbA1C. First, our model was trained using data from GAITRite as input variables to classify and recognize the gait characteristics of non-T2DM, pre-T2DM, and T2DM participants. Second, we evaluated the ML algorithms classifier's performance. Finally, we identified the most relevant gait features to classify diabetes complications.

According to our research results, non-T2DM, pre-T2DM, and T2DM individuals have discernable differences in gait characteristics after data were balanced using SMOTE method. Of the five algorithm classifiers, the XGB Classifier achieved the highest AUC (0.99) for the classification of T2DM complications, followed by LDA (0.98) and LR (0.97). XGB Classifier is an ensemble ML technique based on a decision tree that can improve predictions by matching weak learners (NOH et al., 2021).

Tabela 5.9 – Performance obtained from ML classifiers models on the original and balanced training set using Synthetic Minority Oversampling Technique (SMOTE).

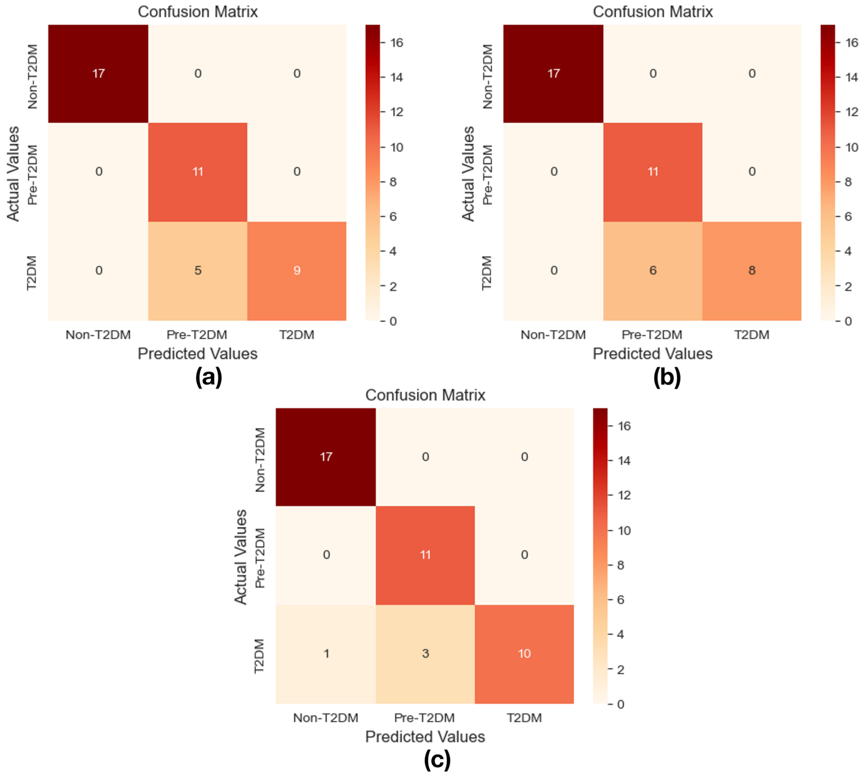
Algorithm	Training set	AUC (macro avg)	Precision (macro avg)	Recall (macro avg)	F1-Score (macro avg)	Accurarcy (%)
LDA	Original	0.84	0.66	0.63	0.64	71
	Balanced	0.98	0.90	0.88	0.87	88
LR	Original	0.80	0.64	0.64	0.59	62
	Balanced	0.97	0.88	0.86	0.84	86
DT	Original	0.62	0.56	0.48	0.52	58
	Balanced	0.88	0.86	0.83	0.81	83
KNN	Original	0.62	0.60	0.61	0.60	83
	Balanced	0.80	0.75	0.64	0.55	62
XGB Classifier	Original	0.74	0.58	0.54	0.56	71
	Balanced	0.99	0.91	0.90	0.89	90

LDA: Linear Discriminant Analysis; LR: Logistic Regression; DT: Decision Tree; KNN: K-Nearest Neighbor; XGB Classifier: Extreme Gradient Boost Classifier; AUC: Area Under the Curve; macro avg: macro average.

The classification AUC after SMOTE (0.80 – 0.88) was higher than all the classifiers of imbalanced data (0.62 – 0.84). AUC describes the possibility of ML algorithms making positive predictions suitable for imbalanced class distribution (HASAN et al., 2020; FERREIRA et al., 2022). For example, AUC over 0.75 may present a relevant discrimination performance (TAN et al., 2021). Similarly to our results, Hasan et al. (2020) showed XGB Classifier as the best performance with AUC (0.946) in classifying diabetes. However, the input features were different from our study, which used only clinical records instead of gait parameters. XGB Classifier is also shown to present a good prediction performance in other studies with different disorders (DU et al., 2020; NOH et al., 2021).

The CNS plays a crucial role in the gait mechanism, which refers to walking and maintaining the balancing process. The primary role of the CNS in the gait mechanism is to generate the necessary neural impulses that activate the muscles responsible for walking (DI RUSSO et al., 2021). Furthermore, the CNS also monitors the gait cycle and adjusts it based on the demands of the environment (DI RUSSO et al., 2021). Without the proper function of

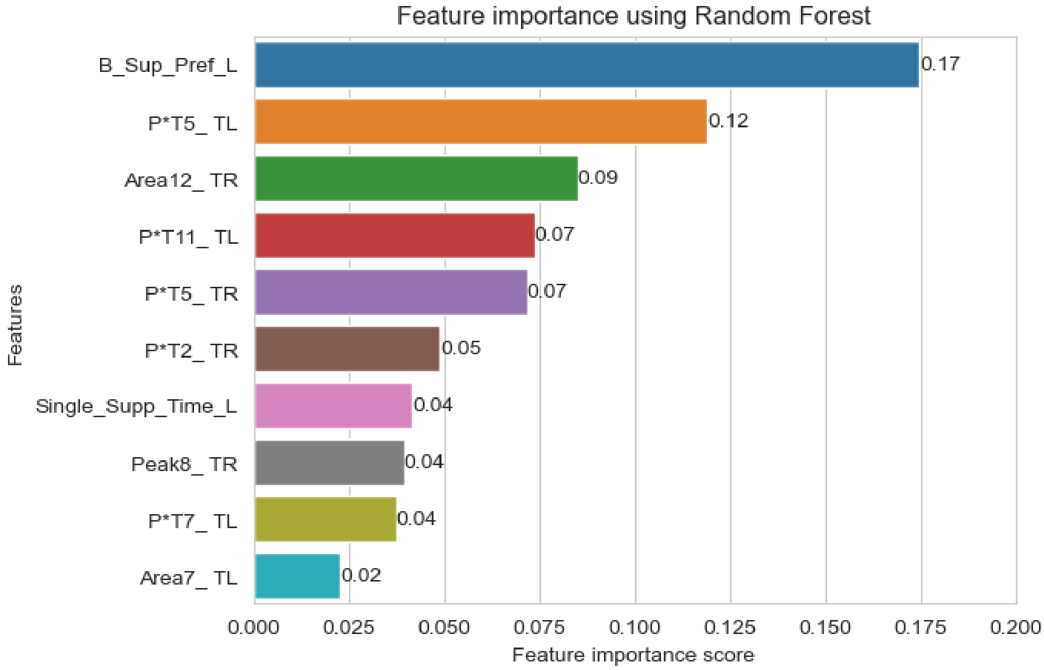
Figura 5.14 – Type 2 diabetes mellitus (T2DM) confusion matrices heatmap for the best-performing algorithms models (a) Linear Discriminant Analysis (LDA), (b) Logistic Regression (LR), and (c) Extreme Gradient Boost Classifier (XGB Classifier).



the CNS, individuals may experience difficulties with walking, such as poor coordination and balance, leading to falls and other complications (BAKER, 2018). In T2DM, the CNS can be affected by an inflammatory cascade caused by hyperglycemia and loss of insulin signaling may affect cognitive function, including memory and movement coordination (FERRIS et al., 2020).

CNS dysfunction can significantly impact gait abnormalities in patients with T2DM, such as reduced step length, increased step width, and increased support base (METTELINGE et al., 2013; TRAMONTI et al., 2022). Our study has similarly found that the left-preferred support base is the top-ranked feature. In T2DM patients, a wider support base may result from a decreased ability to control balance and maintain a narrow support base (METTELINGE et al., 2013). As a compensatory pattern, diabetic individuals tend to keep their left limb on the ground longer to support the activities of the preferred foot (TAN et al., 2022). This may help stabilize the individual during gait, acting as a compensatory sensory information mechanism to improve balance and stability.

Figura 5.15 – Feature importance score found using the Random Forest (RF) classifier.



Furthermore, the extended duration of the left-side limb on the ground is also evident in the second top-ranking feature, namely, the left medial forefoot region. Sacco et al. (2014) studied the stages of diabetic neuropathy and found that moderate to severe neuropathy stages increase plantar pressure distribution in the forefoot region. Based on this study and corroborating our results, we may infer that forefoot pressure distributions are meaningful features for forecast diabetes complications. Therefore, gait changes may be an important indicator of future sensibility alteration. Ko et al. (2011) have observed that gait inefficiencies may be noticeable in the early stages of diabetes, prior to the development of a full range of complications. One limitation of the study is the absence of symmetry analysis, which could have provided additional insights into the gait abnormalities observed in T2DM patients. Nonetheless, it is crucial to highlight the need for further research to gain a better understanding of the underlying mechanisms and validate these findings.

As we know there is no long-term cure for T2DM, although it can be controlled and prevented (HAQUE et al., 2020). Studies with ML to early detection of T2DM can lead to better management of the disease, reducing the chances of further severe complications and healthcare costs (HAQUE et al., 2020; PINCHEVSKY et al., 2020; JAISWAL et al., 2021). Early detection allows starting treatment more effectively to improve glycemic control and minimize damage (CHATTERJEE et al., 2017) that may affect the CNS (FERRIS et al., 2020). When diabetes is not well-controlled, a variety of complications can occur including, peripheral neuropathy, foot ulceration, and amputation (HAQUE et al., 2020). These complications can be costly to treat and lead to significant disability and reduced quality of life (PINCHEVSKY et al., 2020). By detecting T2DM early and initiating treatment, it is possible to delay or prevent the onset of these complications (JAISWAL et al., 2021). This can reduce the overall cost of care for individuals with diabetes resulting in better health outcomes (PINCHEVSKY et al., 2020; HAQUE et al., 2020). In summary, ML tools for early detection of T2DM are a promising approach to significant reductions in healthcare costs and better health outcomes by preventing or delaying the onset of complications and allowing for more efficient treatment.

LDA and LR confusion matrices presented type II errors between pre-T2DM and T2DM. XGB Classifier shows fewer type II errors, although this error appeared between non-T2DM and T2DM; and pre-T2DM and T2DM. False negative errors should be avoided; to overcome this, in future studies, we need to increase the sample size and balance our data without interpolation approaches. Furthermore, we had no T2DM patients with peripheral neuropathy, which should be included in our future analysis. Overall, our findings highlight the importance of identifying gait abnormalities of T2DM patients to improve health and quality of life before worse complications.

In our study, some limitations should be noted. We needed to increase participant's number by interpolation using SMOTE method to overcome an imbalanced and small dataset for ML algorithms training; thus, there is still a chance of variability in the results. Secondly, we had no T2DM patients with peripheral neuropathy. In future works, T2DM patients with peripheral neuropathy should be included in our analysis.

5. Conclusion

We can conclude that among all ML algorithms, XGB Classifier outperformed. Left preferred support base and left medial forefoot region plantar pressure over time were relevant features in detecting T2DM complications. Thus, applying ML algorithms using spatiotemporal and plantar pressure gait parameters as input features could support medical specialists in detecting diabetes complications. The proposed framework of algorithms is expected to help the development of better tools to predict more severe diabetes complications before neurological disorders appear. Hence, aid the clinical practice by identifying specific gait features and further supporting the treatment focused on those features. In the future, we recommend increasing the dataset in the number of participants and features (e.g., more clinical records) to improve the reliability of the use of ML models.

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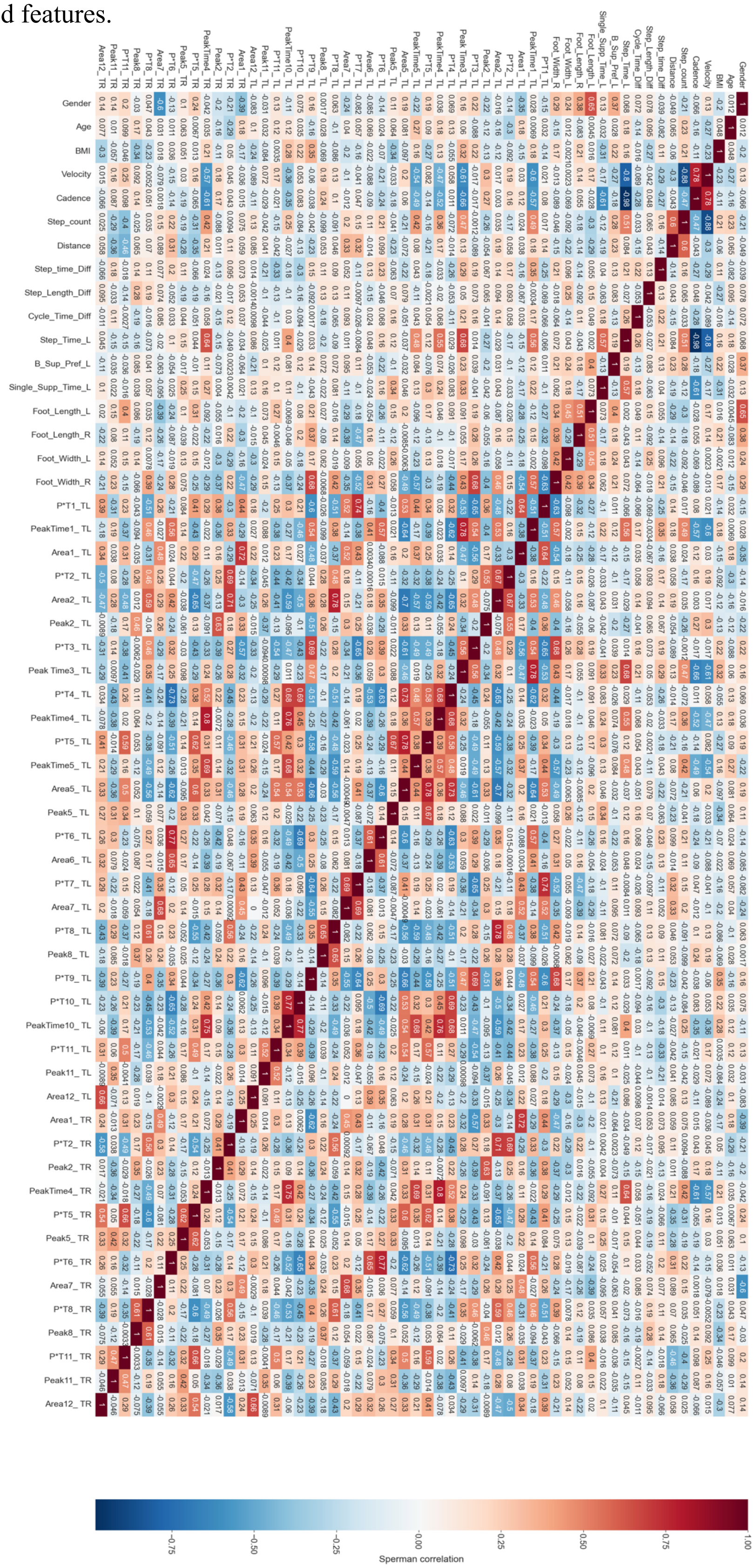
Supplemental material 1. Correlation matrix showing Spearman's correlation coefficients among the selected features.



Supplemental material 2. Optimized hyperparameter found by grid search for the studied ML algorithms for T2DM diabetes complication classification.

Algorithm	Training set	Hiperparameter values
LDA	Original	shrinkage= ‘auto’, solver= 'lsqr', tol= 0.0001
	SMOTE	shrinkage= 0.5, solver= 'lsqr', tol= 0.0001
LR	Original	C= 1e-05, penalty= 'none'
	SMOTE	C= 1, penalty= 'l2'
DT	Original	random_state=0, criterion= 'gini', max_depth= 4
	SMOTE	random_state=0, criterion= 'gini', max_depth= 6
KNN	Original	n_neighbors= 6
	SMOTE	n_neighbors= 2
XGB Classifier	Original	colsample_bytree= 1.0, gamma= 1, max_depth= 3, min_child_weight= 1, subsample= 0.8
	SMOTE	colsample_bytree= 0.6, gamma= 2, max_depth= 4, min_child_weight= 1, subsample= 1.0

LDA: Linear Discriminant Analysis; **LR:** Logistic Regression; **DT:** Decision Tree; **KNN:** K-Nearest Neighbor; **AUC:** Area Under the Curve; **XGB Classifier:** Extreme Gradient Boost Classifier.

6 Conclusões

Os resultados obtidos no presente estudo permitem concluir que:

- Ao verificar evidências na literatura sobre os métodos preditivos usados no padrão de marcha de diabéticos, foi observado poucos estudos na literatura utilizando dados de execução da marcha como preditores da diabetes, fazendo-se necessário mais estudos sobre o tema.
- A análise exploratória dos dados de diabéticos tipo 2 e não diabéticos mostrou alterações nos parâmetros espaço-temporais e de distribuição da pressão plantar da marcha de diabéticos tipo 2. E entre os dados dos diabéticos tipo 2, pode-se observar diferenças na distribuição da pressão plantar dos indivíduos com maiores níveis glicêmicos.
- O uso de AM supervisionada na classificação entre diabéticos tipo 2 e não diabéticos a partir de dados espaço-temporais e de distribuição da pressão plantar mostrou-se promissor. Com uma alta sensibilidade relacionada a distribuição da pressão plantar na região do calcanhar.
- A capacidade preditiva de modelos de AM supervisionada para classificar complicações na diabetes tipo 2 a partir de dados de execução da marcha mostrou-se eficaz. Certas alterações na execução da marcha, se detectadas precocemente, poderão ser fundamentais na prática clínica para o direcionamento de tratamentos, os quais poderão prevenir que os distúrbios neurológicos apareçam.

7 Considerações Finais

A tecnologia está cada vez mais presente em todos os setores, incluindo a saúde. Uma das ferramentas tecnológicas mais utilizadas da atualidade é o emprego da aprendizagem de máquina (AM) na automatização de tarefas, no auxílio de decisões clínicas e desenvolvimento de terapias mediante previsão de doenças e/ou complicações. A AM permite análise de grandes volumes de dados médicos, como dados da execução de marcha, que seriam humanamente impossíveis de serem analisados de forma rápida e eficaz.

A marcha é uma das funções humanas mais comuns e necessárias para as atividades diárias, como a locomoção. Pacientes com diabetes tipo 2 apresentam mudanças na marcha decorrentes de diversas alterações na dinâmica corporal, resultando em uma execução mais lenta e cautelosa dos movimentos. Já se observa na literatura que doenças como a diabetes apresentam alterações em diferentes áreas corticais, como a região sensório-motora. Assim, partimos da hipótese de que pacientes diabéticos podem apresentar complicações neurológicas motoras que afetam a marcha antes das alterações sensoriais mais graves, e que, detectando essas alterações precocemente, é possível direcionar tratamentos adequados para evitar complicações sensoriais mais sérias.

A ideia inicial do desenho metodológico surgiu da mente inquieta da presente autora, que desde muito cedo teve sede de alçar novos voos, saindo de casa aos 11 anos de idade em busca de conhecimento na cidade grande. Na graduação, não sendo diferente, não se contentando apenas com o que era ensinado em sala de aula, realizou graduação sanduíche, morando 1 ano e meio na Austrália. Do outro lado do mundo, participou de um congresso em Cingapura onde percebeu que a fisioterapia era além do cuidado com o paciente e que a tecnologia poderia ser uma grande aliada no cuidado com o próximo. Finalizada a graduação, iniciou o mestrado que permitiu expandir ainda mais os conhecimentos e ir além, unindo a fisioterapia ao mundo da programação. Mestre em neuroengenharia, retornou a sua casa de formação para realizar o doutorado, uma nova jornada para adquirir ainda mais conhecimento e desbravar novos caminhos, somando os conhecimentos prévios adquiridos na formação de base aos conhecimentos de ciências exatas. Seguindo a constante evolução tecnológica e a tendência mundial, adicionou ao leque de conhecimentos a ciência de dados, companheira nos últimos 4 anos, fundamental para a concepção e fechamento desse projeto.

O desenho metodológico desse estudo foi inovador no quesito do tema e na ferramenta tecnológica de estudo abordado. A metodologia foi composta pela integração de vários conhecimentos distintos. O planejamento inicial partiu do pressuposto de desenvolver um jogo de realidade aumentada para treino de marcha no Laboratório de Intervenção e Pesquisa em Realidade Virtual (LIPERV) do Departamento de Fisioterapia da UFRN. Jogo esse que se autorregulasse e se adaptasse ao treinamento conforme a execução de marcha de cada jogador. O recurso tecnológico inicial, para conseguir a autorregulação e adaptação do treino de marcha, seria o emprego da AM. Uma vez empregada a AM, o jogo poderia ser desenvolvido baseado nos resultados da AM. AM e jogo seriam integrados por meio do uso de uma Interface de Programação de Aplicação (API), isso facilitaria a troca de dados entre ambos os sistemas, automatizando o treinamento de marcha. O fator pandemia foi um limitante na execução total do projeto, uma vez que atrasou o andamento do planejamento metodológico inicial. Além de impossibilitar a coleta de novos dados de execução de marcha e aumento do número amostral do estudo.

Iniciei esse estudo com o desenvolvimento de um protocolo de revisão sistemática (já publicado) e de uma revisão sistemática (submetido para publicação) para definir as principais lacunas acerca do tema estudado. Em seguida, definiu-se como seria feita a coleta e análises dos dados, sendo fundamental a parceria com a *Florida International University* (FIU) na pessoa do Dr. Edgar R. Vieira. Depois de muitas incertezas e adiamentos, em setembro de 2021 consegui ir para a FIU dar prosseguimento aos planos desse estudo. Os 10 meses na FIU foram fundamentais para entender o sistema de análise de dados do GAITRite, bem como estabelecer novas parcerias com outros departamentos, como com o Dr. Wei-Chiang Lin do Departamento de Engenharia Biomédica. Trabalhar e colaborar alguns meses com os estudos dos pós-graduandos do Departamento de Engenharia Biomédica, junto com os cursos ofertados pela FIU relacionados à Ciência de dados, foram importantes para as análises dos dados e consolidação metodológica desse estudo. Além disso, essa experiência internacional resultou em crescimento pessoal e profissional, pois me permitiu participar de diversos eventos internacionais, fazer *network* e parcerias com pessoas de diversos países e realizar apresentações orais em outra língua em simpóso organizado pela *McGill University* do Canadá.

Os achados desse estudo foram inovadores, mostrando que a AM na execução da marcha de pacientes diabéticos poderá ser usada para o desenvolvimento de diversas tecnologias e otimização de serviços. Espera-se, em futuros estudos, aplicá-la não só no desenvolvimento de um jogo de realidade aumentada, mas em outras aplicações como em dispositivos vestíveis automático de avaliação e tratamento da marcha de pacientes diabéticos associado a diversos outros *softwares* como um *smart watch* ou um aplicativo para o celular. Dispositivos esses que podem monitorar os pacientes em tempo real, contribuindo para o planejamento fisioterapêutico de reabilitação, auxiliando a traçar condutas que melhorem a performance na execução da marcha dos mesmos. Tal tecnologia servirá como uma ferramenta de suporte para facilitar a atuação dos profissionais da saúde, impactando o modo de reabilitar esses pacientes.

O presente estudo possibilitou a integração da área da saúde com diversas áreas tecnológicas, o qual envolveu professores e alunos de diversos laboratórios pertencentes a diferentes programas de graduação e pós graduação da UFRN (como o LIPERV), da FIU (*Human Performance Laboratory*) e do Instituto Internacional de Neurociências Edmond e Lily Safra (IIN-ELS) na pessoa do Dr. Edgard Morya. Essa integração e parceria resultou em uma Tese, um TCC, sete artigos científicos, um resumo em simpósio internacional e dois resumos publicados em anais de congressos nacionais até o momento. No entanto, espera-se a continuidade desse projeto no desenvolvimento de estudos futuros como sua aplicação no jogo de realidade aumentada e que ele saia da academia, contrindo na otimização da prática clínica, mas que principalmente melhore a qualidade de vida da sociedade.

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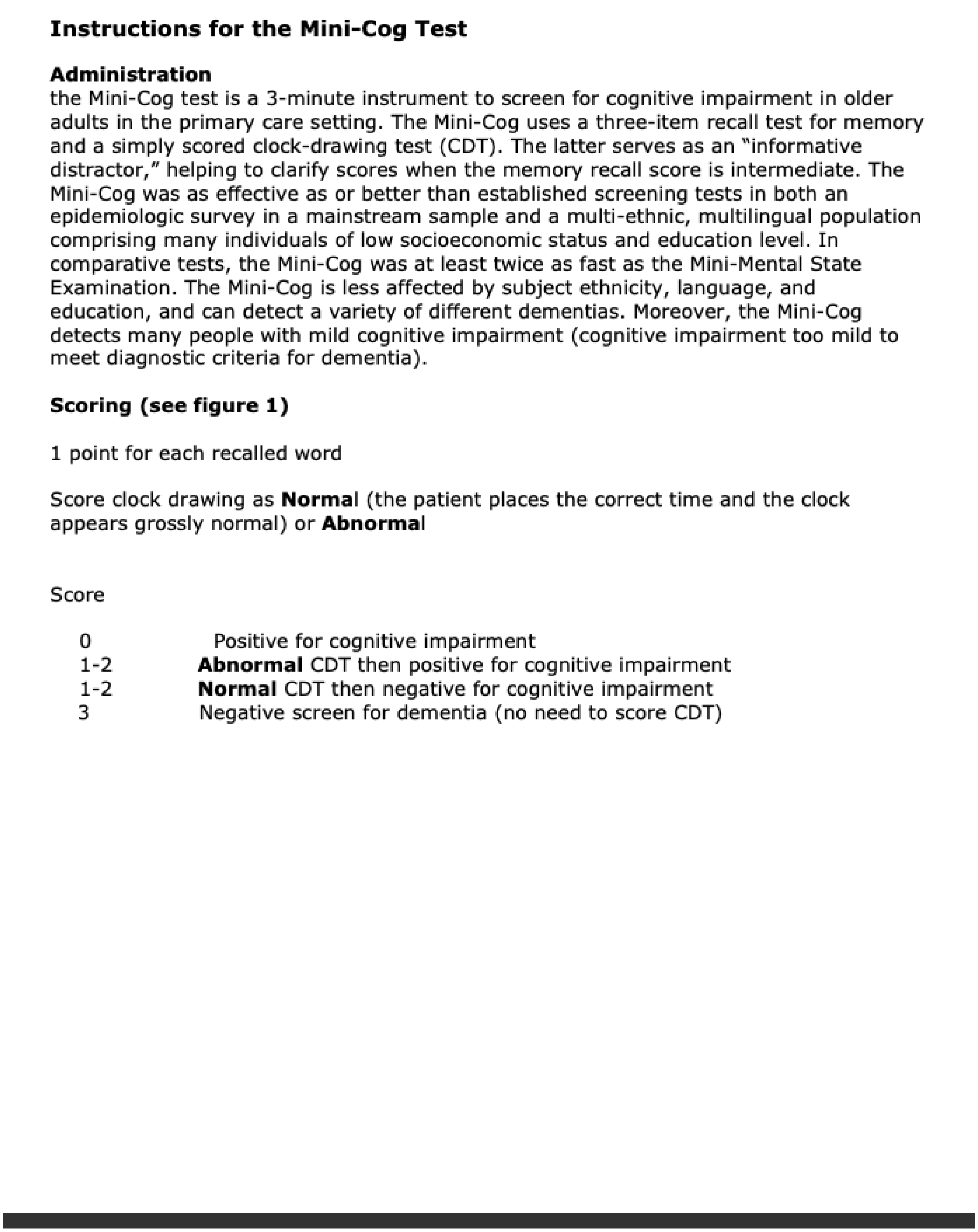
Anexos

ANEXO A – *Mini-Cog Test*



Instructions for the Mini-Cog Test

Administration

the Mini-Cog test is a 3-minute instrument to screen for cognitive impairment in older adults in the primary care setting. The Mini-Cog uses a three-item recall test for memory and a simply scored clock-drawing test (CDT). The latter serves as an "informative distractor," helping to clarify scores when the memory recall score is intermediate. The Mini-Cog was as effective as or better than established screening tests in both an epidemiologic survey in a mainstream sample and a multi-ethnic, multilingual population comprising many individuals of low socioeconomic status and education level. In comparative tests, the Mini-Cog was at least twice as fast as the Mini-Mental State Examination. The Mini-Cog is less affected by subject ethnicity, language, and education, and can detect a variety of different dementias. Moreover, the Mini-Cog detects many people with mild cognitive impairment (cognitive impairment too mild to meet diagnostic criteria for dementia).

Scoring (see figure 1)

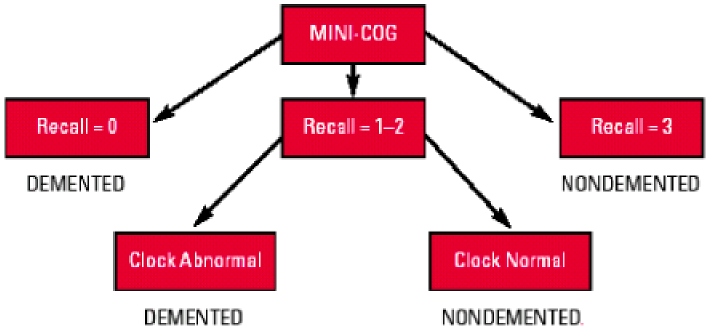
1 point for each recalled word

Score clock drawing as **Normal** (the patient places the correct time and the clock appears grossly normal) or **Abnormal**

Score

0	Positive for cognitive impairment
1-2	**Abnormal** CDT then positive for cognitive impairment
1-2	**Normal** CDT then negative for cognitive impairment
3	Negative screen for dementia (no need to score CDT)

Figure 1. The Mini-Cog scoring algorithm. The Mini-Cog uses a three-item recall test for memory and the intuitive clock-drawing test. The latter serves as an "informative distractor," helping to clarify scores when the memory recall score is intermediate.



Reference

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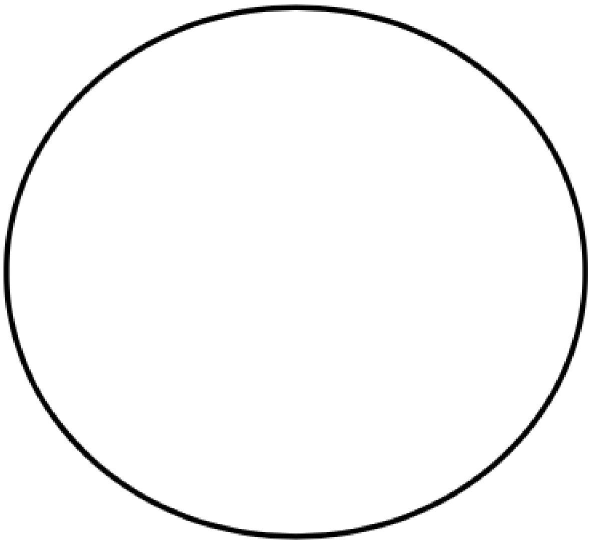
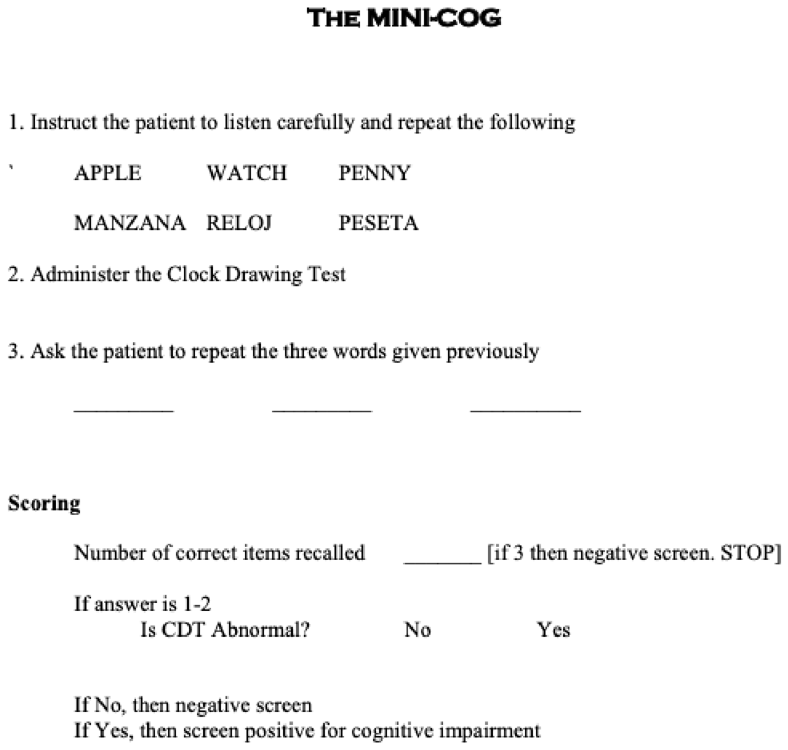
Pt. Name:______________________ DOB:_______________________
Date:__________________________

Instructions
Inside the circle draw the hours of a clock as if a child would draw them
Place the hands of the clock to represent the time "forty five minutes past ten o'clock"

Instrucciones
Dentro del circulo dibuje las horas del reloj como si lo haria un niño.
Ponga las manos del reloj para representar el tiempo "cuarenta y cinco minutos despues de las diez"





THE MINI-COG

1. Instruct the patient to listen carefully and repeat the following

`			
	APPLE	WATCH	PENNY
	MANZANA	RELOJ	PESETA

2. Administer the Clock Drawing Test

3. Ask the patient to repeat the three words given previously

_________ _________ __________

Scoring

Number of correct items recalled _______ [if 3 then negative screen. STOP]

If answer is 1-2
Is CDT Abnormal? No Yes

If No, then negative screen
If Yes, then screen positive for cognitive impairment