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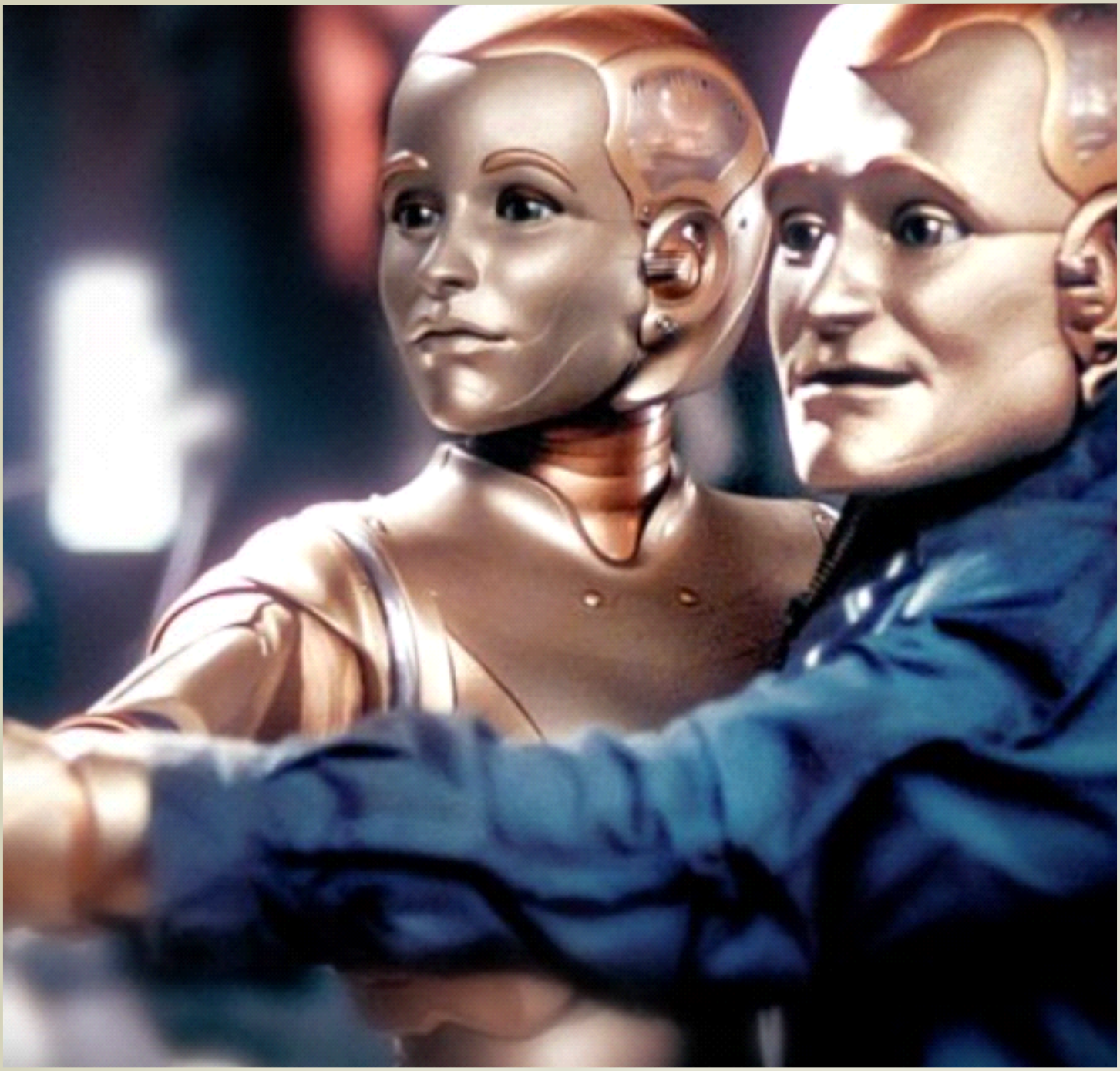

I wonder if artificial intelligence will survive without human intelligence?

EDITORIAL

THE INFLUENCE OF ARTIFICIAL INTELLIGENCE IN ENDOCRINOLOGY AND DIABETES MANAGEMENT

AI is playing a transformative role in endocrinology, particularly in the diagnosis, treatment, and management of diabetes. Endocrinology, which deals with hormonal imbalances, often involves complex and dynamic data, making it a prime field for AI-driven solutions.

Improved Diagnosis of Endocrine Disorders

AI systems enhance the accuracy and speed of diagnosing conditions like diabetes, thyroid dysfunctions, and adrenal disorders.

- **How it works:** AI algorithms analyze patient symptoms, lab results, and imaging data to identify patterns that may indicate endocrine disorders.
- **Impact:** Faster diagnosis reduces delays in initiating appropriate treatments

Optimizing Diabetes Management

a. Continuous Glucose Monitoring (CGM) and Predictive Analytics

AI algorithms analyze CGM data to provide insights into glucose trends and predict future fluctuations.

- **Example:** Systems like Medtronic integrate AI to offer personalized glucose management recommendations.
- **Impact:** Patients gain better control over blood sugar levels, reducing the risk of complications such as retinopathy, neuropathy, kidney disease and cardiovascular diseases.

b. AI-Powered Insulin Delivery Systems

AI is at the heart of advanced insulin pumps and artificial pancreas systems.

- **How it works:** These systems use real-time glucose readings to automatically adjust insulin delivery.
- **Example:** Use AI to predict and prevent hyperglycemia or hypoglycemia.
- **Impact:** Improved glycemic control reduces the burden of manual monitoring and insulin dosing for patients

Personalized Treatment Plans

AI enables the customization of treatment plans based on individual patient profiles.

- **How it works:** Algorithms analyze data from electronic health records, genetics, lifestyle, and CGM devices to recommend optimized interventions.
- **Example:** AI systems help endocrinologists decide on the best combination of medications (e.g., metformin, SGLT2 inhibitors, or GLP-1 receptor agonists) for managing Type 2 diabetes.
- **Impact:** Tailored treatments enhance patient adherence and improve outcomes.

Early Detection and Risk Prediction

a. Prediabetes and Type 2 Diabetes

AI identifies individuals at high risk of developing diabetes by analyzing large datasets, including lifestyle habits, genetics, and lab values.

- **Example:** Predictive tools powered by AI assess HbA1c trends and risk factors to guide early interventions.
- **Impact:** Preventive measures, such as lifestyle modifications and targeted therapies, can delay or prevent the onset of Type 2 diabetes.

b. Complication Prediction

AI systems predict diabetes-related complications, such as kidney disease or diabetic retinopathy.

- **Example:** Google's DeepMind Health developed an AI tool that identifies early signs of diabetic retinopathy with high accuracy.
- **Impact:** Early treatment minimizes long-term damage and improves quality of life

Enhancing Patient Engagement and Education

AI-powered mobile apps and virtual assistants play a crucial role in empowering patients.

- **Capabilities:** Provide dietary recommendations, medication reminders, and feedback on exercise and lifestyle habits.
- **Impact:** Increased patient awareness and adherence to treatment regimens

Advancements in Research and Drug Development

AI accelerates the discovery of new drugs and therapies for diabetes and other endocrine disorders.

- **How it works:** AI identifies molecular targets and predicts drug efficacy using large-scale biological data.
- **Example:** AI tools are aiding in the development of novel GLP-1 receptor agonists for better blood sugar control.
- **Impact:** Faster innovation in treatment options for patients with diabetes and hormonal disorders

Challenges and Ethical Considerations in Endocrinology AI

- **Data Quality and Privacy:** Ensuring the security and accuracy of patient data used by AI systems.
- **Algorithm Bias:** Training AI on diverse datasets to avoid inaccuracies in underrepresented populations.
- **Integration with Clinical Practice:** Balancing AI recommendations with clinical expertise and patient preferences

Future Prospects for AI in Endocrinology

- **Real-Time Decision Support:** AI-powered tools integrated into endocrinologists' workflows for real-time clinical decision-making.
- **Advanced Wearables:** Smart devices that monitor multiple biomarkers, such as glucose, cortisol, and insulin levels, for a holistic view of endocrine health.
- **Precision Medicine:** Further refinement of AI algorithms to deliver hyper-personalized care plans

Conclusion

AI is profoundly influencing endocrinology and diabetes management, offering tools to enhance diagnostic precision, personalize treatments, and predict complications. By bridging gaps in patient care and optimizing resource allocation, AI promises to redefine how endocrine disorders are managed, ultimately improving patient outcomes and quality of life.

I wonder if artificial intelligence will survive without human intelligence?

Mirnaluci Paulino Ribeiro Gama

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ORIGINAL ARTICLE: TOPICS IN MEDICAL CLINIC *ARTIGO ORIGINAL: TÓPICOS EM CLÍNICA MÉDICA*

NOCIPLASTIC PAIN IN RHEUMATOID ARTHRITIS

DOR NOCIPLÁSTICA NA ARTITE REUMATÓIDE

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Background; The main symptom of rheumatoid arthritis (RA) is symmetrical peripheral polyarthritis. This disease causes chronic pain and disability that reduce quality of life. Treatment goal is to control inflammation and to reduce symptoms. Nevertheless, some patients persist having pain despite achieving inflammatory remission. **Aim:** This study aimed to investigate the persistence of pain in patients with RA with the inflammatory process under control. **Methods:** Cross-sectional study encompassing 66 patients with RA with disease in remission for presence of pain through McGill questionnaire, for self-efficacy through Arthritis Self-Efficacy Scale-8 (ASES-8), for depression by Center for Epidemiological Studies Depression, and sleep quality through Pittsburgh questionnaire. Inflammatory activity was evaluated by Disease Activity Score using 28 joints (DAS-28), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). **Results:** About 12.5% of patients scored in the upper 3rd and 4th quartile of McGill questionnaire. Sleep quality (r = 0.37; 95% CI = 0.14 to 0.58; p = 0.001) and depression (r = 0.38; 95% CI = 0.13 to 0.57; p = 0.001) but not ESR, CRP, or DAS-28 CRP correlated with pain (all with p = ns). ASES-8 and duration of remission did not correlate with McGill results (p = ns). **Conclusion:** There is a significant proportion of patients with RA with inflammatory disease under control that still experience pain. The persistence of pain correlates with depression and sleep disturbance.

Keywords: Rheumatoid Arthritis; Pain; Quality of life; Sleep; Depression

Introdução: O principal sintoma da artrite reumatoide (AR) é a poliartrite periférica simétrica. Esta doença causa dor crônica e incapacidade que reduzem a qualidade de vida. O objetivo do tratamento é controlar a inflamação e reduzir os sintomas. No entanto, alguns pacientes persistem com dor, apesar de atingirem a remissão inflamatória. **Objetivo:** Este estudo teve como objetivo investigar a persistência da dor em pacientes com AR com o processo inflamatório sob controle. **Métodos**: Estudo transversal abrangendo 66 pacientes com AR com doença em remissão para presença de dor (por meio do questionário McGill), para autoeficácia (por meio da Escala de Autoeficácia para Artrite-8 ou ASES-8), para depressão (pelo Center for Epidemiological Studies Depression) e qualidade do sono (por meio do questionário de Pittsburgh). A atividade inflamatória foi avaliada pelo Disease Activity Score usando 28 articulações (DAS-28), proteína C reativa (PCR) e velocidade de hemossedimentação (VHS). **Resultados:** Cerca de 12,5% dos pacientes pontuaram no 3º e 4º quartil superior do questionário McGill para dor. A qualidade do sono (r = 0,37; IC 95% = 0,14 a 0,58; p = 0,001) e a depressão (r = 0,38; IC 95% = 0,13 a 0,57; p = 0,001), mas não a VHS, PCR ou PCR DAS-28, correlacionaram-se com a dor (todas com p = ns). ASES-8 e duração da remissão não se correlacionaram com os resultados de McGill (p = ns). **Conclusão:** Há uma

proporção significativa de pacientes com AR com doença inflamatória sob controle que ainda apresentam dor. A persistência da dor se correlaciona com depressão e distúrbios do sono.

Palavras-chave: Artrite reumatoide; Dor; Qualidade de vida; Sono; Depressão.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that can cause progressive bone and cartilage damage; however, the etiology of RA remains unknown.[1] RA affects large and small joints, and most frequently affects the peripheral joints, such as the metacarpal and metatarsophalangeal joints, ankles, and wrists. Most RA treatments attempt to eliminate inflammation to avoid the symptoms of pain and stiffness, prevent structural damage with deformities and loss of function, as well as avoid complications including accelerated atherosclerosis[1]. Nevertheless, some patients continue to experience pain despite apparent good control of the underlying inflammatory process. Such patients are considered to have developed nociplastic pain (NP) secondary to a central sensitization mechanism[1,2].

NP is a subgroup of nociceptive pain that has been identified in many rheumatological diseases, fibromyalgia being the most classic example[2]. No clear evidence for tissue damage that sensitizes the nociceptive receptors has been noted in this setting. Furthermore, in some patients with RA, NP can cause a group of refractory disease without inflammation that has been called non-inflammatory refractory RA.[1] Its recognition is important because the RA treatment with DMARDs or biological drugs are not useful in this context as there is no underlying inflammation, and escalation of immunosuppressive therapy may be detrimental to the patient.[3] Additionally, the usual pain treatment with anti-inflammatory drugs or analgesics are less effective in this situation, while tricyclic antidepressants can be of help[1].

To determine the prevalence of patients with NP as well as the possible clinical associations that may help to identify this group of individuals, we studied a Brazilian sample of patients with RA with inflammatory disease under control.

MATERIALS AND METHODS

This was a cross-sectional study approved by the local Committee of Ethics in Research under protocol number 4.634.128. All participants signed consent.

It included a convenience sample of patients with RA from a single tertiary rheumatological center from the Brazilian Public Health System and that came for regular consultations during the period of August 2021 to December 2021.

Patients of both genders who were older than 18 y old were invited to participate according based on appointment scheduling and were included according to the willingness to do so. Study participants should fill at least six of 2010 RA Classification Criteria from American College of Rheumatology/European League Against Rheumatism[4] and to have their disease under remission according to the Disease Activity Score using 28 joints and C-reactive protein (DAS 28-CRP). The DAS28-CRP evaluates tenderness and swelling of selected 28 joints, patients' general well-being, and values of CRP. The score ranges from 0 and 9.4, with < 2.6 signifying remission, ≥ 2.6 and ≤ 3.2 low disease activity, > 3.2 and ≤ 5.1 moderate disease activity, and values > 5.1 signifying high disease activity %[5].

Pregnant patients with associated chronic inflammatory diseases were excluded.

Data collection comprised:

a. Epidemiological, clinical, and laboratory data: sex, age, tobacco use, auto declared ethnic background, presence of rheumatoid factor, comorbidities, and treatment, values of DAS 28-CRP, erythrocyte sedimentation rate (ESR), CRP, and duration of disease remission.
b. The following questionnaires were applied:
    1. McGill questionnaire. This questionnaire is a pain assessment instrument that characterizes and measures several domains of a patient's pain experience. It has four domains: sensorial, affective, evaluative, and miscellaneous. The sensorial domain describes how the pain feels at the moment that the questionnaire is being answered. The affective domain judges how pain changes with time and monitors the influence of habits or environment. The evaluative domain judges how strong the pain feels. The McGill questionnaire has 78 adjectives divided in 20 groups that are presented to the patient that is instructed to select one from each group that matches best his own pain experience. The

global score is obtained from the sum of the ranks of the chosen word within the group. It ranges from 0 (no pain) to 78 (worst scenario)[6].

2. Arthritis Self-Efficacy Scale-8 (ASES-8): It is an 8-item instrument used to measure self-efficacy in individuals with rheumatic diseases. Self-efficacy is considered as one's belief in the capacity to organize, face challenges, and execute actions to reach goals. Each of the item ranges from 1 (very uncertain) to 10 (very certain) The final score is the mean of individuals scores from the eight items[7].
3. Center for Epidemiological Studies Depression (CES-D): This is a 20-item questionnaire with answers graded on a Likert scale. It ranges from 0 to 60, and it is used to evaluate depressive symptoms. Values under 15 are normal, from 15 to 21 suggest mild to moderate depression and over 21 the possibility of major depression[8].
4. Pittsburgh Sleep Quality Index (PSQI) scale. This is to evaluate the sleep quality. The PSQI questionnaire has 19 questions divided into seven domains: subjective sleep quality, sleep duration, sleep latency, sleep disorders, habitual sleep efficiency, sleep medication, and daytime dysfunction. Each component is assessed by one or several questions. PSQI ≥ 5.0 means a poor sleeper, while PSQI < 5.0 means a good sleeper[9].

Data were collected in frequency tables and expressed in percentage. The obtained results of McGill questionnaire were correlated with ASES-8, DAS 28-CRP, CRP, and ESR, time of remission, CES-D, and PSQI scale by the Spearman test. The adopted significance was of 5%. The tests were performed using GraphPad Prism version 8.0.0 for Windows, GraphPad Software (San Diego, California, USA; www.graphpad.com).

RESULTS

Description of Studied Sample

Sixty-six individuals were included. The main characteristics of the studied sample are presented on Table 1, showing a predominance of female Caucasian middle-aged non-smokers.

The time of RA remission in this sample went from 2 to 72 months (median = 15; interquartile range = 7.2–24).

Table 1. Description of epidemiological, clinical, and laboratory of the studied sample

Variable	*n* or central tendency
Female/male sex	58 (87.9%) /8 (12.1%)
Median age ± SD (yr)	57.9 ± 10.4
Median age of disease onset (IQR) (yr)	48 (37.5-54.0)
Auto declared ethnic background (*n*)	
Euro descendants	42/64 (65%)
Afro descendants	22/64 (34%)
Exposed to tobacco (current and ex-smokers) (*n*)	28/66 (42.4%)
Comorbidities (*n*)	
Diabetes mellitus	8/65 (25%)
Arterial hypertension	29/65 (61%)
Dyslipidemia	28/65 (58%)
Positive rheumatoid factor (*n*)	48/64 (75%)
Treatment	
Methotrexate	35/66 (53%)
Leflunomide	29/66 (43.9%)
Glucocorticoid	27/66 (40.9%)
Biological drugs	19/66 (28.7%)
Anti-Jak	3/66 (4.5%)
Median erythrocyte sedimentation rate (mm) (IQR)	17.5 (10-38.7)
Median C-reactive protein (mg/dL) (IQR)	0.99 (0.49-3.24)
Median DAS 28 ESR (IQR)	2.54 (2.09-2.84)
Median DAS 28 CRP (IQR)	1.90 (1.43-2.16)

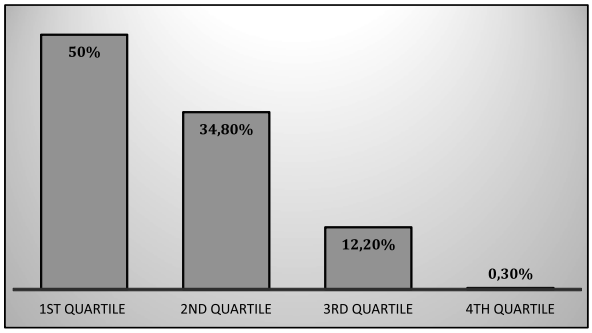
n = number, SD = standard deviation, IQR = interquartile range, DAS-28 = Disease Activity Score using 28 joints, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate.

In this sample, the median PSQI was of 8.0 (6.0–9.2) and only 14/66 (21.2%) had scores ≤ 5 (good sleepers). The median CES-D was 17.5 (14.0-24.0) and 19/66 (28.7%) scored under 15 (normal); 24/66 (36.6%) scored between 15 and 21 (at risk for mild-moderate depression), and 23/66 (34.8%) scored above 21 (at risk for severe depression).

The mean ASES-8 was 6.65 ± 1.14, and the median McGill questionnaire total score was 19.5 (11.0–24.0), with a median value of 2.5 (0–6.0) in the pain-affective domain, median value of 2.0 (1.0–4.0) in the pain-evaluative domain, and median of 11.5 (8.0–19.0) in the sensorial domain.

The proportion of patients according to quartiles of McGill questionnaire total scores is presented in **Figure 1.**

Figure 1. Distribution of rheumatoid arthritis patients in remission according to quartiles of the total McGill questionnaire for pain.



Correlations between results of McGill pain questionnaire and sleep quality, score of depression, ASES-8, and inflammatory parameters

The correlations of total pain scores by McGill questionnaire with depression, sleep quality, RA activities indexes, and the ability to resolve/manage problems by ASES-8 are presented on Table 2. This table shows that pain correlates with sleep quality indexes and depression but not with inflammatory indexes (ESR, CRP, and DAS-28 CRP).

Table 2. Correlation studies of McGill pain questionnaire— (total pain index) with activities index, PSQI, ASES-8, CES-D, and remission time.

	R Spearman	95% CI	*P*
ASES-8	-0.18	-0.41 to 0.06	0.14
PSQI	0.37	0.14 to 0.58	0.001
CES-D	0.38	0.13 to 0.57	0.001
ESR	0.09	-0.17 to 0.34	0.49
CRP	-0.03	-0.29 to 0.23	0.78
DAS 28-CRP	0.07	-0.20 to 0.33	0.60

ASES-8 = Arthritis Self-Efficacy Scale-8 items; PSQI = Pittsburgh Sleep Quality Index; CES-D = Center for Epidemiologic Studies Depression Scale; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; DAS 28 = Disease Activity Score-28 joints for rheumatoid arthritis

When the correlations are done with the different domains of McGill pain questionnaire, Table 3 presents points to a positive correlation of sleep with the three studied domains and depression with the affective and miscellaneous domains.

Table 3. Correlation studies of McGill pain questionnaire domains with activities index, PSQI, ASES-8, CED-D, and remission time.

	R	95% CI	*P*
Sensorial domain			
ASES-8	–0.19	–0.42 to 0.05	0.11
PSQI	0.35	0.11 to 0.55	**0.003**
CES-D	0.33	0.09 to 0.54	**0.005**
ESR	0.05	–0.21 to 0.31	0.68
CPR	–0.03	–0.30 to 0.23	0.77
DAS 28 CRP	0.07	–0.19 to 0.33	0.56
Remission time	0.09	–0.16 to 0.33	0.46
Affective domain			
ASES-8	–0.10	–0.34 to 0.14	0.38
PSQI	0.36	0.12 to 0.56	**0.002**
CES-D	0.25	0.001 to 0.47	**0.04**
ESR	0.01	–0.24 to 0.27	0.92
CRP	–0.07	–0.33 to 0.20	0.62
DAS 28 CRP	0.13	–0.13 to 0.38	0.32
Remission time	0.09	–0.15 to 0.33	0.44
Evaluative domain			
ASES-8	0.002	–0.24 to 0.25	0.98
PSQI	0.293	0.04 to 0.50	0.01
CES-D	0.195	–0.05 to 0.42	0.11
ESR	0.15	–0.11 to 0.39	0.25
CPR	0.0127	–0.25 to 0.27	0.92
DAS 28 CRP	–0.037	–0.30 to 0.23	0.78
Remission time	0.086	–0.16 to 0.33	0.49
Miscellaneous domain			
ASES-8	0.002	–0.24 to 0.25	0.98
PSQI	0.293	0.04 to 0.50	**0.01**
CES-D	0.195	–0.05 to 0.42	0.11
ESR	0.15	–0.11 to 0.39	0.25
CPR	0.0127	–0.25 to 0.27	0.92
DAS 28 CRP	–0.037	–0.30 to 0.23	0.78
REMISSION TIME	0.086	–0.16 to 0.33	0.49

ASES-8 = Arthritis Self-Efficacy Scale-8 PSQI = Pittsburgh Sleep Quality Index; CES-D = Center for Epidemiologic Studies Depression Scale CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; DAS 28 = Disease Activity Score-28 for rheumatoid arthritis

DISCUSSION

The present study shows that almost 12% of patients with RA in clinical remission have significant pain, reaching the upper 3rd and 4th quartile of the total value of McGill questionnaire. Sleep quality and depression scores but not inflammatory parameters correlated with pain.

Corroborating the present findings, a study in British population by Mc Williams et al. have revealed that there is a subgroup of patients with RA in which pain levels are discordant with the degree of inflammation10. Moreover, a study by Lee et al. showed that 11.9% of the patients considered to be in remission still have significant levels of pain that are associated with fatigue, sleep problems, low self-efficacy, catastrophizing behavior, and severity of initial symptom[11].

The results of this study show that, in this context, pain mechanisms are independent of joint synovitis1. Central mechanisms of pain processing may be responsible for this dissociation. The central pain pathways encompass the ascending traits (wherein a harmful peripheral stimulus is required to elicit the pain) and the descending endogenous analgesic traits. Both types of structures may be involved in the occurrence of NP. Although it is expected that the resolution of inflammation would suppress ascending painful stimulus, the degree of the initial noxious stimulus may lower the pain threshold facilitating its persistence[12]. When the pain stimuli become chronic, they can cause neuro-chemical abnormalities that promote an imbalance between inhibitory and excitatory central neurotransmitters leading to central hyperexcitability[13]. It has been described that the amount of pressure eliciting pain is lower in patients with RA than in healthy individuals, even at non-articular sites[14,15].

The association between sleep disturbances, depression, and pain is well recognized, even though the relationship of causality among them is not completely understood. Mood disorders may result from poor sleep quality,[16] and poor sleep may lead to mood alterations[17]. Similarly, sleep disturbance can worsen pain by increasing negative or reducing positive emotions; this in turn impacts pain intensity[18,19]. Hugues et al.[20] conducted a study on 200 patients with RA from UK and found that 86.5% of them had poor sleep quality, which correlated strongly with depression. This number was slightly higher than the rate of 79% found in the present study. However, in the work by Hughes et al., the sample had less than half of patients in disease remission; this may have had some influence on the results.

An unexpected result of the present study was that the self-efficacy (measured by ASES-8) did not correlate with pain scores. This instrument evaluates the self-efficacy for pain control, for control other symptoms (i.e., fatigue, affect, etc.), and for performing functional tasks21. It has been shown that higher levels of self-efficacy in patients with RA are associated with less pain, physical disability, fatigue, and depression[21]. Having studied a sample with patients in clinical remission, in which those with pain may have a nociplastic component, possibly influenced the results.

This work is limited by its cross-sectional design and small sample size. The use of DAS 28-CRP to identify patients in remission may also have caused some bias. This tool includes the count of painful joints and an evaluation of patients' general well-being that may be affected by pain[5]. So, using this instrument to classify those in remission may have selected patients with low degree of pain. On the other hand, this study has the advantage of demonstrating that, in our region, there is a significant proportion of patients with RA with pain despite good inflammatory control of RA. Pain expression has social and cultural influences and may vary according to geographically studied area.

It is vital that clinicians that care for patients with RA recognize that not all pain has an inflammatory background and that these patients may need alternative forms of treatment.

CONCLUSION

Concluding, a significant portion of patients with RA in clinical remission may have pain that associates with sleep disturbance and depression.

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ORIGINAL ARTICLE *ARTIGO ORIGINAL*

THERAPEUTIC *OFF-LABEL* STRATEGIES IN DIABETES MELLITUS COMPLICATION TREATMENT

ESTRATÉGIAS TERAPÊUTICAS *OFF-LABEL* NO TRATAMENTO DE COMPLICAÇÕES DO DIABETES MELLITUS

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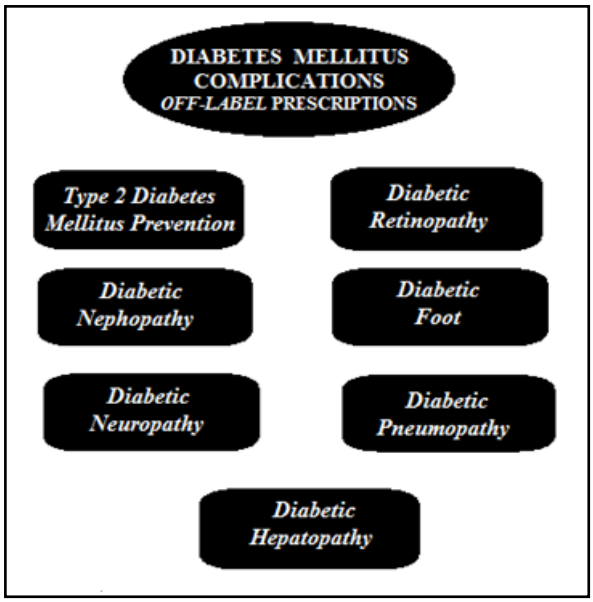
Prescribing medications outside their approved indications, a practice known globally as "*off-label*" prescribing, is relatively common among individuals with diabetes. Despite its prevalence, research in this area remains limited. This review aims to shed light on the topic by initially exploring the *off-label* use of drugs for diabetes prevention. Following that, we will delve into *off-label* treatments for diabetes complications as documented in international scientific literature, focusing on their indications and exploring them through an integrative bibliographic review. It is important to acknowledge that *off-label* prescriptions can offer distinct benefits. In some cases, they may represent the only viable treatment option for a patient. This can occur when approved medications are unavailable, ineffective, or unsuitable due to intolerability. Under such circumstances, *off-label* therapy can become the critical pathway to improved health.

Keywords: Diabetes mellitus, Complications, Off-label, Drugs.

A prescrição de medicamentos fora de suas indicações aprovadas, uma prática conhecida globalmente como prescrição "*off-label*", é relativamente comum entre indivíduos com diabetes. Apesar de sua prevalência, as pesquisas nesta área ainda são limitadas. Esta revisão tem como objetivo lançar luz sobre o tema, inicialmente explorando o uso *off-label* de medicamentos para a prevenção do diabetes. Em seguida, serão analisados os tratamentos *off-label* para as complicações do diabetes, conforme documentado na literatura científica internacional, com foco em suas indicações, por meio de uma revisão bibliográfica integrativa. É importante reconhecer que as prescrições *off-label* podem oferecer benefícios distintos. Em alguns casos, podem representar a única opção de tratamento viável para o paciente. Isso ocorre quando os medicamentos aprovados estão indisponíveis, são ineficazes ou inadequados devido à intolerância. Nesses casos, a terapia *off-label* pode se tornar o caminho crítico para a melhoria da saúde.

Descritores: Diabetes mellitus, Complicações, Off-label, Medicamentos.

Graphical Abstract: Keywords: diabetes mellitus, complications, *off-label*, drugs.



Ussue Section: Reviews.

ESSENTIAL POINTS

- *Off-label* therapy is the utilization of medications for indications that is not mentioned in the approved labeling of the drug.
- The spectrum of *off-label* use includes guideline-recommended practice, last-resort therapy, and first-line therapy. It permits innovation in clinical practice, particularly when approved treatments have failed and allows physicians to adopt new practices based on emerging evidence.
- In endocrinology, the use of *off-label* medications must be considered appropriated based on their known in clinical pharmacology, evidence from clinical studies, and sometimes from the personal experience of the prescriber.
- In diabetes mellitus pharmacotherapy, many drugs are prescribed to be given in ways and for conditions not approved in the marketing authorization. However, before recommending or prescribing any therapeutic agent *off-label*, should review the complete prescribing information, including indications, contraindications, warnings, precautions, and adverse events.

In clinical practice, prescribing a medication for an indication beyond its initial regulatory approval by a national health agency falls under the umbrella of "*off-label*" prescribing. Despite the lack of robust scientific evidence in some cases, this practice is surprisingly common.

Off-label therapy encompasses several scenarios:

- Unlabeled indications: Utilizing a medication for a condition not listed in its officially approved labeling. For example, using an anti-depressant for chronic pain management.
- Dosage or duration deviation: Prescribing outside the recommended dosage range or treatment duration specified in the label. This could involve higher doses or longer treatment courses than approved.
- Unapproved patient populations: Administering medication to groups not included in clinical trials, such as children, pregnant women, or elderly individuals.
- Exploratory use: Intentionally prescribing a medication to a patient without a definitive diagnosis, such as using an antiviral drug for someone with flu-like symptoms but without a confirmed test.
- The practice of prescribing medications for indications not explicitly approved by regulatory agencies, while legally permissible, carries significant implications for healthcare providers and must strictly adhere to relevant guidelines. Extensive research consistently demonstrates the widespread occurrence of *off-label* prescribing across various healthcare settings. In the United States, for instance, it is estimated that *off-label* use accounts for approximately 20% of all prescriptions, translating to roughly 150 million prescriptions annually[1,2]. A comprehensive understanding of this phenomenon is paramount for healthcare professionals. This knowledge is essential to effectively inform and empower their patients regarding treatment options, including those that extend beyond the limitations outlined in the traditional product labeling.

The widespread utilization of medications for indications beyond those explicitly approved by regulatory agencies can be broadly categorized into three primary domains: guideline-supported practice, first-line therapeutic approaches, and treatments employed as a last resort. In certain instances, *off-label* prescribing can serve as a catalyst for advancements in medical practice, particularly when approved treatment options have proven ineffective. This enables physicians to leverage emerging evidence-based methodologies.

However, it is crucial to acknowledge that the pharmaceutical industry may inadvertently facilitate the expansion of *off-label* use by exploiting areas of policy ambiguity, uncertainty, or lax enforcement.

Defining Appropriate *Off-Label* Use: While legally permissible, the practice of *off-label* prescribing necessitates careful ethical consideration and scrutiny. Three key categories can be identified as justifiable grounds for *off-label* use:

Prescriptions Supported by Robust Evidence: When a strong foundation of high-quality clinical research substantiates the *off-label* application, its use may be deemed appropriate.

Utilization Based on Compelling Scientific Rationale: In the absence of definitive empirical evidence, *off-label* use may be considered when supported by a compelling scientific rationale, particularly in the context of rare or complex medical conditions.

Exceptional Cases Guided by Individualized Clinical Scenarios: Under specific circumstances, a physician's expertise and experience, coupled with a meticulous evaluation of ethical considerations, can guide the decision to utilize *off-label* medications for individual patients.

It is imperative to emphasize that each instance of *off-label* prescribing necessitates meticulous documentation of the rationale underpinning the decision, a comprehensive assessment of potential risks and benefits, and unwavering adherence to relevant ethical guidelines[3].

Off-label medication use is prevalent across all medical specialties, but its occurrence may be more pronounced in patient populations underrepresented in clinical trials, such as pediatric, pregnant, or psychiatric populations[4]. Within the field of endocrinology, the utilization of medications for unapproved indications can be considered appropriate when grounded in a comprehensive understanding of their clinical pharmacology, supported by relevant scientific evidence, and, in certain instances, informed by the prescriber's personal clinical experience. However, such decisions must be carefully evaluated and meticulously documented.

In endocrinological pharmacotherapy, a significant proportion of medications are prescribed for purposes and conditions not explicitly approved by regulatory agencies. Nevertheless, prior to recommending or prescribing any therapeutic agent for an *off-label* indication, healthcare providers are obligated to conduct a thorough review of the complete prescribing information. This comprehensive review should encompass indications, contraindications, warnings, precautions, and potential adverse events. This manuscript aims to provide an overview of the available research literature that elucidates the extent of current *off-label* therapeutic utilization in the context of diabetes mellitus (DM).

TYPE 2 DIABETES MELLITUS PREVENTION

Prediabetes identification presents a critical window for proactive intervention in individuals at heightened risk of transitioning to overt type 2 DM (T2DM), a condition significantly increasing susceptibility to a spectrum of complications. Notably, approximately 25% of individuals exhibiting elevated fasting blood glucose levels are likely to progress to T2DM within a 3- to 5-year timeframe. Encouragingly, robust evidence derived from four large-scale, randomized, long-term clinical trials – the Diabetes Prevention Study, the Diabetes Prevention Program, the STOP-NIDDM trial, and the XENDOS study (XENical in the Prevention of Diabetes in Obese Subjects) – unequivocally demonstrates the efficacy of both lifestyle modifications and pharmacological interventions in substantially delaying or even preventing the onset of T2DM among high-risk individuals characterized by impaired glucose tolerance[5].

At present, no pharmacotherapeutic agents have received official approval from the U.S. Food and Drug Administration (FDA) specifically for the prevention of T2DM. Consequently, accurately determining the frequency of *off-label* medication utilization for T2DM prevention remains a challenging endeavor. Therefore, any clinical decision to employ *off-label* pharmacological interventions for the management of prediabetes or impaired fasting glycemia necessitates a meticulous and comprehensive risk-benefit assessment for each individual medication under consideration.

It is noteworthy that several medications currently approved for the treatment of T2DM and obesity are being prescribed *off-label* to mitigate the risk of T2DM development in high-risk individuals. This observation underscores the paramount importance of a rigorous and judicious evaluation of medication use in patients with impaired fasting glycemia, with the ultimate objective of achieving early and effective prevention of T2DM and its associated complications.

Alpha-glucosidase inhibitors

α-Glucosidase inhibitors, a class of medications comprising acarbose, miglitol, and voglibose, exert their therapeutic effect by significantly delaying car-

bohydrate absorption within the small intestinal lumen. This mechanism of action translates to a notable reduction in postprandial blood glucose levels and a concomitant decrease in insulin secretion. Furthermore, emerging evidence suggests that α-glucosidase inhibitors may potentiate the secretion of incretin hormones and modulate the composition of the gut microbiota, potentially contributing significantly to their observed beneficial effects on glycemic control and glucose tolerance[6,7].

Acarbose and miglitol have garnered FDA approval for their utilization as monotherapy or in combination regimens for the management of T2DM[8]. The landmark STOP-NIDDM trial provided compelling evidence, demonstrating a substantial 25% reduction in the incidence of T2DM among high-risk individuals exhibiting impaired glucose tolerance who received acarbose therapy compared to a control group receiving placebo[9]. Moreover, another study reported a noteworthy decrease in platelet-derived microparticles and select adhesion molecules in T2DM subjects undergoing acarbose treatment, suggesting a potential ancillary benefit in the primary prevention of atherothrombosis[10].

Voglibose has demonstrated promising potential in delaying the progression of impaired glucose tolerance to overt T2DM. A rigorous clinical trial revealed a significantly lower hazard ratio for T2DM development among individuals receiving voglibose compared to those receiving placebo, strongly indicating a protective effect. Furthermore, a significantly higher proportion of individuals in the voglibose treatment group achieved normoglycemia compared to the placebo group[11].

Collectively, these findings strongly suggest that the *off-label* utilization of α-glucosidase inhibitors may offer significant preventive benefits against the development of T2DM.

Angiotensin converting enzyme inhibitors

Angiotensin-converting enzyme (ACE), a zinc-dependent dipeptidylcarboxypeptidase, exerts profound and multifaceted effects on various physiological systems through its pivotal role within the renin-angiotensin-aldosterone system (RAAS). By catalyzing the conversion of angiotensin I to the potent vasoconstrictor angiotensin II, ACE exerts a profound influence not only on blood pressure regulation but also on a diverse array of physiological processes, encompassing fluid and electrolyte homeostasis, renal development and function, reproductive function, hematopoiesis, and the modulation of immune system activity[12].

Beyond its direct enzymatic activity, both ACE activity and its product, angiotensin II, have been implicated in the pathogenesis of a multitude of pathophysiological conditions. Of particular significance, angiotensin II has emerged as a key player in the development and progression of insulin resistance (IR) and type 2 DM (T2DM). Several mechanistic pathways contribute to this angiotensin II-mediated effect, including compromised sympathetic nervous system activity and impaired peripheral blood flow, detrimental effects on adipose tissue metabolism, increased oxidative stress, and the disruption of insulin signaling pathways[13].

ACE inhibitors have established themselves as a cornerstone of therapeutic management for hypertension and cardiovascular diseases. Their primary mechanism of action involves competitively inhibiting the conversion of angiotensin I to the potent vasoconstrictor angiotensin II. Moreover, their ability to impede the degradation of bradykinin has generated considerable interest in exploring their potential therapeutic applications beyond traditional cardiovascular indications.

Emerging evidence from large-scale clinical trials strongly suggests a promising role for ACE inhibitors in the prevention of T2DM. These studies provide compelling evidence that ACE inhibitors may effectively preserve pancreatic β-cell function and mitigate the development of T2DM, particularly in hypertensive individuals characterized by impaired glucose tolerance[14]. Notably, these findings highlight a potential 15-30% reduction in T2DM incidence among individuals receiving ACE inhibitors compared to placebo or alternative therapeutic interventions[15].

Metformin

Metformin, a pharmacologically and chemically distinct agent belonging to the biguanide class, has established itself as a cornerstone of oral antihyperglycemic therapy for the management of T2DM and IR. Characterized by a favorable safety and tolerability profile, metformin has enjoyed widespread clinical utilization for many years, solidifying its position as a prime candidate for the prevention of T2DM[16].

Emerging evidence strongly supports the potential of metformin in mitigating the risk of T2DM onset in individuals at heightened risk. The *off-label* utilization of metformin as a preventive measure in these high-risk populations is gaining significant traction, driven by compelling evidence of improved insulin sensitivity and a notable delay in T2DM progression[17]. The compelling combination of efficacy, affordability, and a favorable safety profile renders metformin an attractive therapeutic option for T2DM prevention, par-

ticularly in individuals under 60 years of age, women with a history of gestational diabetes, and those with other established high-risk factors[18].

Multiple clinical studies have unequivocally demonstrated a significant reduction in the risk of developing T2DM, on the order of 31%, among individuals receiving metformin therapy[19]. This robust evidence base solidifies metformin's position as one of the most extensively investigated and efficacious medications for the prevention of T2DM. As a potent insulin sensitizer, metformin exerts its antihyperglycemic effects primarily through the suppression of hepatic gluconeogenesis and the inhibition of mitochondrial oxidative processes, consequently reducing free fatty acid production and enhancing peripheral glucose uptake. Intriguingly, emerging research suggests that the protective mechanisms of metformin extend beyond insulin sensitization to include the preservation of pancreatic β-cell function, further contributing to its therapeutic efficacy without the adverse consequence of weight gain[20].

Beyond its established role in T2DM prevention, the application of metformin may extend to mitigating the risk of gestational diabetes in women with polycystic ovary syndrome. A growing body of research provides compelling evidence for the significant efficacy of metformin treatment in substantially reducing the incidence of gestational diabetes within this specific patient population[21]. Despite ongoing debate surrounding its *off-label* utilization, metformin has also demonstrated potential in effectively managing glycemic control during pregnancy in women diagnosed with gestational diabetes[22].

Orlistat

Orlistat, a synthetic lipase inhibitor, exerts its therapeutic effect by potently inhibiting both gastric and pancreatic lipases, thereby impeding the hydrolysis of triglycerides and consequently reducing dietary fat absorption. Through specific binding to pancreatic lipase, a critical enzyme involved in triglyceride breakdown, orlistat achieves a substantial 30% reduction in dietary fat absorption at a therapeutic dose of 120 mg. The primary site of action for orlistat is within the intestinal lumen, with minimal systemic absorption and negligible hepatic metabolism. Notably, approximately 83% of the administered drug is excreted unchanged in the feces[23].

The XENDOS trial, a large-scale, placebo-controlled clinical investigation, rigorously evaluated the efficacy of orlistat in preventing the onset of T2DM in a cohort of obese participants. This pivotal study yielded compelling evidence, demonstrating a significant 37.3% reduction in the cumulative incidence of diabetes. In participants exhibiting impaired glucose tolerance at baseline, the risk of developing T2DM within a 4-year timeframe was markedly reduced by 45%. Furthermore, this intervention demonstrated favorable effects on several key metabolic parameters, including blood pressure, lipid profiles, and waist circumference[24].

Smaller-scale clinical studies have corroborated these findings, further supporting the positive impact of orlistat on various metabolic parameters[25]. Notably, a European multicenter trial observed significant improvements in serum insulin and glucose levels within the orlistat treatment group compared to the placebo group[26].

Collectively, clinical investigations conducted to date provide strong evidence suggesting that orlistat administration exerts a beneficial influence on carbohydrate homeostasis, even exhibiting the potential to prophylactically impede the onset of T2DM in obese individuals with normoglycemic glucose tolerance. However, a crucial question that remains to be definitively addressed is whether the preventive effects of orlistat truly reflect a genuine reduction in T2DM incidence or merely delay the diagnosis of the condition.

Thiazolidinediones

Thiazolidinediones constitute a synthetic class of medications characterized by a common thiazolidinedione ring structure, which is hypothesized to be responsible for their antihyperglycemic effects. Substituent moieties exert a significant influence on their pharmacokinetic and pharmacodynamic profiles. Developed primarily for the treatment of T2DM, thiazolidinediones function as potent agonists of peroxisome proliferator-activated receptor gamma (PPAR-γ). By binding to specific gene response elements, they modulate the expression of genes involved in regulating insulin action and lipid metabolism. This translates into enhanced glucose uptake by adipose and muscle tissues, coupled with a concomitant reduction in hepatic gluconeogenesis, ultimately resulting in increased free fatty acid capture. These pleiotropic effects ultimately contribute to the normalization of glycemic levels, as evidenced by sustained improvements in glycated hemoglobin levels over time[27].

Beyond their FDA-approved indication for the treatment of T2DM, thiazolidinediones find *off-label* applications in a diverse range of clinical settings. These include managing impaired glucose tolerance in individuals with cerebrovascular disease, addressing

T2DM-associated nephropathy, preventing cardiovascular complications in patients with T2DM, and even exploring their potential role in the primary prevention of T2DM itself[28].

Several studies have investigated the potential utility of thiazolidinediones in preventing the onset of T2DM. Emerging evidence suggests that early administration of thiazolidinediones may effectively hinder the progression from IR to overt T2DM[29]. This notion is further supported by interventional studies demonstrating the capacity of thiazolidinediones to delay, stabilize, and potentially even prevent the onset of T2DM in high-risk individuals. Clinical evidence strongly suggests that thiazolidinediones exert a beneficial influence on pancreatic β-cell function, potentially improving insulin secretion, preserving islet architecture and β-cell mass, and shielding β-cells from the deleterious effects of oxidative stress. Furthermore, thiazolidinediones have been shown to enhance key β-cell function metrics, such as the insulinogenic index and homeostasis model assessment[30].

Multiple clinical studies provide compelling evidence for the ability of thiazolidinediones to delay or arrest the progression of metabolic decline. Four landmark studies stand out:

Diabetes Prevention Program: This study demonstrated a significant reduction in the relative risk of T2DM progression by 55-62% among individuals receiving thiazolidinediones[31].

Pioglitazone in Prevention of Diabetes Study and TRIPOD Study: These studies provided robust evidence for sustained β-cell function preservation in a subset of individuals receiving thiazolidinediones, strongly supporting their potential for genuine T2DM prevention. The proposed mechanism underlying this effect involves a reduction in insulin secretory demands secondary to improved chronic IR[32,33].

Diabetes Reduction Assessment with rosiglitazone and ramipril Medication Study (DREAM Study): This study revealed a significant 62% relative risk reduction for T2DM development over a 4-year period among individuals receiving rosiglitazone, whereas ramipril did not exert a significant impact on T2DM incidence[34].

DIABETIC NEPHROPATHY

Diabetic nephropathy stands as a formidable complication of diabetes, significantly contributing to global morbidity and mortality, driven by the escalating prevalence of T2DM.

Podocyte injury and the subsequent development of albuminuria are widely recognized as pivotal events in the pathogenesis of diabetic kidney disease. The progression of diabetic nephropathy typically follows a predictable trajectory, characterized by distinct stages. The initial phase is characterized by an increase in glomerular filtration rate and intra-glomerular capillary pressure, followed by the development of glomerular hypertrophy and the onset of microalbuminuria. Microalbuminuria often serves as an early harbinger of the eventual elevation in serum creatinine levels[35].

Developing novel therapeutic avenues for the effective management of diabetic nephropathy presents a significant challenge, underscored by the paucity of innovative treatment strategies since the *off-label* introduction of angiotensin II receptor blockers (ARBs) over a decade ago. While *off-label* administration of ARBs, targeting the RAAS, has demonstrably slowed the progression to end-stage renal disease, it falls short of providing complete prevention of this devastating complication.

Angiotensin II Receptor Blockers

ARBs selectively target the Angiotensin II type 1 receptor (AT1) receptor, effectively negating the downstream effects of angiotensin II, irrespective of its production pathway. This targeted inhibition translates into vasodilation and a reduction in fluid retention, while simultaneously sparing the bradykinin pathway – a key differentiator that minimizes the occurrence of side effects such as cough and angioedema[36]. Currently, a spectrum of seven ARBs is clinically available for therapeutic use: candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan. Several controlled clinical trials have rigorously evaluated the efficacy of ARBs in managing diabetic nephropathy among patients with T2DM[37]. Notably, only losartan and irbesartan have received regulatory approval for the specific treatment of renal disease within this patient population.

Candesartan is primarily prescribed for the management of hypertension and heart failure with reduced ejection fraction. While its *off-label* use in diabetic nephropathy has been explored, the available evidence remains limited. A single clinical study comparing candesartan to placebo in preventing the onset of microalbuminuria in diabetes failed to provide compelling support for its use in this specific scenario[38]. However, multiple studies have suggested potential renoprotective benefits of candesartan. A large, double-blind Japanese trial investigated the effect of candesartan on proteinuria in diabetic patients

with established proteinuria. Patients were randomly assigned to receive candesartan or placebo for a 12-week period. The candesartan group demonstrated significantly greater reductions in proteinuria compared to the placebo group[39].

Eprosartan stands out due to its unique "double block" mechanism. Unlike other ARBs, it targets both presynaptic and postsynaptic AT1 receptors, leading to a significantly greater reduction in sympathetic nerve activity. This dual mechanism of action translates into potent therapeutic effects:

Blocking angiotensin II binding: Eprosartan effectively blocks the binding of angiotensin II to AT1 receptors within vascular smooth muscle, resulting in vasodilation and a subsequent reduction in blood pressure.

Inhibiting norepinephrine production: Additionally, eprosartan directly inhibits the production of norepinephrine, a potent vasoconstrictor released by the sympathetic nervous system.

These combined effects render eprosartan particularly compelling for the management of blood pressure, especially in individuals with chronic renal failure[40]. Clinical studies have demonstrated its efficacy in completely reversing the pressure-raising effects, aldosterone secretion, and renal vasoconstriction induced by angiotensin II. A notable advantage of eprosartan is its lack of sodium retention, even at blood pressure-lowering doses, which represents a potential drawback of some other ARB agents[41].

Olmesartan exhibits remarkably high selectivity for the AT1 receptor subtype over the type 2 receptor (AT2). This translates into potent inhibition of the AT1 pathway, effectively bypassing angiotensin II synthesis. Consequently, olmesartan triggers negative feedback mechanisms that decrease renin secretion, ultimately leading to a reduction in aldosterone production and vasoconstriction. This cascade of events culminates in vasodilation, diminished peripheral resistance, and ultimately, a significant reduction in blood pressure[42]. The ROADMAP study (Randomized Olmesartan And Diabetes Microalbuminuria Prevention) investigated whether more stringent blood pressure control and blockade of the renin-angiotensin system (RAS), achieved through olmesartan therapy, could effectively prevent or delay the onset of microalbuminuria. The study findings revealed that pharmacological AT1 receptor inhibition significantly reduces the risk of developing new-onset albuminuria in patients with T2DM[43]. Further analysis of the hypertensive subpopulation within the ROADMAP study demonstrated that patients with greater blood pressure reductions exhibited a lower risk of microalbuminuria. Importantly, olmesartan treatment independently delayed the onset of microalbuminuria, irrespective of baseline blood pressure or the extent of achieved blood pressure reduction[44].

Telmisartan, a non-peptide antagonist of the AT1 receptor, selectively targets this specific receptor subtype without affecting other cardiovascular regulatory pathways[45]. In patients with T2DM, telmisartan offers a spectrum of renal benefits across various stages of disease progression. A recent study revealed that telmisartan not only improves insulin sensitivity and glucose tolerance but also effectively prevents the gradual decline in kidney function typically associated with diabetic nephropathy. This was evidenced by a reduction in microalbuminuria and the prevention of glomerulosclerosis, renal inflammation, and interstitial fibrosis[46]. The AMADEO trial (A comparison of telMisartan versus losArtan in hypertensive type 2 DiabEtic patients with Overt nephropathy), comparing telmisartan and losartan in hypertensive T2DM patients with overt nephropathy, investigated both renal and cardiovascular outcomes. The results demonstrated that telmisartan exhibited superior efficacy in reducing proteinuria compared to losartan within this specific patient population. This observed advantage is attributed to its dual mechanism of action, encompassing partial agonism of the PPAR-γ and antagonism of the AT1 receptor[47].

Valsartan selectively inhibits the AT1 receptor, leaving the beneficial AT2 receptor unaffected[48]. The MicroAlbuminuria Reduction WithVALsartan (MARVAL) study assessed the independent effect of valsartan on protein excretion in T2DM patients with microalbuminuria, irrespective of any concomitant changes in blood pressure. Results revealed that, compared to amlodipine, valsartan was more effective in reducing elevated protein excretion, even in normotensive patients[49]. This compelling evidence demonstrates that valsartan offers renoprotective benefits in T2DM with diabetic nephropathy, extending beyond its well-established blood pressure-lowering effects.

DIABETIC NEUROPATHY

Diabetic neuropathy, characterized by nerve dysfunction in individuals with diabetes, represents a significant and often debilitating complication of the disease. This chronic condition, a direct consequence of prolonged hyperglycemia, manifests as a spectrum of symptoms, including pain, discomfort, and functional disability. The San Antonio Consensus Statement on Diabetic Neuropathy[50] defines diabetic neuropathy as

a verifiable dysfunction of the nervous system, either clinically apparent or subclinical, observed in individuals with diabetes, while excluding other specific etiologies of peripheral neuropathy. The profound impact of diabetic neuropathy on the quality of life of individuals with diabetes cannot be overstated, given the significant burden of pain, discomfort, and functional limitations it imposes. Furthermore, the efficacy of currently available treatment options remains inconsistent and often suboptimal.

Selecting appropriate analgesic medications for the management of pain in diabetic neuropathy remains a significant clinical challenge, lacking clear evidence-based guidelines. The comparative effectiveness of various analgesic agents remains uncertain, and no single class of medication or specific drug consistently demonstrates superior efficacy. Effective pharmacological management of neuropathic pain in diabetes aims to maximize pain relief while minimizing the occurrence of adverse side effects, ultimately improving the patient's overall quality of life and functional capacity. The optimal therapeutic approach necessitates a highly individualized treatment plan, tailored to each patient's unique clinical presentation. The frequent utilization of *off-label* prescriptions underscores the significant unmet clinical need for the development of diverse and effective treatment options for diabetic neuropathy.

Antiepileptic

Beyond their primary role in the management of epilepsy, certain antiepileptic drugs have found valuable applications in other medical fields. In endocrinology, they are frequently prescribed *off-label* for the treatment of various conditions, including diabetic neuropathy and, more recently, eating disorders or obesity.

For the management of diabetic peripheral neuropathic pain, specific anticonvulsant medications have demonstrated clinical efficacy. Among these, gabapentin stands out as a particularly promising therapeutic option, characterized by an excellent safety profile, good tolerability, and a minimal propensity for drug interactions[51]. While the precise mechanisms underlying the therapeutic effects of gabapentin in diabetic neuropathy remain to be fully elucidated, several potential explanations have been proposed. These include alterations in the production and release of gamma-aminobutyric acid (GABA), modulation of voltage-gated sodium and calcium channels, alterations in serotonin levels, and the regulation of monoamine neurotransmitter release[52].

Carbamazepine, another anticonvulsant medication, initially found *off-label* application in the management of trigeminal neuralgia following its introduction in 1962. This occurred prior to the establishment of our current understanding of the neurophysiology of nociception and the neuropathology of neuropathic pain[53]. Carbamazepine exerts its therapeutic effects by inhibiting the repetitive firing of action potentials in depolarized neurons through the blockade of frequency-, use-, and voltage-dependent sodium channels. It undergoes hepatic metabolism, with its active epoxide metabolite subsequently being hydrolyzed to an inactive diol metabolite that is ultimately excreted through the kidneys[52,54].

Although diabetic neuropathy represents a common clinical concern in primary healthcare settings, the available evidence base assessing the efficacy of carbamazepine for the management of neuropathic pain in diabetes remains relatively limited[55]. Nevertheless, clinical experience suggests that the *off-label* use of carbamazepine can be effective in managing chronic pain in the context of diabetic neuropathy[56].

Oxcarbazepine, a newer antiepileptic drug, has emerged as a potential therapeutic option for the management of painful diabetic neuropathy, exhibiting promising antineuralgic properties in preclinical animal models. Following oral administration, oxcarbazepine undergoes a unique metabolic pathway involving conjugation and reduction, with the monohydroxy derivative representing the primary pharmacologically active metabolite[57]. While sharing mechanistic similarities with carbamazepine, oxcarbazepine offers a more favorable side effect profile[58]. This advantage has been corroborated by double-blind, placebo-controlled clinical trials, which suggest its efficacy in managing *off-label* painful diabetic neuropathy at a well-tolerated dosage of 1800 mg/day, offering hope for improved long-term pain management within this patient population[58].

Lamotrigine, an antiepileptic medication, possesses a distinct mechanism of action. It modulates the activity of voltage-gated sodium channels at the presynaptic terminal, specifically inhibiting the release of glutamate and aspartate, neurotransmitters triggered by the sodium channel activator veratrine, while minimally affecting the release of acetylcholine or GABA[59]. While lamotrigine has established utility in the treatment of epilepsy and bipolar disorder, its *off-label* application for the management of neuropathic pain, particularly diabetic neuropathy, presents a more nuanced clinical picture. While some studies have demonstrated promising results for lamotrigine

in alleviating diabetic neuropathic pain[60], other studies have indicated limited clinical efficacy[61]. Furthermore, the potential for adverse side effects and the requirement for slow medication titration raise concerns regarding its suitability as a first-line treatment option. Therefore, while lamotrigine exhibits certain pharmacological properties suggestive of potential pain-relieving effects, its definitive efficacy in managing diabetic neuropathy remains inconclusive. Further rigorous research is necessary to establish its precise role and optimal positioning within the broader therapeutic landscape for this condition.

Topiramate, an antiepileptic drug with a multifaceted mechanism of action, exerts its effects through a combination of pharmacological pathways. It blocks voltage-gated sodium channels, enhances GABAergic signaling, and inhibits excitatory neurotransmission by targeting α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor sites[62]. This multifaceted mechanism of action may explain its potential for anticonvulsive, antinociceptive, and neuroprotective effects. Beyond its primary role in the management of epilepsy, topiramate has found *off-label* applications in diverse clinical conditions, including bulimia nervosa, obesity, and neuropathic pain. Notably, its therapeutic potential in these conditions may be attributed to its ability to modulate the activity of the central nervous system's GABA and glutamate neurotransmitter systems[63].

Studies have documented instances of pain relief in patients with diabetic peripheral neuropathy following topiramate treatment, with some initial pilot studies even suggesting the potential for nerve fiber regeneration. However, larger-scale investigations have not consistently demonstrated a statistically significant difference in pain scores compared to placebo[64]. This conflicting evidence underscores the critical need for well-designed, randomized controlled trials specifically investigating the efficacy of topiramate in managing painful diabetic peripheral neuropathy. Only through such focused research can we accurately evaluate the true potential of topiramate as an *off-label* treatment option for this complex pain syndrome.

Valproic acid, traditionally employed as an antiepileptic medication, has demonstrated potential therapeutic efficacy in the management of chronic neuropathic pain, despite lacking official regulatory approval for this indication. Its multifaceted mechanism of action encompasses several key targets, including sodium channel blockade, enhanced GABAergic neurotransmission, and modulation of N-methyl-D-aspartate receptors. Primarily metabolized by the liver through β-oxidation and glucuronidation pathways, its metabolites are predominantly excreted renally[65]. Clinical studies have provided evidence for the significant role of valproic acid in subjectively improving pain perception in patients with diabetic neuropathy, offering the distinct advantages of a favorable safety profile and a generally well-tolerated side effect profile. Furthermore, valproic acid has been shown to induce noteworthy improvements in both subjective pain scores and objective electrophysiological parameters[66]. However, a recent comprehensive review concludes that the current evidence base is insufficient to definitively endorse valproic acid as a first-line treatment option for neuropathic pain[67]. While valproic acid exhibits promising therapeutic potential in the management of neuropathic pain, further rigorous research is necessary to definitively establish its efficacy and safety profile. Until such evidence is firmly established, its use in this context should be approached with caution and reserved for specific clinical scenarios under close medical supervision.

Zonisamide, another antiepileptic medication, possesses a unique mechanism of action that suggests potential efficacy in controlling the symptoms of neuropathic pain. These mechanisms include blockade of T-type calcium channels, sodium channel blockade, scavenging of free radicals, and inhibition of nitric oxide synthesis. However, the precise link between these pharmacological actions and the observed analgesic effects of zonisamide remains to be fully elucidated[68-71].

Clinical evidence regarding the efficacy of zonisamide in managing neuropathic pain is currently equivocal. Larger-scale, well-designed, randomized controlled trials are urgently needed to definitively establish the efficacy and tolerability of zonisamide in the treatment of painful diabetic neuropathy[72].

Antidepressant

The history of managing neuropathic pain with antidepressants encompasses three distinct generations of these medications. Tricyclic antidepressants (TCAs), characterized by their three-ringed molecular structure, represent the first generation. The second generation of antidepressants, while exhibiting diverse chemical structures, shares a common mechanism of action: selective serotonin reuptake inhibition. Similarly, third-generation antidepressants, although structurally and pharmacodynamically varied, are primarily characterized by their selective norepinephrine reuptake inhibition properties[73].

Within this evolving therapeutic landscape, certain antidepressants have emerged as particularly ef-

fective in the *off-label* treatment of neuropathic pain. Amitriptyline, doxepin, imipramine, venlafaxine, and bupropion stand out as the most successful agents in this context, with desipramine and nortriptyline demonstrating moderate efficacy. In contrast, fluoxetine has exhibited limited efficacy in managing neuropathic pain.

Several TCAs have established clinical utility in the *off-label* management of neuropathic pain. Specifically, clinical studies have confirmed their effectiveness in alleviating painful diabetic neuropathy, particularly in patients with diabetes. Notably, the dosage of TCAs prescribed for pain management is typically significantly lower than that typically employed for the treatment of depression.

For many years, clinicians have utilized TCAs to manage neuropathic pain, despite the absence of formal FDA approval for this indication. TCAs remain a first-line therapeutic option for diabetic peripheral neuropathic pain in suitable patients. While the primary mechanism of action of TCAs involves inhibiting the presynaptic reuptake of norepinephrine and serotonin, additional mechanisms, such as ion channel blockade and NMDA receptor antagonism, likely contribute to their observed pain-relieving properties[74,75].

Among the TCAs, amitriptyline has demonstrated clinical efficacy in treating painful diabetic neuropathy, with studies reporting significant pain reduction[76]. The clinical evidence supporting the use of imipramine and nortriptyline in this context has been less consistent; however, nortriptyline is often favored due to its generally more favorable side effect profile compared to amitriptyline[77,78].

Venlafaxine, a representative of the newer generation of antidepressants, exhibits growing significance in the management of pain. Beyond its established capacity to inhibit serotonin and norepinephrine reuptake, venlafaxine demonstrates diverse pharmacological actions, including antagonism of α1-adrenergic, nicotinic, muscarinic, and histaminic receptors, blockade of calcium, sodium, and potassium channels, weak dopamine reuptake inhibition, and mild NMDA receptor antagonism[79,80]. These multifaceted pharmacological actions suggest a potential advantage over classic TCAs for neuropathic pain relief, irrespective of the presence or absence of coexisting mood disorders.

Bupropion, a β-ketoamphetamine and substituted cathinone, exhibits selective binding affinity for the dopamine transporter. However, its behavioral effects are often attributed to its potent norepinephrine reuptake inhibitor[81], as well as its nicotinic acetylcholine receptor antagonist activity[82]. Chemically classified as an aminoketone, bupropion shares structural similarities with diethylpropion, cathinone, and the broader phenethylamine class. Initially approved by the FDA in 1989 for the treatment of depression[83], bupropion has found valuable applications beyond its labeled indications. In endocrinology, bupropion finds *off-label* use for weight management, improvement in sexual function in patients with T2DM, and the management of diabetic neuropathy. Clinical trials provide growing support for its role in treating diabetic neuropathy, attributed to its specific inhibition of neuronal norepinephrine reuptake and its weak inhibition of dopamine reuptake[84].

Paroxetine, a selective serotonin reuptake inhibitor (SSRI) established for the treatment of depression, exhibits potential in the *off-label* management of diabetic neuropathy symptoms[85]. A clinical study demonstrated that daily administration of 40 mg of paroxetine significantly reduced symptoms in patients with peripheral diabetic neuropathy, without the common occurrence of autonomic side effects[86].

Citalopram, another SSRI, holds FDA approval for the treatment of major depressive disorder but finds *off-label* use in the management of various conditions, including symptom relief in diabetic neuropathy[87]. A comprehensive systematic review and meta-analysis encompassing 25 randomized controlled trials evaluated the efficacy and safety of citalopram in a cohort of 2,984 patients with painful diabetic neuropathy compared to placebo. The analysis revealed that citalopram treatment resulted in pain reduction exceeding 50% or moderate pain relief in a significant proportion of patients[88].

DIABETIC RETINOPATHY

Diabetic retinopathy, a microvascular complication of diabetes, is characterized by distinct retinal lesions that develop over time in individuals with diabetes. This condition transcends a mere ocular manifestation, emerging as a neurovascular disease. Neurodegeneration precedes and coexists with the microvascular changes observed in diabetic retinopathy. Beyond its impact on vision, diabetic retinopathy signifies an increased risk of developing severe systemic vascular complications[89].

Recent advancements in our understanding of the complex pathophysiology of diabetic retinopathy have revealed the involvement of numerous cell types in its development. Among these, vasoactive and pro-inflammatory molecules, such as vascular

endothelial growth factor (VEGF), play an important role in driving the disease process. Ongoing research investigating the role of additional agents involved in angiogenesis and vasopermeability holds significant promise for the development of future management strategies, despite the continued threat of vision loss associated with this debilitating condition[90].

The classification system for diabetic retinopathy, established at the 2002 International Congress of Ophthalmology in Sydney, categorizes the disease into the following stages: no apparent retinopathy, mild, moderate, or severe non-proliferative diabetic retinopathy, and proliferative diabetic retinopathy[91].

The standard of care for diabetic retinopathy encompasses a multi-pronged approach, including strict metabolic control, rigorous blood pressure monitoring, laser photocoagulation, and vitrectomy[92]. While the emergence of VEGF-blocking agents has revolutionized the treatment landscape for diabetic retinopathy, particularly for diabetic macular edema, incomplete treatment responses highlight the multifactorial nature of this complex disease[89]. *Off-label* therapies currently employed in the management of diabetic retinopathy include antiplatelet agents, bevacizumab, corticosteroids, fenofibrate, lisinopril, pegaptanib, and statins.

Antiplatelet agents

Aspirin exerts its potent anti-inflammatory effects through mechanisms beyond solely inhibiting cyclooxygenase enzymes via acetylation and suppressing specific transcription factors[93]. Studies conducted in animal models of diabetes have suggested that aspirin may possess the ability to stall the progression of diabetic retinopathy, raising the intriguing possibility that anti-inflammatory drugs may offer beneficial effects in mitigating diabetic retinal pathology[94]. The potential of aspirin as a preventive measure for diabetic retinopathy in individuals with diabetes has garnered considerable interest. An experimental study demonstrated its potential for both primary and secondary prevention, suggesting potential therapeutic value[94]. However, the evidence supporting the use of aspirin in the management of diabetic retinopathy remains somewhat conflicting. The Early Treatment Diabetic Retinopathy Study (ETDRS) concluded that daily administration of 650 mg of aspirin did not yield any significant benefit in treating established retinopathy[95]. Nonetheless, the ETDRS did not identify any contraindications to the use of aspirin in patients with retinopathy when prescribed as a platelet antiaggregant for the prevention of coronary artery disease or other established cardiovascular indications.

Bevacizumab

Diabetic retinopathy, a microvascular complication of diabetes, is characterized by the development of retinal lesions and represents a significant cause of vision loss. This complex condition involves both neurodegenerative and microvascular changes. Beyond its impact on visual function, diabetic retinopathy is associated with an increased risk of systemic vascular complications[89].

Recent advancements in our understanding of the intricate pathophysiology of diabetic retinopathy have revealed the involvement of numerous cellular and molecular pathways. Among these, vasoactive and pro-inflammatory molecules, such as VEGF, play a important role in driving the disease process. Ongoing research investigating the role of additional signaling pathways and cellular interactions involved in angiogenesis and vasopermeability holds significant promise for the development of novel therapeutic strategies, despite the continued challenges posed by this sight-threatening condition[90].

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The standard of care for diabetic retinopathy encompasses a multi-pronged approach, including strict glycemic control, rigorous blood pressure management, laser photocoagulation, and vitrectomy[92]. While the emergence of VEGF-targeting therapies has revolutionized the treatment landscape for diabetic retinopathy, particularly for diabetic macular edema, incomplete treatment responses highlight the multifactorial nature of this complex disease and the need for ongoing therapeutic innovation[89]. *Off-label* therapies currently employed in the management of diabetic retinopathy include antiplatelet agents, bevacizumab, corticosteroids, fenofibrate, lisinopril, pegaptanib, and statins.

Bevacizumab

Bevacizumab, a recombinant humanized monoclonal antibody, specifically targets and neutralizes all isoforms of human VEGF, effectively blocking its biological activity. This mechanism of action prevents VEGF from interacting with its receptors, thereby halting the intracellular signaling pathways that trigger endothelial cell proliferation and the formation of new blood vessels[96]. Initially developed as an anti-angiogenic therapy for the treatment of solid tumors, bevacizumab's

humanization significantly reduces its immunogenicity and extends its circulating half-life. Despite its *off-label* use, intravitreal bevacizumab has emerged as a viable and cost-effective therapeutic option for diabetic retinopathy, experiencing a significant increase in clinical utilization[97]. Numerous studies have demonstrated its efficacy in reducing fibrovascular proliferation and vascular permeability in various ocular pathologies, including macular edema associated with central vein occlusion, retinal neovascularization in proliferative diabetic retinopathy, and choroidal neovascularization in age-related macular degeneration[98]. A two-year study evaluating anatomical and functional outcomes in subjects with diffuse diabetic macular edema treated with intravitreal bevacizumab with or without laser photocoagulation, compared to laser photocoagulation alone, provides strong evidence supporting the use of primary intravitreal bevacizumab, with or without grid laser, for the management of this condition[99].

Corticosteroids

Corticosteroids, a class of hormones naturally produced by the adrenal glands and also synthesized for clinical use, exert a profound influence on a diverse array of physiological processes, including immune response, stress response, inflammation regulation, protein breakdown, carbohydrate metabolism, and electrolyte balance. While offering short-term improvements in anatomical and visual outcomes in some patients, *off-label* intravitreal administration of corticosteroids necessitates multiple injections, which can accumulate over time and increase the risk of complications such as cataracts, endophthalmitis, and elevated intraocular pressure[100].

Triamcinolone, a synthetic glucocorticoid with low aqueous solubility and sustained-release properties, exhibits rapid bioavailability following intravitreal administration. Beyond suppressing inflammation and the proliferative response in proliferative retinopathy, it can also inadvertently impede the healing process, as inflammation plays a crucial role in tissue repair. Introduced in 1979 for the management of refractory diabetic macular edema, intravitreal triamcinolone has gained traction as a treatment option for select patients due to its ability to attenuate VEGF-mediated retinal capillary permeability, a presumed contributor to the pathogenesis of diabetic macular edema. Studies have documented its effectiveness in improving visual acuity, reducing macular thickness, and promoting the resorption of hard exudates[101,102].

Dexamethasone, a potent water-soluble corticosteroid, is available as an intravitreal implant. This biodegradable implant, composed of lactic and glycolic acid copolymers, releases micronized dexamethasone gradually within the vitreous cavity following insertion through a small pars plana puncture using a specialized applicator[103]. FDA-approved for the treatment of uveitis, intermediate/posterior segment diseases, macular edema, and non-infectious ocular inflammation, dexamethasone implants find *off-label* use in the management of diabetic macular edema. Clinical trials have demonstrated statistically significant improvements in both macular edema and visual acuity in vitrectomized eyes receiving dexamethasone implants, with an acceptable safety profile.

Fluocinolone, a synthetic derivative of hydrocortisone, exhibits potent anti-inflammatory properties within the ocular environment and potentially restores blood-retina barrier integrity by increasing the expression of tight junction proteins[104]. Fluocinolone acetonide intravitreal implants are utilized *off-label* for the management of chronic diabetic macular edema that has not responded adequately to standard treatment modalities. The FAME (Fluocinolone Acetonide in Diabetic Macular Edema) study, a prospective, randomized, double-blind, multicenter trial, evaluated the efficacy and safety of sustained-release fluocinolone acetonide in participants with persistent diabetic macular edema despite prior macular laser treatment. Compared to the sham group, both low- and high-dose fluocinolone groups demonstrated improved mean best-corrected visual acuity at follow-up. However, the study also revealed a higher incidence of cataract and glaucoma surgery in the implant groups[105].

Fenofibrate

Fenofibrate, a medication belonging to the fibrate class and acting as a PPAR agonist, is clinically indicated for the treatment of hypertriglyceridemia and mixed dyslipidemia. Emerging evidence suggests promising effects of fenofibrate in patients with diabetic retinopathy[106].

Specifically, preclinical studies have demonstrated that fenofibrate prevents endothelial cell apoptosis in the human retina induced by serum deprivation through a PPAR-independent but AMP-activated protein kinase-dependent signaling pathway[107]. Clinical trials suggest a multifaceted role for fenofibrate in diabetic retinopathy, extending beyond its well-established lipid-modifying effects. Evidence indicates that fenofibrate exerts anti-inflammatory and anti-atherosclerotic effects on the arterial wall, potentially contributing to a slowing of disease progression[108]. However, the precise mechanisms underlying these

beneficial effects in diabetic retinopathy remain under investigation.

Large-scale clinical trials, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, with its dedicated ACCORD-EYE sub-study, provide robust evidence supporting the beneficial effects of fenofibrate in reducing the risk of diabetic retinopathy progression. In the ACCORD study, randomization to fenofibrate therapy revealed a significant reduction in the risk of diabetic retinopathy progression compared to placebo. These findings confirm and build upon prior research from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. In the FIELD study, individuals with T2DM receiving fenofibrate demonstrated a significantly lower frequency of laser therapy for diabetic retinopathy, slower rates of retinopathy progression, and an overall improvement in composite measures of retinopathy outcomes[109,110].

Pegaptanib

Pegaptanib sodium, a first-in-class VEGF RNA aptamer, represents a significant advancement in the field of therapeutic aptamer development. This novel agent specifically targets and binds to VEGF-A isoform 165, a key protein driving angiogenesis and vascular permeability. Approved by the FDA in December 2004 for the treatment of neovascular age-related macular degeneration, pegaptanib has found *off-label* application in the management of diabetic retinopathy[111].

The ability of intravitreal pegaptanib to induce regression of diabetic retinopathy neovascularization was first demonstrated in 2009. A clinical study evaluating the efficacy of intravitreal injections of 0.3 mg pegaptanib every six weeks for a duration of 30 weeks revealed regression of retinal neovascularization within three weeks in a remarkable 90% of treated patients, highlighting its potential as a promising *off-label* therapeutic option for this challenging condition[112].

Renin-angiotensin system blockers

Chronic hyperglycemia triggers the activation of the RAS, leading to elevated vitreous fluid levels of angiotensin II in patients with proliferative diabetic retinopathy and diabetic macular edema. Proposed interactions between angiotensin II and VEGF, potentially involving autocrine and paracrine signaling mechanisms within ocular tissues, have fueled significant interest in the potential role of ACE inhibitors and ARBs in preventing the progression of diabetic retinopathy[113].

Indeed, the Eurodiab Controlled trial of Lisinopril in Insulin-dependent Diabetes (EUCLID) provided compelling evidence that inhibiting the RAS with the ACE inhibitor lisinopril could effectively decrease both the incidence and progression of retinopathy in patients with type 1 DM (T1DM)[114]. Similarly, the Diabetic Retinopathy Candesartan Trials (DIRECT) demonstrated that the angiotensin receptor blocker candesartan significantly reduced the incidence of retinopathy in patients with T1DM[115] and may even induce improvement in patients with T2DM exhibiting mild-to-moderate retinopathy[116]. These findings underscore the potential renoprotective and retinoprotective effects of RAS inhibition in patients with diabetes.

Statins

Statins, a class of medications that inhibit 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the rate-limiting enzyme in cholesterol biosynthesis, are widely used for lipid-lowering therapy in patients with dyslipidemia. Given the recently recognized link between hyperlipidemia and diabetic retinopathy, statins have emerged as potential therapeutic agents for the management of this ocular complication.

While the lipid-lowering effects of statins are well-established, the precise mechanisms underlying their potential benefits in diabetic retinopathy remain under investigation. These mechanisms likely involve both lipid-lowering effects and pleiotropic influences on VEGF-induced signaling pathways[117].

Initial evidence supporting the potential role of statins in the management of diabetic retinopathy emerged in 1991, with a study of six patients demonstrating pravastatin-induced reductions in microaneurysms and hard exudates[118]. Subsequent studies have provided further compelling evidence. Simvastatin demonstrated the ability to improve visual acuity in hypercholesterolemic diabetic patients, while atorvastatin effectively prevented the development of microaneurysms and hard exudates in subjects with diabetic macular edema and improved retinal blood flow in patients with various stages of diabetic retinopathy[119]. These findings strongly suggest that statin therapy may offer a viable treatment option for individuals with diabetic retinopathy, providing a potential adjunct to established therapies.

DIABETIC FOOT

Diabetic foot encompasses a spectrum of debilitating complications, including diabetic neuropathy, peripheral arterial disease, Charcot neuroarthropathy, foot ulceration, and osteomyelitis, culminating in the potentially devastating consequence of limb ampu-

tation[120]. A comprehensive understanding of the underlying pathophysiology of diabetic foot is crucial for effective monitoring and intervention, as targeting the causative factors is paramount for foot preservation and maintaining limb health.

Charcot neuroarthropathy and chronic ulcers represent the most prevalent clinical manifestations of diabetic foot. While potentially preventable, these complications of diabetes contribute significantly to the global burden of disease, with a staggering statistic of one lower limb amputation occurring every 30 seconds worldwide[121]. The primary drivers of diabetic foot complications include impaired metabolic control, leading to nerve damage, and compromised arterial blood flow to the lower extremities. Consequently, meticulous glycemic control is paramount for optimizing wound healing and minimizing the risk of complications in patients with diabetic foot ulcers.

The management of diabetic foot ulcers necessitates a tailored approach that addresses the underlying etiology, which may include ischemia, neuropathy, or a combination of both. Effective treatment strategies encompass a multidisciplinary approach, including consistent offloading of the affected foot to alleviate pressure, meticulous infection control measures, improvement of circulatory deficits through appropriate interventions, and comprehensive local wound care, encompassing debridement and the application of specialized dressings. Given the multifaceted nature of diabetic foot complications, a multidisciplinary team approach involving podiatrists, endocrinologists, vascular surgeons, and infectious disease specialists is strongly recommended to optimize patient outcomes.

While many institutions advise against *off-label* applications of medications in diabetic foot management, certain antibiotics are frequently utilized *off-label* to address the complex microbial challenges associated with these wounds.

Antibiotics

Despite the presence of positive wound cultures, evidence supporting the routine use of antibiotics in the management of chronic diabetic foot ulcers remains limited. Individuals with diabetes exhibit an accelerated deterioration of their infection response due to factors such as leukocyte dysfunction and ischemic complications. While functional neutrophil changes may suggest the need for extended treatment with bactericidal antibiotics, the presence of ischemia often necessitates the administration of higher antibiotic doses[122].

Topical application of antimicrobial agents such as neomycin, polymyxin, gentamicin, and mupirocin lacks substantiation from high-quality clinical studies regarding their impact on wound healing or amputation rates[123].

Systemic antibiotics are frequently employed *off-label* in the management of diabetic foot infections, with antibiotic selection often adjusted based on subsequent microbiological findings. This empirical approach is guided by the severity of the infected lesion and local epidemiological data regarding the prevalence of drug-resistant pathogens. Aminoglycosides, vancomycin, and amphotericin B are commonly employed *off-label* for the treatment of diabetic foot infections, particularly in cases of severe or complicated infections[124].

Bioengineered tissues dressing

Significant advancements have been made in the development of bioengineered wound dressings for the management of diabetic foot ulcers. These innovative approaches aim to mimic the physiological processes of wound healing by providing a supportive environment for tissue regeneration.

Cell-based constructs: These include keratinocyte-populated constructs layered on fibroblast-populated type I collagen lattices, which aim to recreate the epidermal-dermal interface.

Three-dimensional scaffolds: These scaffolds, often composed of polymers seeded with human diploid fibroblasts derived from neonatal foreskin, provide a three-dimensional environment that supports cellular growth and tissue remodeling.

Acellular dermal matrices: Processed from human tissue, these grafts retain the extracellular matrix components, facilitating revascularization and promoting host tissue integration.

Xenograft-derived matrices: Xenograft collagen dressings, such as those derived from porcine small intestinal submucosa, have found *off-label* applications in wound healing.

Modified collagen matrices: The portfolio of collagen-based dressings has expanded significantly, with the incorporation of various bioactive components such as silver, alginate, and protease inhibitors to enhance antimicrobial properties and promote a more favorable wound healing environment.

Other innovative approaches: This includes collagen gel, bone marrow-impregnated collagen matrices, and amniotic membrane dressings, all employed outside their approved indications[125].

These bioengineered approaches represent a promising avenue for the development of more effec-

tive wound healing strategies for diabetic foot ulcers, offering the potential to accelerate tissue regeneration and improve patient outcomes.

Vasodilators and Hemorheologic Agents

Diabetic neuropathy and peripheral vascular disease are intertwined conditions that significantly contribute to the development of diabetic foot ulcers. Impaired microvascular function, characterized by endothelial dysfunction and smooth muscle cell abnormalities, leads to reduced blood flow to the extremities, hindering wound healing. This complex interplay between vascular and neural pathologies demands innovative therapeutic approaches.

Vasodilators offer a potential avenue for improving blood flow to nerves, which may in turn enhance nerve conduction velocities. Given the concurrent nature of microvascular and neural dysfunction in diabetes, therapeutic strategies that address both pathologies simultaneously are highly desirable. Vasodilator therapy may represent a promising approach in this regard, as it could potentially mitigate the severity of clinical, functional, and structural impairments associated with diabetic foot.

Off-label use of certain vasodilators, such as cilostazol, a phosphodiesterase type III inhibitor, has demonstrated potential in improving blood flow to nerves and enhancing nerve conduction velocities. This may translate to a reduction in the severity of clinical, functional, and structural alterations observed in diabetic foot patients[126].

Blood rheology, encompassing factors such as red blood cell deformability, platelet aggregation, and blood viscosity, significantly influences vascular resistance and blood flow. Clinical studies have consistently demonstrated alterations in blood rheology in individuals with DM. These changes, including impaired red blood cell deformability, increased platelet aggregation, and elevated blood viscosity, can compromise oxygen delivery to tissues, thereby hindering wound healing, particularly in the context of diabetic foot ulcers.

Pentoxifylline, a medication known for its hemorheological properties, has been shown to improve red blood cell deformability, thereby enhancing blood flow to peripheral tissues. While primarily utilized in the treatment of peripheral vascular disease, emerging evidence suggests a potential role for pentoxifylline as an *off-label* treatment for diabetic foot ulcers, particularly when administered at higher doses for extended durations. However, it is crucial to acknowledge that the current evidence base supporting the use of pentoxifylline in this context is limited, generally positioning it as a treatment option to be considered when other therapies have been exhausted[127].

DIABETIC PNEUMOPATHY

Early recognition of pulmonary involvement in diabetes dates back to the late 1990s[128]. Similar to other organs, the lungs are susceptible to the detrimental effects of diabetic microangiopathy, characterized by the accumulation of advanced glycation end products (AGEs) resulting from non-enzymatic glycation of proteins[129].

A significant structural consequence of this diabetic microangiopathy is thickening of the alveolar-capillary barrier, leading to impaired gas exchange, primarily manifesting as diminished oxygen diffusion[130]. While traditionally, infectious pulmonary conditions such as pneumonia, tuberculosis, and fungal infections posed significant risks for individuals with diabetes, advancements in treatment have mitigated their impact[131]. However, recent research has unveiled a progressive decline in pulmonary function even in the absence of overt lung diseases in diabetic individuals, suggesting that chronic hyperglycemia can directly impact lung function, effectively transforming the lungs into a target organ for diabetic complications[132].

Diabetic pneumopathy presents with a spectrum of clinical manifestations, necessitating individualized treatment approaches. Notably, the therapeutic armamentarium for diabetic pneumopathy includes various medications employed *off-label*.

Anti-acid therapies

The frequent clinical observation of gastroesophageal reflux disease (GERD) alongside pulmonary fibrosis (PF) presents a complex and intriguing clinical challenge. Although a definitive causal link remains to be established, several theoretical mechanisms propose a potential contribution of chronic acid reflux to the development and progression of fibrotic lung disease. One prominent hypothesis posits that GERD-mediated inflammation may exacerbate existing fibrosis, potentially leading to a reduction in lung volume and a subsequent upward displacement of the diaphragm. This anatomical shift could then induce an increase in negative intrathoracic pressure, placing further stress on the already compromised, stiffened lung tissue.

However, the predominantly peripheral pattern of idiopathic PF (IPF), in contrast to the central airway involvement typically observed in inhalation-related lung injuries, raises questions regarding a direct patho-

genic role for GERD in IPF. Furthermore, the seemingly logical assumption that aspiration of gastric contents would worsen fibrosis does not align with findings from clinical investigations.

Conversely, accumulating evidence suggests a potential therapeutic benefit of acid suppression in PF. Notably, studies have indicated that anti-acid treatment in PF patients is associated with improved survival outcomes[133]. Furthermore, a retrospective analysis of participants in PF clinical trials demonstrated a positive correlation between anti-acid medication use and enhanced forced vital capacity (FVC) in individuals diagnosed with IPF[134]. These compelling findings contributed to the tentative recommendation of anti-acid therapy in the 2015 IPF clinical practice guidelines, based on the then-available evidence[135].

Despite these observations, the precise nature of the intricate interplay between GERD and PF remains incompletely understood. Further rigorous investigation is crucial to fully elucidate this complex relationship, which could ultimately pave the way for the development of more targeted and effective therapeutic interventions for patients with PF.

Autotaxin-lysophosphatidic acid pathway inhibitors

Lysophosphatidic acid (LPA), predominantly produced from lysophosphatidylcholine by the enzyme autotaxin, has been identified as a significant modulator of fibrotic processes in a variety of organ systems, including the pulmonary system[136]. Consequently, therapeutic strategies aimed at modulating the autotaxin-LPA signaling pathway, through either inhibition of autotaxin activity or blockade of LPA receptors, are under active investigation for the management of several fibrotic conditions, such as PF, dermal fibrosis, and hepatic fibrosis[137].

Nintedanib, which received regulatory approval from the FDA and the European Medicines Agency in 2014 and 2015, respectively, has become an integral component of the therapeutic approach for IPF[138]. This small molecule tyrosine kinase inhibitor exerts its therapeutic effects by selectively inhibiting several receptor tyrosine kinases, including fibroblast growth factor receptors, VEGFRs, and platelet-derived growth factor receptors, all of which play critical roles in the development and progression of PF[139].

Essential clinical trials, such as the INPULSIS (Idiopathic Pulmonary Fibrosis Patients) I and II studies (conducted in patients with IPF), have provided robust evidence supporting nintedanib's ability to attenuate the progressive deterioration of lung function, as assessed by FVC, in individuals with IPF[140]. By reducing the rate of FVC decline, nintedanib demonstrably slows the progression of the disease, providing a clinically meaningful benefit to affected patients.

Beyond its established indication in IPF, nintedanib's therapeutic potential is being further explored. Current research is actively investigating its efficacy, both as a monotherapy and in combination with other therapeutic modalities, in various oncological contexts outside of its approved indication, suggesting its potential as a broadly applicable therapeutic agent.

Pirfenidone

Pirfenidone, a first-in-class antifibrotic agent, employs a multi-pronged therapeutic approach, leveraging both antioxidant and anti-inflammatory mechanisms to effectively mitigate fibroblast proliferation and the excessive deposition of collagen, key characteristics of the fibrotic cascade[141]. This agent, as the first pharmacotherapy specifically approved for the management of IPF, has offered a significant source of optimism for individuals confronting this relentlessly progressive pulmonary condition.

Initial clinical investigations suggested pirfenidone's capacity to attenuate the deterioration of pulmonary function, as quantified by FVC, in Japanese patients diagnosed with IPF[142]. Subsequent investigations, notably the CAPACITY trials, which comprised two independent studies, further evaluated the effects of a higher dose of pirfenidone compared to a placebo control group in individuals with IPF, revealing potentially statistically significant advantages associated with the active treatment[143].

Notwithstanding these encouraging observations, important considerations persist regarding the generalizability of these positive results to the subpopulation of IPF patients with concurrent DM. The complex interaction between diabetes and PF necessitates further dedicated research to ensure optimized clinical management and therapeutic efficacy within this specific patient group.

Rituximab

Recent investigations have indicated a potential involvement of autoantibodies in the development and progression of PF. A preliminary study exploring the therapeutic application of plasma exchange combined with rituximab in PF patients experiencing critical illness yielded encouraging outcomes, leading the researchers to suggest that therapeutic interventions directed at autoantibodies may represent a promising avenue for improving outcomes in this challenging patient population[144].

DIABETIC HEPATOPATHY

The established correlation between DM and hepatic dysfunction encompasses a diverse range of pathological states, spanning from hepatic steatosis to metabolic dysfunction-associated steatotic liver disease (MASLD), cirrhosis, insulin-mediated hepatic glycogen accumulation, and Mauriac syndrome[145]. Moreover, a robust association has been consistently observed connecting obesity, DM, and the development of hepatocellular carcinoma[146]. Notwithstanding this recognized connection, comprehensive clinical and pathological resources explicitly characterizing hepatic lesions as "diabetic hepatopathy" are surprisingly limited.

Diabetic hepatopathy, recognized as a potential indicator of severe DM, originates from underlying metabolic disturbances. Sustained hyperglycemia and increased concentrations of AGEs contribute to heightened lipid peroxidation, resulting in the formation of byproducts that trigger vasoconstriction and promote the adhesion and aggregation of platelets. This cascade of events ultimately culminates in the thickening of the basement membrane and small arterial vessels[147]. Early descriptions of this condition stemmed from two small case series and an individual case report, which described sinusoidal fibrosis exhibiting notable parallels with diabetic microangiopathy[148,149].

Although histopathological observations provide evidence for the existence of diabetic hepatopathy, its clinical relevance remains incompletely understood. The clinical presentation of this condition exhibits considerable variability, ranging from overt cholestasis to entirely asymptomatic presentations. The cholestatic features observed are frequently a consequence of mechanical compression or ischemic injury to the biliary ducts resulting from perisinusoidal fibrosis, as corroborated by several investigations[150,151,152].

Laboratory investigations may also reveal a cholestatic profile, characterized by increased levels of bilirubin (especially direct bilirubin), gamma-glutamyl transferase, and alkaline phosphatase[153]. Therefore, in the context of differential diagnosis for cholestasis in individuals with DM, diabetic hepatopathy should be taken into consideration.

Regrettably, there are currently no officially approved therapeutic interventions specifically for diabetic hepatopathy. However, accumulating scientific data suggests the potential utility of *off-label* pharmacotherapy, supported by encouraging findings from therapeutic studies employing clinically relevant endpoints.

Betaine

Betaine, a trimethylglycine derivative, is produced endogenously within the liver and kidneys, obtained through dietary intake, and is present within human plasma. Although existing data supports its use as an *off-label* therapeutic intervention for diabetic hepatopathy, the precise molecular mechanisms responsible for its effects are not fully elucidated[154].

A clinical investigation spanning two months was conducted to assess the safety profile and therapeutic potential of orally administered betaine glucuronate in individuals with MASLD. The study involved 191 participants, who were divided into two groups. The first group (n=95) received a placebo, while the second group (n=96) received a combination of betaine glucuronate, diethanolamine glucuronate, and nicotinamide ascorbate. It is important to acknowledge that the absence of liver biopsies for MASLD diagnosis restricts the ability to draw definitive conclusions from this study. However, the group receiving the combined treatment demonstrated statistically significant decreases in liver enzyme levels, hepatomegaly, and clinical indicators suggestive of amelioration of MASLD compared to the placebo group[155].

Beta-carotene

Beta-carotene, a robust lipophilic antioxidant, plays several essential physiological roles. Of particular importance is its function as a provitamin A, influencing cholesterol biosynthesis, and its subsequent metabolic conversion to retinoic acid, a signaling molecule that modulates gene expression across a range of metabolic pathways. Considering the well-established contribution of oxidative stress to the development and progression of MASLD, coupled with beta-carotene's substantial antioxidant properties and its role as a vitamin A precursor, it is plausible that individuals affected by MASLD may present with reduced circulating levels of this micronutrient. This hypothesis has prompted investigations into the potential therapeutic application of beta-carotene in the context of MASLD[156].

A research study investigated the relationship between metabolic syndrome, MASLD, and circulating carotenoid concentrations by recruiting 350 participants, who were subsequently classified into three distinct groups according to the extent of hepatic fat accumulation, as determined by ultrasonographic assessment (normal, mild, and severe). The findings of this study revealed a statistically significant correlation between the presence of metabolic syndrome and the severity of hepatic steatosis. Moreover, a negative association was observed between serum beta-carotene

levels and MASLD severity, raising the possibility of its use as an *off-label* therapeutic strategy for this complex hepatic disorder[157].

Ezetimibe

Ezetimibe, a highly effective agent that inhibits the absorption of cholesterol in the intestines, has demonstrated variable outcomes in clinical trials assessing its therapeutic potential in MASLD. A contemporary meta-analysis, encompassing a thorough evaluation of existing research, determined that although certain studies reported encouraging enhancements in serum hepatic enzyme levels and hepatocyte ballooning following ezetimibe administration, the cumulative evidence base does not currently permit definitive conclusions regarding its efficacy[158]. The authors of this meta-analysis emphasize the critical requirement for more extensive, meticulously designed randomized, placebo-controlled clinical trials to conclusively establish the actual therapeutic value of ezetimibe in the clinical management of MASLD.

N-Acetyl-cysteine

N-Acetyl-cysteine (NAC) is being explored as a potential therapeutic agent in the management of MASLD. Its proposed mechanism of action centers on its function as a thiol-based antioxidant modulator, which enhances intracellular glutathione concentrations, especially within hepatocytes. This increase in glutathione levels provides a protective effect against substances harmful to the liver and neutralizes reactive oxygen species that contribute to damage within liver cells[159].

A clinical study was conducted to evaluate the effects of NAC on reducing liver damage in the context of MASLD. Thirty participants were randomly assigned to receive either vitamin C or NAC, and their hepatobiliary systems were subsequently assessed using ultrasonography and liver enzyme profiles over a three-month period. Although the study demonstrated statistically significant improvements in liver enzyme levels following NAC administration compared to vitamin C treatment, the ultrasonographic evaluations did not reveal a statistically significant effect on the underlying MASLD condition itself[160].

Oligofructose

Oligofructose, synonymous with oligofructan, represents a prebiotic oligosaccharide complex characterized by its resistance to human digestive enzymes and its susceptibility to fermentation by the intestinal microbial community[161]. Preclinical investigations utilizing animal models have suggested a potential therapeutic role for oligofructose in mitigating MASLD, thereby motivating subsequent research in human subjects.

A preliminary, randomized, double-blind, crossover trial was designed to evaluate the impact of oligofructose supplementation on individuals diagnosed with MASLD. This pilot study recruited seven participants with histologically confirmed MASLD, who were randomly allocated to receive either 16 grams per day of oligofructose or an equivalent dose of maltodextrin as a placebo control for a period of eight weeks. Assessments of body composition, hepatic steatosis (quantified by appropriate imaging or biochemical markers), and relevant hematological and biochemical parameters were conducted at baseline, week four, and week eight. Although constrained by the limited number of participants, the observed data offer initial, albeit tentative, evidence supporting the potential utility of oligofructose in the clinical management of human hepatic pathologies characterized by aberrant lipid accumulation. Consequently, these findings underscore the necessity for more extensive and prolonged clinical investigations to definitively ascertain the therapeutic efficacy and safety profile of oligofructose in this context[162].

Omega-3 fatty acids

Omega-3 polyunsaturated fatty acids (PUFAs), widely recognized for their purported metabolic and anti-inflammatory properties, have demonstrated variable efficacy in the therapeutic management of MASLD. Although certain investigations have indicated potential therapeutic benefits, the cumulative evidence base remains inconclusive and marked by inconsistencies.

Notwithstanding the prevailing ambiguity, one particular study offered promising insights. This investigation explored the effects of omega-3 PUFA supplementation in a cohort of individuals with histologically confirmed MASLD. The researchers documented statistically significant enhancements in both circulating lipid profiles and hepatic histological characteristics within the examined population[163]. It is, however, crucial to recognize the inherent limitations associated with drawing definitive conclusions based on a single study.

Orlistat

Orlistat, a clinically established inhibitor of enteric lipase with demonstrated efficacy in promoting weight reduction, has also garnered considerable interest

regarding its potential therapeutic application in the management of MASLD[164].

A randomized, double-blind, placebo-controlled clinical trial was conducted to evaluate the effects of orlistat in a cohort of individuals diagnosed with MASLD through ultrasonographic assessment. Fifty-two participants were randomly assigned to receive either orlistat for a period of six months or a placebo control, while concurrently participating in a standardized behavioral weight management program. Monthly evaluations encompassed abdominal ultrasonography, comprehensive lipid and hepatic enzyme profiling, insulin level measurement, anthropometric measurements, and dietary intake monitoring. Of the initial participant group, forty individuals had a baseline MASLD diagnosis confirmed by hepatic biopsy, with twenty-two of these participants undergoing a repeat biopsy upon completion of the study. The administration of orlistat yielded encouraging results, including demonstrable improvements in hepatic enzyme profiles and hepatic ultrasound parameters among the participants with MASLD[165].

Consequently, orlistat, a medication approved for the treatment of obesity, has attracted attention for its potential *off-label* utilization in the context of diabetic hepatopathy, specifically MASLD.

Emerging scientific evidence suggests that orlistat may offer therapeutic advantages for this patient population, thereby justifying further research to comprehensively establish its long-term efficacy and safety profile.

Pentoxifylline

Pentoxifylline, a non-selective phosphodiesterase inhibitor derived from methylxanthine, possesses both anti-tumor necrosis factor-alpha and antioxidant properties. These pharmacological attributes provide a rationale for its *off-label* utilization in the management of MASLD, primarily through the modulation of pro-inflammatory cytokine production and the inhibition of nuclear factor-kappa B signaling pathways[166].

Several investigations have examined the therapeutic potential of pentoxifylline in the context of MASLD. Of particular note, a double-blind, randomized, placebo-controlled clinical trial evaluated the influence of pentoxifylline administration on circulating levels of oxidized fatty acids. The results of this study demonstrated that, in comparison to the placebo group, treatment with pentoxifylline resulted in improved histological scores for both fibrosis and lobular inflammation, a finding likely attributable to the observed reduction in oxidized fatty acid concentrations. This research provides evidence supporting the potential clinical utility of *off-label* pentoxifylline interventions in individuals diagnosed with MASLD[167,168].

Probiotics

Probiotics, characterized as non-pathogenic microorganisms that constitute a component of the healthy human gastrointestinal microbiota, exert a vital influence on the maintenance of overall well-being across a spectrum of physiological and pathological states. Their capacity to modulate intestinal permeability has stimulated considerable interest in their potential application for enhancing gastrointestinal barrier integrity and, as a consequence, augmenting protein absorption at the level of the intestinal mucosa[169].

The complex interplay between the gut microbiota and the pathogenesis of MASLD has become a focal point of extensive research, with the field of microbiota modulation for therapeutic intervention undergoing rapid advancement. Groundbreaking investigations by Miele et al.[170] established a correlation between heightened intestinal permeability and MASLD in human subjects, demonstrating the presence of small intestinal bacterial overgrowth in affected individuals.

An *open-label*, randomized controlled clinical trial was conducted to evaluate the efficacy of probiotic administration, in comparison to standard care protocols, in reducing hepatic fat content in individuals with a histologically confirmed diagnosis of MASLD. Participants were randomly allocated to receive a six-month regimen of a probiotic formulation containing a defined combination of Lactobacillus and Bifidobacterium strains. Assessments of metabolic profiles, intrahepatic triglyceride content, and hepatic enzyme levels were performed at baseline and at the conclusion of the study. The findings revealed statistically significant improvements in all measured parameters within the probiotic intervention group, suggesting a potential therapeutic advantage for individuals living with MASLD[171].

Renin-Angiotensin System blockers

The RAS is now recognized as a critical modulator in the development of hepatic fibrosis. Clinically validated therapies targeting components of this system, such as ACE inhibitors (ACE-I) and ARBs, have demonstrated efficacy in mitigating tissue damage and fibrotic processes, effects observed independently of their blood pressure-lowering actions[172].

Accumulating data suggest a significant role for the RAS in the advancement of MASLD, thereby raising the possibility of repurposing ACE-Is and ARBs as therapeutic agents in this context[173].

A comparative study investigated the therapeutic potential of two distinct ARBs, telmisartan and valsartan, in a cohort of 54 MASLD patients exhibiting mild to moderate hypertension. This 20-month trial specifically evaluated the impact of these agents on IR, hepatocellular injury (cytolysis), and overall MASLD status. Participants were randomly assigned to receive either valsartan at a dosage of 80mg/day (n=26) or telmisartan at 20mg/day (n=28). All participants fulfilled the diagnostic criteria for metabolic syndrome as defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) and had histologically confirmed MASLD. Key metabolic and hepatic parameters, including liver enzymes, lipid profiles, IR indices, body mass index, and blood pressure, were meticulously monitored at baseline and at four-month intervals throughout the study. The findings indicated that telmisartan administration led to statistically significant improvements in both cytolysis and IR, although complete normalization of liver enzyme levels was not achieved. This enhancement in metabolic parameters correlated with a substantial reduction in MASLD severity and a favorable modulation of the lipid profile. In contrast, while the valsartan group also demonstrated improvements in liver enzymes and IR, no significant changes were observed in liver histology or lipid profiles. These observations suggest that telmisartan may offer a more effective approach compared to valsartan in mitigating IR and the hepatic manifestations associated with MASLD[174].

Silymarin

Silymarin, a complex of flavonolignans derived from the milk thistle plant (Silybum marianum), has a long history of use in traditional medicine for the treatment of hepatic and biliary disorders. Its therapeutic effects are attributed to a multifaceted mechanism of action, encompassing four key processes: (1) suppression of hepatic stellate cell transdifferentiation into myofibroblasts, a crucial step in fibrogenesis; (2) maintenance of cellular membrane integrity and modulation of membrane permeability; (3) exertion of antioxidant effects and regulation of intracellular glutathione homeostasis; and (4) stimulation of ribosomal RNA synthesis, thereby promoting hepatic regeneration[175-177].

An investigation was conducted to assess the potential of silymarin to enhance liver function in individuals diagnosed with MASLD. In this study, a cohort of 72 MASLD patients received a combined intervention consisting of a dietary restriction regimen and a daily oral dose of 3.5 grams of silymarin for a period of three months. Before and after this intervention, several parameters were evaluated, including hepatic ultrasound findings, markers of inflammation, and liver enzyme profiles. The study's findings revealed statistically significant improvements in both hepatic ultrasound parameters and liver enzyme profiles following the combined dietary and silymarin intervention. However, the study did not demonstrate a statistically significant reduction in inflammatory markers at the conclusion of the treatment period[178].

Vitamin E

Tocopherol (vitamin E) has exhibited a therapeutic capacity to decrease transaminase activity – a critical biomarker of hepatic injury – in a notable proportion of individuals diagnosed with MASLD. This observation has led to its recommendation for patients with histologically confirmed MASLD. Nonetheless, vigilant surveillance for potential undesirable consequences associated with Vitamin E supplementation is essential[179].

A retrospective investigation conducted by Chalasani and colleagues[180] evaluated the sustained efficacy of vitamin E as a therapeutic intervention in a cohoort of 17 patients with MASLD, verified through biopsy. The participants received a daily 300mg dose of the vitamin for a period exceeding two years and were subsequently stratified into subgroups according to the presence or absence of fibrosis regression. The research demonstrated substantial enhancements in hepatic enzyme profiles, IR indicators, and markers of hepatic fibrosis within both subgroups. These outcomes intimate that extended administration of vitamin E may confer advantages in attenuating the advancement of fibrosis in MASLD.

Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA) manifests its therapeutic actions against inflammation and cholestasis through several key pathways. These include the upregulation of vital bile acid transporters, such as the canalicular bile salt export pump, the ATP-binding cassette transporter B4, and the basolateral multidrug resistance-associated protein 3. Furthermore, the replacement of potentially damaging hydrophobic bile acids with the more biocompatible hydrophilic UDCA has been shown to lessen damage to both hepatocytes and cholangiocytes[181].

The potential of UDCA as a therapeutic intervention in MASLD has been the subject of extensive investigation. Across numerous studies, consistent evidence points to substantial enhancements in markers of liver function, as measured by standard liver function tests. Moreover, post-treatment histological analysis of liver

biopsies and evaluations of hepatic steatosis scores have demonstrated marked improvements compared to pre-treatment baselines.

A longitudinal study spanning a decade, conducted by Pietu and colleagues[182], assessed the long-term safety and effectiveness of a combined therapeutic approach using UDCA and vitamin E in a cohort of 101 adult patients diagnosed with MASLD. All participants presented with persistently elevated liver enzymes and had received histological confirmation of the disease. The study's findings revealed significant and sustained positive changes in liver enzyme profiles over the extended observation period, with the combined treatment demonstrating a favorable safety profile.

In a separate investigation, Troisi et al.[183] explored the efficacy of UDCA in a population of 87 elderly MASLD patients also diagnosed with metabolic syndrome. This six-month study employed ultrasound imaging and laboratory analyses for diagnostic purposes. Participants were randomly assigned to either a UDCA treatment group or a control group receiving dietary management alone. Assessments conducted both before and after the intervention included hepatic ultrasonography, comprehensive lipid and liver enzyme profiling, symptom evaluation, and body mass index measurement. While both groups exhibited notable improvements in MASLD -related parameters at the three-month mark, the UDCA treatment did not induce significant changes in the parameters associated with metabolic syndrome.

SUMMARY AND CONCLUSIONS

Repurposing pharmaceuticals for clinical applications beyond their initially approved indications, a practice globally recognized as *off-label* prescribing, spans a spectrum from experimental approaches to established standard-of-care and even innovative, leading-edge therapies. This practice has become increasingly commonplace in contemporary medical practice, with a substantial number of *off-label* uses endorsed by authoritative sources such as medical textbooks, research organizations, professional medical societies, and standard pharmaceutical compendia. Provided that no suitable on-label therapeutic alternative is available and that healthcare practitioners exercise sound clinical judgment grounded in established medical principles, *off-label* prescribing remains a legitimate and widely adopted practice across a broad range of medical specialties.

Nevertheless, the existing framework permits the utilization of medications approved for one specific indication to be extended to other clinical contexts without consistent and robust oversight mechanisms. While *off-label* use should not be automatically categorized as equivalent to experimental or investigational therapies, there are documented instances where its application has proven invaluable in effectively managing severe and life-threatening conditions. Conversely, there exists a potential hazard that an *off-label* application, despite appearing initially promising, may ultimately prove to be ineffective or even detrimental to patient health, yet continue to be employed without adequate scrutiny. The process of weighing the relative benefits, potential harms, and economic implications of medical interventions becomes significantly more complex within the context of rapid technological progress, the inherent limitations of available clinical evidence, and the constraints imposed by finite healthcare resources.

Within the specific population of individuals with DM, *off-label* drug utilization offers a potential therapeutic avenue for addressing and managing disease-related complications. This strategic approach has been shown to produce tangible improvements in patient signs and symptoms in clinical scenarios where specifically indicated *on-label* medications have not yet received regulatory approval.

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ORIGINAL ARTICLE: TOPIC IN MEDICAL CLINIC *ARTIGO ORIGINAL: TÓPICO EM CLÍNICA MÉDICA*

THE SPONDYLOARTHRITIS PATIENT WITH ANTERIOR UVEITIS

O PACIENTE COM ESPONDILOARTRITE E UVEITE ANTERIOR

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Background: Anterior acute uveitis (AAU) is a common complication in Spondylarthritis (SpA) patients and may have important morbidity, affecting the patient's visual ability. **Objective:** To study the prevalence and possible clinical associations of UAA in a sample of Brazilian patients with SpA. **Methods:** Retrospective study with chart review of 140 SpA patients from a single Rheumatology outpatient clinic seen in the last 10 years. Data collected included: epidemiological, clinical data and presence of HLA B27. **Results:** Of the 140 patients, 59 were female and 81 were male with mean age of 52.7 years. Uveitis was present in 25%. Patients with UAA were younger at diagnosis (p=0.02), had more the axial radiographical spondyloarthritis subtype (p<0.0001), had fewer cutaneous manifestations (p=0.001) and less peripheral arthritis (p=0.003). HLA B27 was more commonly found in patients with uveitis (p=0.001). **Conclusions:** The presence of UAA marks a special phenotype of SpA where the disease has an earlier diagnosis. UAA is less common in those with cutaneous changes and peripheral joint changes and more common in those HLAB27.
Key words: Acute anterior uveitis. Spondyloarthritis. Ankylosing Spondylitis. HLA B27.

Introdução: A uveíte aguda anterior (UAA) é uma complicação comum em pacientes com espondilartrites (EpA) e pode apresentar morbidade importante, afetando a capacidade visual do paciente. **Objetivo:** Estudar a prevalência e possíveis associações clínicas da UAA em uma amostra de pacientes brasileiros com EpA. **Métodos:** Estudo retrospectivo com revisão de prontuários de 140 pacientes com EpA de um único ambulatório de Reumatologia, atendidos nos últimos 10 anos. Os dados coletados foram: dados epidemiológicos, clínicos e presença de HLA B27. **Resultados:** Dos 140 pacientes, 59 eram do sexo feminino e 81 do sexo masculino, com média de idade de 52,7 anos. A uveíte esteve presente em 25%. Os pacientes com UAA eram mais jovens ao diagnóstico (p=0,02), eram mais do subtipo espondiloartrite axial radiográfica (p<0,0001), apresentavam menos manifestações cutâneas (p=0,001) e menos artrite periférica (p=0,003). O HLA B27 foi mais comumente encontrado em pacientes com uveíte (p=0,001). **Conclusão:** A presença de UAA marca um fenótipo especial de EpA, onde a doença tem um diagnóstico mais precoce. A UAA é menos comum naqueles com alterações cutâneas e alterações articulares periféricas e mais comum naqueles com HLA-B27.
Palavras chave: Uveite anterior aguda. Espondiloartrite. Espondilite anquilosante. HLA B27.

INTRODUCTION

The acute anterior uveitis (AAU) is considered to be the most common extra articular manifestation of Spondyloarthritis (SpA), a group of diseases that affects axial skeleton causing inflammatory back pain[1].

Anterior uveitis, also known as iritis, commonly presents with red eye associated with vision impairment and it is the most common form of uveitis associated to SpA, although these patients may also have involvement of the posterior eye segment[1]. It is more commonly unilateral and usually undertakes an acute but recurrent evolution. It can complicate with anterior and/or posterior synechiae, cataract and glaucoma that can compromise the patient's visual capacity[1,2]. It had been estimated that uveitis account for 10–15% of cases of blindness in the developed world[3].

Several factors may influence the uveitis occurrence in a patient with SpA. The patient's genetic background is one of them[4]; the SpA subtype is another. SpA encompasses a number of heterogeneous conditions such as psoriatic arthritis, reactive arthritis, arthritis associated with inflammatory bowel diseases and ankylosing spondylitis and each subtype may have a different prevalence of UAA[5-9]. A large French cohort with 902 SpA patients found no association of uveitis with SpA disease activity[10] but Maini et al.[11] associated its appearance with SpA severity.

Herein a sample of Brazilian patients with SpA was studied aiming to known the prevalence of UAA as well as the associated clinical characteristics.

MATERIAL AND METHODS

This is a retrospective study approved by the Institutional Committee of Ethics in Research (CAAE 67016723.0.0000.0103) under protocol 5.902.342 that included patients with SpA that came for regular consultation to a Rheumatology Outpatient Clinic of a tertiary hospital that cares for rheumatic patients from the Public Health System, during the period of 10 years (January, 2012 to December, 2022).

To be included patients should be older than 18 years of age, fulfil the ASAS SpA classification criteria[12] and have had diagnosis after 16 years of age. Incomplete charts were excluded.

Data collected comprised: epidemiological data (sex, age, age at diagnosis, auto declared ethnic background, use of tobacco), clinical data (subtype of SpA divided in axial, peripheral or mixed, presence of cutaneous manifestations, presence of gastrointestinal manifestations, dactylitis, enthesitis ad presence of HLA B27.

Statistical analysis: Data was collected in frequency and contingency tables. Nominal data of patients with and without uveitis were compared by fisher and chi-squared test; numerical data by unpaired t test or Mann Whitney according to data distribution. Ther adopted significance was 5%. Data was studied with help of the software GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com.

RESULTS

One hundred and forty patients were included. Epidemiological data is displayed at table 1. On this sample 35/140 (25%) have had AAU.

Table 1. Description of studied sample: 140 individuals with spondyloarthritis.

Sex	Male- 81/140 – 57.8% Females – 59/140 – 42.1%
Mean age ± SD (years)	52.7± 13.0
Mean age at diagnosis± SD (years)	39.9±13.5
Ethnic background	Euro descendants – 131/140 – 93.5% Afro descendants - 9/140 – 6.4%
Exposure to tobacco	48/140 – 34.2%
Subtype	Reactive arthritis – 2/140 – 1.4% Psoriatic arthritis – 58/140- 41.4% Ankylosing spondylitis – 75/140 – 53.3% Indiferenciated – 5/140 – 3.5%
Main involvement	Axial – 46/140 Peripheral – 25/140 Mixed - 69/140
Enthesitis	43/140- 30.7%
Dactilytis	19/140 – 13.5%
Cutaneous manifestations	65/140 – 46.4%
Intestinal manifestations	32/140 – 22.8%
Presence of HLA B27	56/100 – 56%

Table 2 shows the comparison of epidemiological data of patients with and without uveitis. This table displays that age at diagnosis was lower in those with AAU.

Table 2. Comparison of epidemiological data in spondyloarthritis patients with and without uveitis.

	With uveitis N = 35	Without uveitis N = 105	P
Male sex (n)	22/35	59/105	0.48
Euro descendant ethnic background (n)	32/35	99/105	0.69
Smokers (n)	9/35	39/105	0.30
Age (years)	50.4±14.2	53.4±12.6	0.23
Age at diagnosis (years)	35.3±14.8	41.5±12.7	**0.02**

Table 3 shows the comparison of SpA subtypes according to the presence of AAU; ankylosing spondylitis had a higher prevalence than all the others.

Table 3. Comparison of spondyloarthritis subtypes according to the presence of uveitis.

	With uveitis N=35	Without uveitis N=105	P
SUBTYPES (n)			<0,0001
Ankylosing Spondilitis	30/35 - 85.7%	45/105 - 42.8%	
Psoriatic arthritis	3/35 - 8.5%	55/105 - 52.3%	
Others	2/35 - 5.7%	3/105 - 2.8%	
MAIN INVOLVMENT (n)			0.74
Axial	13/35- 37.1%	33/105 - 31.4%	
Peripheral	5/35 - 14.2 %	20/105 - 19.0%	
Mixed	17/35 - 48.5%	52/105 - 49.5%	

Table 4 shows the prevalence of AAU according to clinical parameters.

Table 4. Comparison of clinical parameters in spondyloarthrtis patients according to presence or not of uveitis.

	With uveitis N=35	Without uveitis N=105	P
Sacroiliitis (n)	17/35 (48.5%)	46/105 (43.8%)	0.62
Enthesitis (n)	9/35 (25.7%)	34/105 (32.3%)	0.45
Cutaneous manifestations (n)	8/35 (22.8%)	57/105 (54.2%)	**0.0016***
Intestinal involvement (n)	11/35 (31.4%)	21/105 (20%)	0.16
HLA B27 (n)	24/30 (80%)	32/70 (45.7%)	**0.0015****
Peripheral arthritis (n)	9/35 (25.7%)	57/105 (54.2%)	**0.0034*****
Dactilitis (n)	4/35 (11.4%)	15/105 (14.2%)	0.78

(*)OR=4.0; 95% IC=1,6-9.2; (**)OR=4.7; 95% IC=1,7 a 12,9; (***)OR=3,4; 95% IC=1,4 a 8,1.

DISCUSSION

The etiopathogenesis of SpA and uveitis is unknown. Both appear to result from the interaction of a shared genetical background (HLA-B27 and others), external influences such as bacterial infections, microbiome, or mechanical stress that causes activation of the immune system with subsequent inflammation. Up to 40% of patients presenting with AAU have an undiagnosed SpA[13]. This fact stresses the importance of awareness of this association as the ophthalmologist may refer these patients early, avoiding diagnosis delays that could preclude an early effective treatment.

This study shows that almost ¼ of SpA patients from this sample had AAU. Also shows that UAA was more commonly seen in those with earlier diagnosis of the disease, with ankylosing spondylitis diagnosis and with presence of HLA B27 and less common in those with peripheral arthritis and cutaneous lesions.

The rate of uveitis occurrence found in the present sample was consistent with the range described in the literature: between 18 and 25%[14]. The present study also shows that the patients with AAU have a phenotype that differs from those without it, with greater prevalence of ankylosing spondylitis (also

called axial radiographic spondyloarthritis), and lower prevalence of peripheral arthritis, and dermatological manifestations. Another study in Asian patients with axial SpA corroborated the finding that AAU was more common in those with earlier disease onset but they found, unlike the present results, association with history of psoriasis and previous dactylitis[15] . Different genetic background and the sample having only axial disease may explain the found differences.

The link between AAU and HLA B27 found presently is already known from previous works[16]. The HLA system is the human form of a major histocompatibility complex (MHC) and plays an important role in the differentiation between endogenous and exogenous structures by the immune system, via MHC-restricted antigen recognition[17]. It is critical for self-tolerance, certifying that the immune system evades targeting the body's own tissues. It is presumed that HLA-B27 may influence the development of autoimmune conditions by controlling the immune response to specific microbial antigens and is linked with both, intestinal tolerance as well as the loss of ocular immune privilege occurring in AAU, but it is not completely understood how[17] . Modulation of gut microbioma is one of given explanations[18].

The lack of association of AAU with peripheral arthritis presently found corroborates the results from previous work that observed a negative association of HLA B27 (and therefore, with AAU) and peripheral manifestations[16] .

CONCLUSION

The present study shows that AAU occurs in 25% of SpA patients and it is more common in patients with early onset disease and in patients positive for HLA B27 and less common in those with peripheral arthritis and skin manifestations. Recognizing this phenotype may help the physician to stay alert for AAU diagnosis.

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ORIGINAL ARTICLE *ARTIGO ORIGINAL*

QUANTUM BIOINFORMATICS: A NOVEL APPROACH TO UNDERSTANDING DIABETES MELLITUS

BIOINFORMÁTICA QUÂNTICA: UMA NOVA ABORDAGEM PARA COMPREENDER O DIABETES MELLITUS

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Introduction: Diabetes mellitus (DM) is a complex metabolic disorder posing a significant global health concern. While classical biochemical models have provided valuable insights, the underlying molecular mechanisms of this disease remain incompletely understood. Recent advancements in quantum mechanics and bioinformatics have opened new avenues for exploring the quantum nature of biological processes, including those involved in DM. **Objective:** To investigate the potential role of quantum mechanics in the pathophysiology of DM by employing a multidisciplinary approach that integrates quantum mechanical calculations with bioinformatics analysis. **Methods:** A comprehensive dataset of proteins implicated in DM was curated from the Protein Data Bank. Quantum mechanical calculations, including Density Functional Theory and Time-Dependent Density Functional Theory, were performed to elucidate the electronic structure, vibrational properties, and potential quantum effects in key amino acid residues and active sites of these proteins. Bioinformatics tools were used to analyze protein-protein interaction networks, identify allosteric sites, and predict the impact of mutations on protein structure and function. **Results:** Our findings provide strong evidence that quantum effects, particularly vibrational coherence and electronic tunneling, may play a crucial role in regulating enzymatic activity, protein-ligand interactions, and energy transfer processes involved in glucose metabolism and insulin signaling. Key findings include the identification of quantum tunneling pathways in key enzymes, evidence for quantum coherence in protein-protein interactions, and the role of vibronic coupling in modulating protein function. **Conclusion:** This study offers a novel perspective on the molecular mechanisms underlying diabetes mellitus by integrating quantum mechanics and bioinformatics. Our findings suggest that quantum effects may contribute to the pathogenesis of DM, opening new avenues for the development of innovative diagnostic and therapeutic strategies.

Keywords: Diabetes mellitus, Quantum mechanics, Bioinformatics, Metabolic pathways.

Introdução: O diabetes mellitus (DM) é um distúrbio metabólico complexo que representa um significativo problema de saúde global. Embora modelos bioquímicos clássicos tenham fornecido valiosos insights, os mecanismos moleculares subjacentes a essa síndrome ainda não são completamente compreendidos. Avanços recentes na mecânica quântica e na bioinformática abriram novas perspectivas para explorar a natureza quântica dos processos biológicos, incluindo aqueles envolvidos no DM. **Objetivo**: Investigar o potencial papel da

mecânica quântica na fisiopatologia do DM, empregando uma abordagem multidisciplinar que integra cálculos de mecânica quântica com análise bioinformática. **Métodos**: Um conjunto de dados abrangente de proteínas envolvidas no DM foi retirado do Protein Data Bank. Cálculos de mecânica quântica, incluindo Teoria Funcional da Densidade e Teoria Funcional da Densidade Dependente do Tempo, foram realizados para elucidar a estrutura eletrônica, propriedades vibracionais e potenciais efeitos quânticos em resíduos de aminoácidos-chave e sítios ativos dessas proteínas. Ferramentas bioinformáticas foram usadas para analisar redes de interação proteína-proteína, identificar sítios alostéricos e prever o impacto de mutações na estrutura e função proteica. **Resultados:** Nossos achados fornecem fortes evidências de que efeitos quânticos, particularmente coerência vibracional e tunelamento eletrônico, podem desempenhar um papel importante na regulação da atividade enzimática, interações proteína-ligante e processos de transferência de energia envolvidos no metabolismo da glicose e sinalização da insulina. Principais descobertas incluem a identificação de vias de tunelamento quântico em enzimas-chave, evidências de coerência quântica em interações proteína-proteína e o papel do acoplamento vibônico na modulação da função proteica. **Conclusão**: Este estudo oferece uma nova perspectiva sobre os mecanismos moleculares subjacentes ao DM, integrando a mecânica quântica e a bioinformática. Nossos achados sugerem que efeitos quânticos podem contribuir para a patogênese do DM, abrindo novas perspectivas para o desenvolvimento de estratégias diagnósticas e terapêuticas inovadoras.
Palavras-chave: Diabetes mellitus, Mecânica quântica, Bioinformática, Vias metabólicas.

INTRODUCTION

Quantum mechanics is a cornerstone of modern physics, having revolutionized our understanding of the universe at microscopic scales, particularly at atomic and subatomic levels. Principles such as superposition, entanglement, and uncertainty have proven instrumental in explaining a broad spectrum of phenomena across physics, chemistry, and materials science. However, the application of quantum principles to biological systems especially in the context of human diseases remains largely underexplored[1,2].

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia, influenced by a combination of genetic, environmental, and lifestyle factors. Despite extensive research, many aspects of its underlying mechanisms remain poorly understood. Traditional studies of diabetes have predominantly focused on classical biochemical and physiological processes[3].

While the quantum nature of biological systems has often been overlooked, growing evidence suggests that quantum effects may play a significant role in biological processes such as photosynthesis, olfaction, and enzymatic catalysis[4]. Quantum mechanics provides a foundational framework to describe interactions at the atomic and molecular levels, which are essential for comprehending complex biochemical reactions involved in glucose metabolism.

At first glance, the connection between quantum mechanics and diabetes might appear tenuous. However, recent advances in quantum biology propose that quantum effects could influence the behavior of biomolecules associated with glucose regulation. For instance, quantum tunneling a phenomenon in which particles traverse energy barriers might affect enzymatic reactions critical to glucose metabolism. Additionally, quantum superposition and coherence may be relevant to the functionality of biological systems, potentially impacting processes underlying diabetes[5,6].

Despite the potential relevance of quantum mechanics to diabetes, the precise role of quantum processes in this disease remains largely speculative. Most research in quantum biology has been conducted using simplified model systems, limiting our understanding of how quantum effects manifest in complex biological phenomena like glucose metabolism[7].

This paper seeks to address this gap by exploring the application of quantum mechanics to the study of DM. The study aims to develop a novel theoretical framework that integrates quantum mechanical principles with bioinformatics to elucidate the molecular mechanisms underpinning diabetes. In particular, the quantum properties of biomolecules involved in glucose metabolism will be analyzed, and potential alterations of these properties in diabetic conditions will be discussed.

MATERIALS AND METHODS

The computational and bioinformatics approach applied herein investigates the quantum mechanical underpinnings of DM. It has been focused on quantum properties of biomolecules implicated in glucose metabolism to investigate the molecular mechanisms of the complex disease.

Data Acquisition and Preparation

A total dataset of proteins implicated in DM was compiled from Protein Data Bank (PDB) databases,

representing high-resolution structural information on proteins participating in glucose metabolism, insulin signaling, and other pathways of relevance. Selection of the proteins was done based on their established involvement in the pathophysiology of diabetes and their suitability for quantum mechanical simulations. It contained proteins that were involved in insulin signaling, glucose transport, and glycolysis. To make it relevant to DM, we filtered PDB using bioinformatics tools with keywords associated with the disease, such as "insulin receptor," "GLUT4," and "hexokinase."

Quantum Mechanical Simulations

Exploring the quantum properties of such biomolecules requires resorting to state-of-the-art quantum chemistry methods. More precisely, Density Functional Theory (DFT) methods have been used in calculating electronic structures and vibrational spectra for some of the amino acid residues and key fragments. Time-DFT has been employed toward investigating electronic excitations, hence exploring the possibility for quantum coherence. These calculations are illustrative of the electronic and vibrational properties of such molecules and their possible role in quantum phenomena relevant to biological processes.

- **DFT**: The electronic structure and vibrational spectra of selected amino acids and protein residues were obtained by performing DFT calculations using Gaussian software. All the calculations were performed using the B3LYP functional and a suitable basis set.
- **TD-DFT**: Calculations of TD-DFT were carried out to investigate electronic excitations and possible quantum coherence within the protein structures. The calculated excitation energies and oscillator strengths provided information on the electronic properties of chromophores within the proteins.

Bioinformatics Analysis

We used bioinformatics tools to analyze protein-protein interaction networks, identification of potential allosteric sites, and prediction of mutation impacts on protein structure and function. Molecular dynamics simulation was used to study the time-dependent behavior of proteins in their interactions with ligands. Quantum mechanical calculation integrated with bioinformatics analysis, we sought to identify possible quantum signatures of diabetes that may implicate the progress of the disease.

- Protein-Protein Interaction (PPI) Networks: PPI networks for proteins participating in glucose metabolism were constructed from the STRING database in order to detect functional associations of proteins. Networks were analyzed to detect hub proteins and potential regulatory modules.
- Molecular Dynamics (MD) Simulation: The molecular dynamics of proteins in aqueous solution have been studied using the GROMACS software package. From MD simulations, information concerning protein flexibility, conformational changes, and the possible influence of mutations on protein structure and function could be obtained.
- Quantum Mechanics/Molecular Mechanics (QM/MM) Simulations: We perform QM/MM simulations of quantum mechanical effects by some residues or cofactors inside the protein environment. Such an approach allowed us to study the interplay between quantum and classical regions of the system.

Ethical Considerations

Since this study was completely dependent on computational approaches and public data, no human subjects or animal models were used in this study. Hence, no approval from the ethical committee was required.

RESULTS

A comprehensive dataset of 18 proteins implicated in DM was curated from the PDB. This dataset encompasses high-resolution structural information for biomolecules central to glucose metabolism, insulin signaling, and other pathways relevant to the disease's pathophysiology **(Table 1**).

Protein Categories and Functional Relevance

The dataset was categorized into three primary groups based on the proteins' biological roles:

1. Insulin Signaling Proteins: Insulin receptor (IR), Insulin receptor substrate-1 (IRS-1), Akt B, mTOR.
2. Glucose Transport (GLUT) Proteins: GLUT4, GLUT1.
3. Glycolytic Enzymes: Hexokinase, Phosphofructokinase-1 (PFK-1), Pyruvate kinase.

Quantum Mechanical Characterization of Important Biomolecules

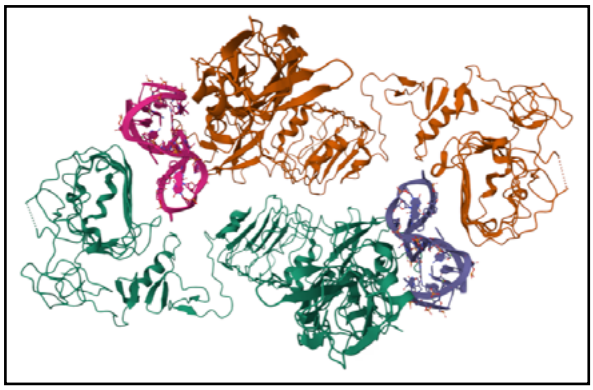
The detailed analysis of protein structures obtained from PDB allowed the identification of the poten-

Table 1. Proteins Implicated in Diabetes Mellitus

Protein Category	Protein Name	PDB ID(s)
Insulin Signaling	Insulin Receptor (IR)	7YQ6, 6BNT
	Insulin Receptor Substrate-1 (IRS-1)	1IRS, 5U1M
	Protein Kinase B (Akt)	1P6S, 1GZK
	Mammalian Target of Rapamycin (mTOR)	5FLC, 6ZWM
Glucose Transport	Glucose Transporter 4 (GLUT4)	7WSM, 7WSN
	Glucose Transporter 1 (GLUT1)	4PYP, 6THA
Glycolysis	Hexokinase	6KRJ, 3B8A
	Phosphofructokinase-1 (PFK-1)	4XYJ, 1PFK
	Pyruvate Kinase	2VGB, 2G50

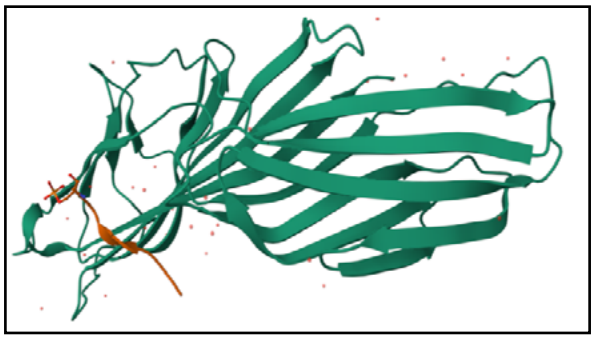
tial sites for quantum mechanical effects as specific amino acid residues of key proteins involved in the disease process of DM. These amino acid residues are located within critical regions of proteins such as the insulin receptor (PDB ID: 7YQ6, 6BNT) (Figure 1,2), IRS-1 (PDB ID: 1IRS, 5U1M) (Figure 3,4), and glycolytic enzymes.

Figure 1. Human insulin receptor bound with A62 DNA aptamer



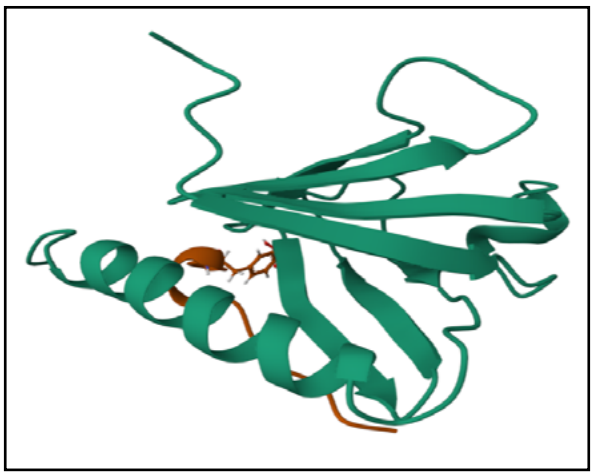
Source: https://www.rcsb.org/3d-view/7YQ6/1

Figure 2. Crystal structure of AP2 mu1 adaptin C-terminal domain with IRS-1 peptide



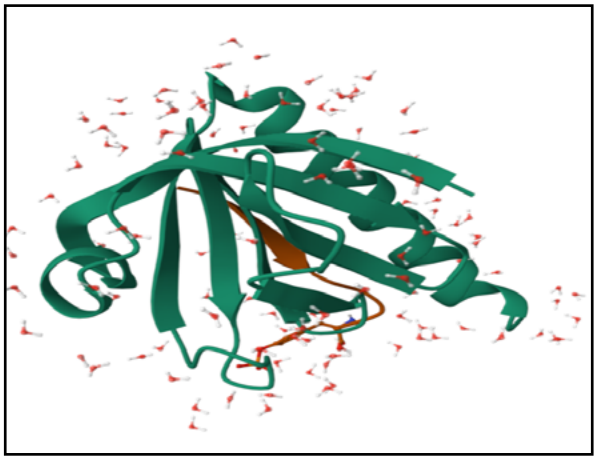
Source: https://www.rcsb.org/3d-view/6BNT/1

Figure 3. IRS-1 PTB domain complexed with a IL-4 receptor phosphopeptide, nmr, minimized average structure



Source: https://www.rcsb.org/3d-view/1IRS/0

Figure 4. Structure of the IRS-1 PTB Domain Bound to the Juxtamembrane Region of the Insulin Receptor



Source: https://www.rcsb.org/3d-view/5U1M/1

Electronic Structure and Vibrational Spectra Characterization

DFT calculations were performed to elucidate the electronic structure and vibrational spectra of such identified residues. The calculations provided a valuable insight into the electronic and vibrational properties of these molecules, indicating the possibility of involvement in quantum phenomena such as quantum tunneling and vibrational energy transfer.

Quantum Coherence

TD-DFT calculations were performed to assess quantum coherence within these domains when part of protein structures. The computational results indicate that quantum coherence may be significant in several biological processes involved with the DM.

Quantum Mechanical Characterization of Key Proteins

DFT calculations revealed important information about the electronic structure and vibrational properties of amino acid residues and active site fragments in these proteins. The main findings were:

- ***Insulin Receptor Kinase Domain***: The tyrosine residues in the active site showed delocalized electronic charge, suggesting possible quantum tunneling mechanisms during phosphorylation events. Vibrational analysis identified modes associated with phosphate group dynamics that may be important in enzymatic activity.
- ***GLUT4 Transporter:*** The residues in the transmembrane domain showed electronic properties compatible with the stabilization of glucose molecules. Vibrational modes were identified which may support quantum-assisted substrate translocation.
- ***Hexokinase:*** The active site presented electronic configurations favorable to quantum tunneling of protons in the process of ATP-dependent phosphorylation, in agreement with experiments.

Electronic Excitations and Quantum Coherence

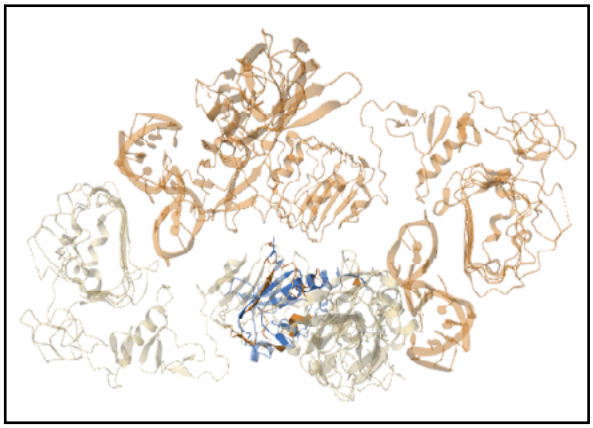
Some TD-DFT calculations considered the possibility of quantum coherence and electronic excitations within the protein structures. Several chromophore-like regions and key residues were observed to be the potential site for quantum effects. For instance:

- ***Phosphofructokinase-1:*** Strong electronic excitations in chromophore-like regions close to allosteric binding sites could allow coherent energy transfer mechanisms to be involved in the regulation of the enzyme.
- ***Pyruvate Kinase:*** TD-DFT revealed transitions involving aromatic residues in the active site that support the role of quantum coherence in substrate binding and catalytic turnover.

Vibronic Coupling and Quantum Effects

Our computational study revealed vibronic coupling in the system, as evidenced by the coupled electronic and vibrational transitions depicted in Figure 5. The 96 atom QM region, which is used in the 7YQ6-7WSM QM/MM simulations, is shown in the color-codec. The $C4^{+}$ and C_{α} atoms. The atoms refer to the atoms that are not included in the high-level QM region, int which the indicated C5' and C_{β} atoms are replaced by the hydrogen-link atoms. For clear presentation, all hydrogen atoms are not shown. Therefore, it might show vibronic effects that may enhance quantum tunneling or coherence; this, in turn, is indicative of a possibly essential role of quantum mechanics in the function of these proteins, and consequently in the development of DM.

Figure 5. Coupling between electronic transitions and nuclear vibrational modes



DISCUSSION

Our study bridges a critical gap in our understanding of DM by demonstrating the significant role of quantum mechanics in biological processes. By integrating quantum chemical calculations with bioinformatics analysis, we have identified specific residues within key proteins, such as the insulin receptor and GLUT4, that exhibit quantum mechanical properties. These properties, including quantum tunneling, coherence, and vibronic coupling, can influence en-

zymatic activity, substrate binding, and signal transduction. Our results question traditional biochemical models and give a new framework for interpreting the dynamic and electronic behavior of biomolecules involved in DM.

The direct correlation between quantum mechanics and metabolic diseases such as diabetes mellitus remains an emerging and controversial area of research. While theories and studies have explored the possibility of quantum phenomena influencing biological processes, experimental evidence is still limited, and scientific consensus has yet to be reached. Nevertheless, quantum mechanics offers an innovative perspective on understanding DM by exploring molecular processes at a subatomic level. Given that traditional models focus on biochemical pathways, often neglecting quantum phenomena such as tunneling, coherence, and vibronic coupling, quantum biology may significantly impact enzymatic reactions and protein-ligand interactions central to glucose metabolism[8].

Bioinformatics, the application of computational techniques to biological data, has been instrumental in assessing and comprehending biological processes[9]. The integration of bioinformatics with quantum mechanics as a tool for analyzing biological systems has significantly enhanced our understanding of these processes[10,11]. Our study employed the synergy between bioinformatics and quantum mechanics, often termed quantum bioinformatics, to investigate the onset of DM.

The insulin signaling pathway is a pathway involving multiple protein molecules[12]. It follows an elaborate course, typically originating from the binding of insulin to its receptor, upon which the insulin receptor subsequently phosphorylates IRS1; IRS1 recruits and activates mTOR and Akt B, where Akt B is regarded to be an important determinant of glucose metabolism due to the promotion of glucose uptake and glycogen synthesis[13]. Further, Akt B phosphorylates mTOR, which in turn determines the rate of protein synthesis and cell growth. Changes in this pathway lead to insulin resistance (IR) and type 2 DM, which was the reason for explaining, on a molecular level, the interaction between the insulin receptor, IRS1, Akt B, and mTOR[14].

The human body expresses 14 distinct GLUT isoforms, each with unique substrate specificities beyond glucose, including fructose, myo-inositol, and urate. For half of these isoforms, the primary physiological substrates remain uncertain. The well-characterized GLUT isoforms 1-4 exhibit distinct regulatory and kinetic properties, reflecting their specialized roles in cellular and systemic glucose homeostasis[15]. GLUT-1, a transmembrane glycoprotein, along with other glucose transporters, regulates glucose uptake[16]. GLUT-4, fundamental for whole-body glucose homeostasis, undergoes complex insulin-mediated regulation; disruptions in this process contribute to IR observed in obesity and type 2 DM[17].

The glycolytic pathway is controlled at a number of important steps, largely by three enzymes: hexokinase, phosphofructokinase-1 (PFK-1), and pyruvate kinase. Hexokinase catalyzes the initial phosphorylation of glucose, committing it to glycolysis. PFK-1, often considered the rate-limiting enzyme of glycolysis, catalyzes the irreversible conversion of fructose-6-phosphate to fructose-1,6-bisphosphate. Pyruvate kinase catalyzes the final step of glycolysis, converting phosphoenolpyruvate to pyruvate[18]. All of these enzymes are allosterically regulated by various metabolites to assure that glycolysis proceeds at a rate that meets the energy requirements of the cell.

We analyzed PDB structures of insulin signaling proteins, GLUTs, and glycolytic enzymes, identifying potential sites for quantum mechanical effects in specific amino acids linked to diabetes mellitus onset. DFT calculations support the hypothesis of quantum phenomena, including tunneling and vibrational energy transfer, playing a role in these processes. Bioinformatics analysis suggested that quantum coherence may play a significant role in various biological processes related to DM.

Quantum coherence, a fundamental aspect of quantum mechanics, refers to the capacity of quantum systems to preserve a consistent phase relationship over time. In biological systems, this phenomenon is particularly relevant in processes involving electron transfer. On the other hand, electronic excitation occurs when an electron in an atom or molecule absorbs energy and transitions to a higher energy level. In biological contexts, electronic excitation is frequently triggered by the absorption of light, initiating a series of events[19,20]. Our TD-DFT calculations revealed significant electronic excitations in chromophore-like regions near allosteric binding sites of phosphofructokinase-1, suggesting the potential involvement of coherent energy transfer mechanisms in its regulation. Furthermore, TD-DFT calculations on pyruvate kinase indicated transitions involving aromatic residues within the active site, supporting a role for quantum coherence in substrate binding and catalytic turnover.

The interplay between electronic and nuclear motions, known as vibronic coupling, is important in determining the properties and reactivity of molecules[21]. In the field of quantum chemistry, the QM/MM

approach offers a powerful framework to investigate these effects. By treating the active site of a molecule using high-level quantum mechanical methods and the surrounding environment with classical molecular mechanics, QM/MM calculations can provide insights into the nature of vibronic coupling and its implications for various chemical processes[22]. This hybrid approach allows for the study of large-scale systems while capturing the quantum mechanical effects that are essential for understanding the underlying mechanisms of many biological and chemical phenomena[23]. Our computational analysis revealed the presence of vibronic coupling within the system, manifested by coupled electronic and vibrational transitions among insulin signaling, glucose transport, and glycolytic enzymes. These results suggest that vibronic coupling plays a crucial role in the quantum mechanical basis of protein function and may contribute to the development of DM.

Quantum bioinformatics studies have revealed a significant potential for quantum effects to influence the molecular mechanisms implicit DM. By employing quantum mechanical and molecular mechanical techniques in conjunction with bioinformatics tools, we can identify specific amino acid residues within key proteins involved in glucose metabolism and insulin signaling that exhibit quantum mechanical behavior. Thus, quantum effects such as vibrational coherence and electronic tunneling may play a role in regulating enzymatic activity, protein-ligand interactions, and energy transfer processes.

CONCLUSION

Our study combined quantum mechanics with bioinformatics to study the complex molecular processes of DM. Key knowledge on electronic structures and vibrational characteristics of key proteins participating in glucose metabolism and insulin signaling was obtained through quantum mechanical analysis. From this, it can be concluded that there is significant participation by quantum mechanical phenomena in these biological pathways, offering a new view on the pathophysiology of DM.

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CASE REPORT *RELATO DE CASO*

IS IT CANCER OR IS IT AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE 2? THE DIAGNOSIS DURING THE INVESTIGATION OF CONSUMPTIVE SYNDROME

É CANCER OU SÍNDROME POLIGLANDULAR AUTOIMUNE TIPO 2? DIAGNÓSTICO DURANTE INVESTIGAÇÃO DE UM SÍNDROME CONSUMPTIVO

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Autoimmune Polyglandular Syndrome type 2 (APS-2) is a complex condition that may include autoimmune adrenal insufficiency, type 1 diabetes mellitus, and thyroid disease, among other endocrinological and non-endocrinological manifestations. Weight loss in patients with APS-2 is multifactorial, and detailed clinical and laboratory evaluation is essential to distinguish between etiologies of weight loss and ensure accurate diagnosis and appropriate treatment. This clinical case aims to detail the investigative journey in a patient with APS type 2.

A Síndrome Poliglandular Autoimune tipo 2 (SPA-2) é uma condição complexa que pode incluir insuficiência adrenal autoimune, diabetes mellitus tipo 1 e doenças da tireoide, entre outras manifestações endocrinológicas e não endocrinológicas. A perda de peso em pacientes com SPA-2 é multifatorial e a avaliação clínica e laboratorial detalhada é essencial para distinguir entre etiologias de perda ponderal e garantir um diagnóstico preciso e tratamento adequado. Esse caso clínico visa detalhar a jornada investigativa em uma paciente com SPA tipo 2.

Keywords (deCS): Autoimmune Polyendocrinopathies; Adrenal insufficiency; Hashimoto's disease.

INTRODUCTION

Autoimmune polyglandular syndromes (APS) are a heterogeneous group of rare diseases characterized by autoimmune activity against more than one endocrine organ, although non-endocrine tissues can also be affected[1].

There is coexistence of at least two autoimmune endocrine diseases, dependent on genetic and environmental factors, differing in terms of age of presentation, for example type I/juvenile APS and adult APS (classified in types II to IV, depending on the combination of autoimmune diseases). Patients with APS are associated with a higher risk of developing other types of non-glandular autoimmune diseases[2,3,4].

This case report aims to focus in clinical investigation and diagnosis on type II adult APS, which is more common in females and has an autosomal dominant inheritance with incomplete penetrance and is linked to HLA-DR3 and HLA-DR4 haplotypes. Its major and obligatory endocrine component is autoimmune adrenal insufficiency (Addison's disease) accompanied by autoimmune thyroid disease (ATD) and/or type 1 diabetes mellitus (T1D), as well as other endocrine and non-endocrine autoimmune disorders[5,6].

CASE REPORT

A 54-year-old female patient was referred to the Endocrinology Outpatient Service of the Mackenzie Evangelical Hospital in Paraná in April 2024 for investigation of consumptive syndrome (weight loss of 30 kg in a period of 1 year) associated with episodes of hypoglycemia, asthenia, dizziness, nausea, visual darkening and symptomatic hypotension.

She had a pathological history of Hashimoto's hypothyroidism (diagnosed in December 2023), a history of dyslipidemia, and xerosis under follow-up with a dermatologist. She was using levothyroxine 75 mcg/day and simvastatin 20 mg/night. And had no family history of type 1 diabetes mellitus, thyroid diseases, primary hypogonadism, among others.

She reported several visits to the emergency room, and initially, due to the severity of consumptive syndrome, had been referred to the oncology service. More frequent causes such as malignant diseases, non-malignant gastrointestinal diseases and psychiatric conditions had already been ruled out by the clinical and oncological team.

On admission, in co-management with the endocrinology team, endocrinological etiologies were investigated, and the following findings were found:

On physical examination: the patient was afebrile, blood pressure was 110/80 mmHg and BMI: 21 kg/m², she had the presence of scaly lesions in the upper and lower limbs, brownish keratoses and oral mucosa with hyperpigmented areas (**Figure 1**).

The patient's tests (**Table 1**) showed hyperkalemia, hyponatremia, adequate thyroid function and suppression of adrenal function demonstrated by hypocortisolism, and increased ACTH. Therefore, the diagnosis of primary adrenal insufficiency combined with Hashimoto's thyroiditis was confirmed, confirming Schmidt's syndrome (APS 2).

Figure 1: Photos of the patient before, at the time of diagnosis and after treatment

Table 1. Laboratory tests of the hospitalization

Exams	Results	Referencevalue
Hemoglobin	16 g/dL	11.5-14.9 g/dL
Baselineserum cortisol	0.41 ug/dL	5,5-30 ug/dL
Anti-TPO	497 UI/mL	< 35 UI/mL
Dehydroepiandrosterone (DHEA)	0.31 ng/dL	120-870 ng/dL
Adrenocorticotropichormone (ACTH)	1250 pg/mL	5-46 pg/mL
Dehydroepiandrosterone Sulfate (SDHEA)	< 2 µg/dL	8-188 µg/dL
Potassium	5.6 mEq/L	3.6-5.2 mEq/L
Sodium	133 mEq/L	135-145 mEq/L
T4L	1.65 ng/dL	0.7-1.48 ng/dL
TSH	3.54 mU/L	0.4-4.5 mU/L
Anti-GAD	3 UI/ml	<10 UI/ml (negativo)

Corticosteroid therapy with prednisone 5 mg/morning, 2.5 mg/afternoon, and fludrocortisone 0.1 mg in the morning was started and levothyroxine underwent progressive adjustment until the dose of 75 mcg in the morning in the fasting state. The patient returns to the service with clinical improvement and progressive weight gain, with a notable reduction in skin pigmentation and a better quality of life.

DISCUSSION

Autoimmune polyglandular syndrome (APS) is a rare group of immune-mediated disorders characterized by simultaneous or sequential dysfunction of multiple endocrine or non-endocrine glands due to autoimmune processes. There are different types of APS, each with distinct clinical and genetic characteristics.

APS type 1 (APS-1) is a rare hereditary disease caused by mutations in the autoimmune regulatory gene (AIRE). Clinically, it is diagnosed by the presence of at least two of the three main criteria: chronic mucocutaneous candidiasis, hypoparathyroidism and adrenal insufficiency (Addison's disease)[7,8,9]. APS-1 is a complex condition, with chronic and debilitating complications, and management is challenging due to its complexity[7].

APS type 3 is defined by the presence of autoimmune thyroid disease and other autoimmune diseases, excluding Addison's disease and hypoparathyroidism[10,11]. This type is subdivided into subtypes based on the specific combinations of autoimmune diseases present[12].

APS type 2 (APS-2), also known as Schmidt Syndrome, is an autoimmune condition characterized by the coexistence of autoimmune adrenal insufficiency (Addison's Disease) with autoimmune thyroid disease and/or type 1 diabetes mellitus[13-17]. This syndrome is the most common form of autoimmune polyglandular syndrome in adults and usually presents in the third or fourth decade of life[3]. It corresponds to the diagnosis of the patient in this clinical case and will therefore be discussed further below.

APS-2 is often associated with specific major histocompatibility complex (HLA) alleles, such as HLA-DR3 and HLA-DR4, which confer genetic susceptibility to the disease[3]. It is estimated that 40 to 50% of all cases diagnosed with Addison's disease have an additional autoimmune disease capable of clinically defining APS-2, so screening and clinical surveillance is essential[1,18].

Furthermore, 1 year after the onset of adrenal insufficiency, less than 50% of these cases are detected, due to the wide variety of nonspecific symptoms and the interval between the occurrence of different endocrine disorders - evaluation by a specialist in endocrinology and metabolism is a priority[19]. In addition to clinical symptoms, serological tests are indispensable for screening patients with polyglandular autoimmunity.

Adrenal insufficiency is an essential and necessary component of the syndrome, present in 100% of cases[2]. Other autoimmune conditions, such as pernicious anemia, vitiligo, alopecia, myasthenia gravis, celiac disease, and autoimmune diabetes insipidus, may be associated with APS-2[14]. Furthermore, considering female patients, autoimmune ovarian failure (AOF), also known as primary ovarian failure, is also part of the spectrum, as one of the manifestations of APS. The presence of autoantibodies against steroidogenic enzymes and ovarian steroidogenic cells is an important marker[20,21].

The diagnosis of APS-2 is clinical, based on the presence of characteristic endocrinopathies, and can be aided by the determination of specific autoantibodies, such as antibodies against 21-hydroxylase, which are frequently elevated in patients with autoimmune adrenal insufficiency[15,17]. It is worth noting that the syndrome may also involve non-endocrinological autoimmune (**Table 2**) involvement and for this reason clinical suspicion and symptom assessment must be even more detailed.

Treatment involves adequate hormone replacement for each of the endocrine deficiencies present, such as glucocorticoids for adrenal insufficiency, levothyroxine for thyroid dysfunction and insulin for type 1 diabetes[17,26]. With special care when replacing levothyroxine, this is because patients on thyroxine supplementation increase metabolic rate and glucocorticoid demand, in patients with APS II there is an inability to metabolically compensate for this need. The clinical suspicion for the patient reported above was an Addisonian crisis with probable precipitant levothyroxine replacement without associated corticosteroid therapy[27].

APS-2 also can be induced by immune checkpoint inhibitors, such as anti-PD1, which can trigger the syndrome in genetically predisposed individuals[26,28].

This clinical case began with the suspicion of oncological disease: we highlight however that malignant diseases, although frequently suspected, are not the most common cause of unintentional weight loss, but still account for a significant proportion of cases, especially in older populations[29]. Gastrointestinal diseases, both malignant and non-malignant, are common causes, with disorders of the gastrointestinal tract accounting for

Table 1. Estimated prevalence of autoimmune diseases in APS-2 (References 20-25) - *Adapted by the author*

Prevalence of autoimmune diseases in Polyglandular autoimmune syndrome type 2			
Endocrine		**Nonendocrine**	
Adrenal insufficiency	100%	*Vitiligo	4%
Autoimmune thyroid disease	70%	*Alopecia *Pernicious anemia *Myasthenia gravis *Immune thrombocytopenia purpura *Sjögren syndrome *Rheumatoid arthritis	≤1%
Type 1 diabetes mellitus	50%		
Primary hypogonadism	5 to 50%		
Autoimmune ovarian failure	10 to 16%		
Diabetes insipidus	<1%		

about one-third of cases[30]. Psychiatric conditions, such as depression, are also important causes of unintentional weight loss, especially in older adults. In addition, social factors, such as isolation and financial constraints, can contribute to unintentional weight loss[30].

Medication use and polypharmacy are factors that should not be overlooked, as they can interfere with taste or cause nausea, contributing to weight loss. In some cases, the cause of weight loss remains undetermined, even after a comprehensive diagnostic evaluation, and it is in this situation that less common diagnoses should be considered, such as autoimmune polyglandular syndromes.

Early identification and appropriate management are crucial to prevent potentially fatal complications, such as the adrenal crisis and to improve the prognosis and morbidity and mortality of patients[17,26].

CONCLUSION

This case highlights the importance of extensive clinical investigation and screening of other autoimmune diseases, as well as the role of endocrinological disorders in the investigation of consumptive syndrome and as a range of differential for complaints, which at first glance appear to be nonspecific. And reinforces that in cases of diagnostic challenge, where the cause was initially undetermined, rarer causes such as the one described in this case must be evaluated.

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CASE REPORT *RELATO DE CASO*

ANTI-SYNTHETASE SYNDROME AS A PRECIPITANT OF DECOMPENSATED HYPOTHYROIDISM: A CASE REPORT

SINDROME ANTI-SINTHETASE COMO UM PRECIPITANTE DA DESCOMPENSAÇÃO DO HIPOTIREOIDISMO: APRESENTAÇÃO DE CASO

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Autoimmune diseases are occasionally diagnosed together. Furthermore, the presence of another autoimmune condition can impact the treatment and management of known diseases. Refractory hypothyroidism is an example of it. This case report aims to address the challenges in treating autoimmune hypothyroidism in the presence of anti-synthetase syndrome, before its proper diagnosis and treatment.

Doenças autoimunes são ocasionalmente diagnosticadas associadas. Além disso, a presença de outra condição autoimune pode impactar o tratamento e o manejo de doenças conhecidas. O hipotireoidismo refratário é um exemplo disso. Este relato de caso visa abordar os desafios no tratamento do hipotireoidismo autoimune na presença da síndrome antissintetase, antes de seu diagnóstico e tratamento adequados.

Keywords (deCS): Anti-synthetase syndrome; autoimmune diseases; refractory hypothyroidism.

INTRODUCTION

Refractory hypothyroidism is a challenging condition in the field of thyroidology, characterized by the inability to achieve disease control, even with the use of levothyroxine (LT4) doses of 1.9 µg/kg/day or more. Non-pathological causes include non-adherence to treatment, changes in the LT4 brand, pregnancy, dietary and medication interference. Pathological causes may include lactose intolerance, Helicobacter pylori infection, giardiasis, among others. Diagnosis involves a detailed medical history and laboratory tests to identify causes of treatment resistance, and the LT4 absorption test can be used to identify cases of malabsorption[1].

The relationship between refractory hypothyroidism and autoimmune diseases is complex. Autoimmune thyroid diseases, such as Hashimoto's thyroiditis and Graves' disease, are T-cell mediated and result from an altered immune response that leads to autoimmune attack on the thyroid[2]. And, in the context of autoimmune

diseases, refractoriness may occur due to the almost total destruction of thyroid hormone-secreting cells, which limits the effectiveness of immunosuppressants and corticosteroids[3]. This is particularly relevant in diseases such as Hashimoto's thyroiditis, where destruction of thyroid cells can be extensive, making tissue recovery difficult even after immune suppression[3].

However, less frequent autoimmune diseases can also be the underlying cause of this change and this clinical case aims to highlight anti-synthetase syndrome as a precipitant of uncontrolled hypothyroidism.

CASE REPORT

This report details a 29-year-old woman with decompensated primary hypothyroidism secondary to anti-synthetase syndrome, a rare autoimmune rheumatologic condition.

The patient had Hashimoto's thyroiditis and was diagnosed in-hospital with anti-synthetase syndrome, which caused gastrointestinal disturbances, primarily affecting striated muscles and resulting in dysphagia.

Despite initial treatment with 3.77 µg/kg/day off levothyroxine, hypothyroidism (both clinically and by laboratory results) remained uncompensated until the underlying rheumatologic condition was managed.

This patient had been under dermatological care 5 months before admission on account of desquamative skin lesions on her palms and soles, predominantly affecting the interphalangeal joints. In July 2024, she presented to the Hospital Universitário Evangélico Mackenzie's emergency department, in Paraná Brazil, with insidious onset dysphagia (for solids), microstomia, and aphasia. Also with progressive weakness, beginning in her lower extremities and spreading to her upper extremities and spine, necessitated wheelchair use.

Over 30 days, she experienced a 20 kg weight loss, resulting in a current weight of 53 kg, and exhibited xerostomia and xerophthalmia. She reported no other known pre-existing comorbidities and, at the moment, was only taking: levothyroxine 100 mcg/day.

On examination, she exhibited desquamative skin lesions on her palms and soles, with a mildly erythematous base and slightly indurated papules on the dorsum of her metacarpophalangeal joints bilaterally, suggestive of Gottron papules (**Figure 1**). No shawl sign was present, although a Koebner phenomenon was observed at her cesarean scar. She demonstrated significant proximal muscle weakness affecting both upper and lower extremities and microstomia (**Figure 2**).

Figure 1: Desquamative skin lesions on palms and soles with a mildly erythematous base and slightly indurated papules on the dorsum of her metacarpophalangeal joints bilaterally.

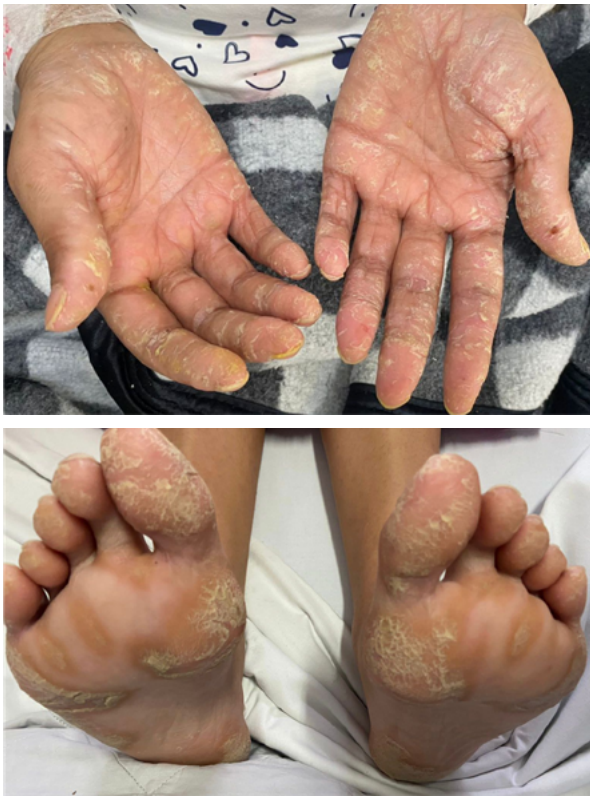
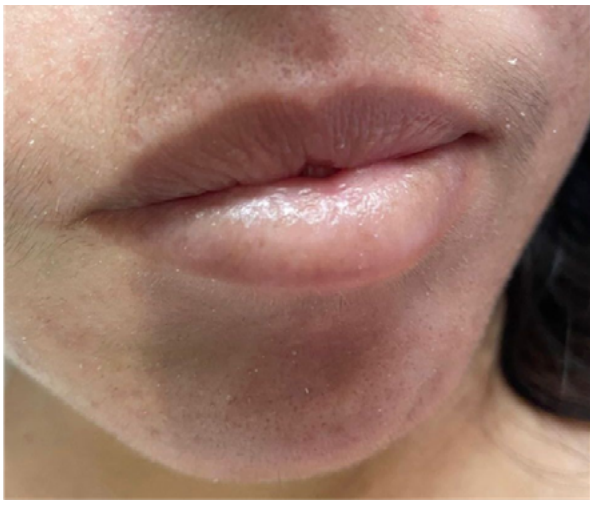


Figure 2: Microstomia



Laboratory tests were ordered during her hospitalization and are shown in **Table 1.**

Table 1: Laboratory tests. RV: Reference Value. NR: Non Reagent. ''>'': represents the temporal sequence/evolution of laboratory tests during hospitalization.

Exams	Results	Exams	Results
Hemoglobin	15,2 g/dl	**Neutrophils**	**75% mm³**
White blood cells	**10.000 mm³**	**VHS**	**27 > 24 mm**
LDH	**1640 U/L> 998 U/L > 977 U/L** (RV < 378 U/L)	**CPK**	**3736 U/L > 2039 U/L > 933 U/L** (RV < 145 U/L)
Platelets	**37.900** µL	**C-Reactive Protein**	**12,3 mg/L**> 0.55mg/L> 0,21 mg/L (RV < 0,1 mg/L)
Creatinine	0.32mg/dL	Anti-SCL	NR
Urea	17 mg/dL	Anti-centromere	NR
Antinuclear antibody	**1/640 (Fine Stippling)**	**Anti-thyroidperoxidase**	**Reagent**
Aldolase	**122,7 U/L** (RV < 7.6)	**Sodium**	**133 mmol/L**
Potassium	4.2 mmol/L	Anti-Ro	NR
Aldolase	**122,7 U/L** (RV < 7.6)	Anti-LA	NR
AST	**93 U/L>45 U/L** (RV <45 U/L)	**ALT**	**79 U/L> 86 U/L** (RV<45 U/L)
Anti-RNP	NR	Anti-DNA	NR
TSH	**49,2 mU/L** (RV: 0.4 - 4.5 mU/L)	**Free T4**	**0,7 ng/dL>1.38 ng/dl** (RV: 0.61–1,12 ng/dl)
Rheumatoid factor	**19,3 UI/mL**	Serologies	NR

Endocrinology consultation was sought due to her underlying autoimmune condition and elevated TSH levels, coupled with an enlarged thyroid gland on admission:

Thyroid ultrasound revealed an enlarged gland with heterogeneous echotexture and lobulated margins. A multinodular pattern was evident, with several hypo- and isoechoic, well-defined nodules (consistent with TIRADS 3), measuring up to 10 mm, except for two larger nodules (15 x 14 x 12 mm and 26 x 24 x 16 mm).

Laboratory findings, including elevated aldolase, CPK, CRP e transaminases, especially AST, suggested inflammatory myopathy, alongside characteristic cutaneous lesions (“mechanic’s hands” and “hiker’s feet”), confirming a diagnosis of anti-synthetase syndrome.

Treatment involved three days of pulse methylprednisolone (1g) and five days of intravenous immunoglobulin (400 mg/kg/day via continuous infusion) to alleviate dysphagia.

Despite receiving 200 mcg/day of levothyroxine, decompensated hypothyroidism persisted during hospitalization. After excluding poor medication adherence, the underlying autoimmune disease, affecting gastrointestinal absorption, was identified as the cause.

Following a decrease in inflammatory markers, a repeat free T4 test yielded a value of 1.38ng/dL. Control of the underlying autoimmune disease resulted in significant clinical improvement. The patient was subsequently referred to endocrinology for follow-up and returned to his usual dose of levothyroxine.

DISCUSSION

Hypothyroidism, characterized by deficient thyroid hormone production, is commonly classified as central (hypothalamic or pituitary dysfunction) or primary (thyroid gland dysfunction)[4]. The patient in this clinical case has the primary form of hypothyroidism: a disease that most commonly is caused by chronic autoimmune thyroiditis (Hashimoto’s thyroiditis), marked by anti-peroxidase antibodies and decreased thyroid hormone levels (leading to compensatory increases in TSH and TRH)[5].

These antibodies are also associated with other autoimmune disorders, including rheumatoid arthritis, vitiligo, and anti-synthetase syndrome, all recognized risk factors for hypothyroidism and the reason why screening for hypothyroidism is indicated in at-risk individuals[5].

It is already well recognized that one autoimmune disease can trigger another, and this case reinforces this concept: the patient, during hospitalization, was diagnosed also with anti-synthetase syndrome (ASSD),

an autoimmune disease characterized by the presence of autoantibodies against one of several aminoacyl-tRNAsynthetases (aaRSs).

Clinically, the ASSD is manifested by a combination of symptoms that include interstitial lung disease, myositis, Raynaud's phenomenon, arthritis, mechanic's hands, and fever[6]. Dysphagia is also a relatively common manifestation in patients with ASSD, occurring in approximately 29% of cases, as reported in a study that analyzed patients with idiopathic inflammatory myositis and anti-ARS antibodies[7]. This symptom is associated with muscle weakness, which is a characteristic of the syndrome and may be indicative of more extensive muscle involvement, including the esophageal muscles[7].

Therefore, the relationship between anti-synthetase syndrome and esophageal problems, such as dysphagia, is mainly linked to the muscular involvement that characterizes the disease, also affecting the muscles responsible for swallowing, and consequently being a precipitant for difficulty in absorbing medications.

Autoantibodies there are most commonly associated with ASSD include anti-Jo-1, anti-PL-7, anti-PL-12, antinuclear antibody, rheumatoid factor, among others, and each may be associated with different clinical manifestations. The presence of these autoantibodies is an essential criterion for diagnosing the syndrome, although the clinical presentation can be quite heterogeneous[8].

The pathogenesis of both autoimmune diseases involves the activation of the immune system. Hashimoto's thyroiditis is characterized by a lymphocytic infiltration of the thyroid gland. On the other hand, ASSD is characterized by antigen activation where aaRSs act as antigens and play roles similar to chemokines and cytokines, initiating innate and adaptive immune pathways[9].

This report highlights the potential for autoimmune diseases, such as anti-synthetase syndrome, to precipitate other autoimmune disorders and contribute to diverse mechanisms of hypothyroid decompensation and refractory hypothyroidism.

Refractory hypothyroidism is a condition in which patients are unable to achieve adequate disease control despite the use of adequate doses of levothyroxine (LT4). Some references define it as an unnormalized thyroid function despite LT4 doses exceeding 1.9 µg/kg/day[10]. This patient was receiving 3.77 µg/kg/day and while poor adherence is frequently implicated and the most common cause of this condition, the supervised hospital setting makes this less likely. Instead, impaired levothyroxine absorption secondary to gastrointestinal involvement, corroborated by the clinical presentation and improvement in free T4 levels alongside improvement in the underlying condition, points to anti-synthetase syndrome as the cause of treatment resistance.

The causes of refractory hypothyroidism can be divided into non-pathological and pathological (**Table 2**):

Table 2: Causes of refractory hypothyroidism (References 1, 11-15) - *Adapted by the author*

Causes of refractory hypothyroidism		
Non-pathological:	*Non-adherence to treatment	
	*Changes in the LT4 mark	
	*Food and drug interactions (e.g., interactions with mineral supplements - iron, calcium, magnesium; proton pump inhibitor or aluminum hydroxide use; sertraline, phenytoin, carbamazepine, rifampicin, phenobarbital, and ritonavir-containing antiviral regimens)	
	*Physiological conditions such as pregnancy	
	*Inadequate storage of LT4, such as exposure to humidity, light and high temperatures, may compromise the effectiveness of the medicine	
Pathological causes: Conditions that affect the absorption of LT4 stand out, such several conditions that impair gastric acid secretion or intestinal absorption/ jejunal abnormalities.	*Short bowel syndrome	*Lactose intolerance
	*Intestinal bypass	*Celiac disease
	*Chronic giardiasis	*Atrophic gastritis
	*Other intestinal parasites	*Gastrectomy
	*Helicobacter pylori infection	
	*Inflammatory bowel disease (e.g., Crohn's disease)	
	Other autoimmune diseases (e.g: anti-synthetase syndrome)	

Addressing these causes often lowers the required LT4 dose[16]. This is what happened in this clinical case, where the patient resumed her usual dose of levothyroxine after the underlying disease was stable.

CONCLUSION

For patients who frequently require high doses of levothyroxine and yet fail to achieve normal serum TSH levels, a thorough assessment should include an evaluation of factors that may influence absorption.

Once other causes of descompensation, such as external factors and malabsorption, have been excluded, rare etiologies should be investigated, particularly those involving gastrointestinal disorders. Other conditions that may contribute to refractory hypothyroidism include significant weight gain, cystic fibrosis, nephrotic syndrome and wasting diseases, such as Addison's disease.

This case illustrates that, while uncommon, autoimmune conditions impacting gastrointestinal motility should be included in the differential diagnosis of refractory hypothyroidism. Also, reinforces that early identification and appropriate management of autoimmune diseases are crucial due to their significant impact on morbidity and mortality.

It is important to identify and treat the underlying cause of refractory hypothyroidism to avoid excessive use of LT4, which can lead to cardiovascular and bone complications.

Therefore, the management of refractory hypothyroidism in patients with autoimmune diseases requires a careful approach to identify and treat the underlying causes of malabsorption or non-adherence, in addition to considering the extent of autoimmune damage to the thyroid gland or other systems such as the gastrointestinal tract.

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SCOPING REVIEW *REVISÃO DE ESCOPO*

"IN-SITU INSULIN RESISTANCE – LOCALIZED TYPE 2 DIABETES MELLITUS OR TYPE 6 DIABETES MELLITUS?": A SCOPING REVIEW

"RESISTÊNCIA À INSULINA IN SITU – DIABETES MELLITUS TIPO 2 LOCALIZADO OU DIABETES MELLITUS TIPO 6?": UMA REVISÃO DE ESCOPO

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In the context of type 2 diabetes mellitus (T2DM), the concept of organ-specific insulin resistance (IR) as a localized manifestation has garnered increasing attention. A scoping review was conducted to investigate the clinical relevance of IR confined to individual organs without systemic metabolic implications. Utilizing a methodological framework adapted from Arksey and O'Malley, a comprehensive search of PubMed was performed, focusing on the period between January 1990 and October 2024. The search strategy combined Medical Subject Headings terms and keywords related to IR and specific organs. Notably, while "insulin resistance" yielded a substantial number of results, the subset of "organ-specific insulin resistance" returned a more limited dataset, highlighting a gap in current literature. The systematic selection process encompassed identification, screening, eligibility, and inclusion stages to ensure robust inclusion criteria. This scoping review underscores the importance of exploring organ-specific IR in the diabetic milieu and sets the stage for further research to elucidate its role in the pathogenesis of T2DM. **Conclusion:** The findings suggest that investigating organ-specific IR in the context of T2DM is a promising avenue for future research to deepen our understanding of disease pathophysiology. Thus, this scoping review answers the following question "In-Situ Insulin Resistance - Localized Type 2 Diabetes Mellitus or Type 6 Diabetes Mellitus?", emphasizing the need for targeted investigations into localized manifestations of IR and their implications for DM management strategies.
Keywords: Insulin resistance, Organ-specific insulin resistance, Diabetes mellitus, Scoping review.

No contexto do diabetes mellitus tipo 2 (DM2), o conceito de resistência insulínica (RI) órgão-específica como uma manifestação localizada tem ganhado crescente atenção. Uma revisão de escopo foi conduzida para investigar a relevância clínica da RI restrita a órgãos individuais sem implicações metabólicas sistêmicas. Utilizando a ferramenta metodológica adaptada de Arksey e O'Malley, uma busca abrangente no PubMed foi realizada, no período entre janeiro de 1990 e outubro de 2024. A estratégia de busca combinou termos dos Medical Subject Headings e palavras-chave relacionadas à RI e órgãos específicos. Notavelmente, enquanto o termo "resistência insulínica" gerou um número substancial de resultados, o subconjunto de "resistência insulínica órgão-específica" retornou um conjunto de dados mais limitado, destacando uma lacuna na literatura atual. O processo de seleção sistemática abrangeu as

etapas de identificação, triagem, elegibilidade e inclusão para garantir critérios de inclusão robustos. Esta revisão de escopo sublinha a importância de explorar a RI órgão-específica no ambiente diabético e estabelece o cenário para pesquisas futuras para elucidar seu papel na patogênese do DM2. **Conclusão**: Os achados sugerem que investigar a RI órgão-específica no contexto do DM2 é uma via promissora para pesquisas futuras, a fim de aprofundar nosso entendimento da fisiopatologia da doença. Assim, esta revisão de escopo responde à seguinte pergunta: "Resistência à insulina In-Situ - Diabetes Mellitus Tipo 2 Localizado ou Diabetes Mellitus Tipo 6?", enfatizando a necessidade de investigações direcionadas às manifestações localizadas da RI e suas implicações para as estratégias de manejo do DM.

Palavras-chave: Resistência à insulina, Resistência à insulina órgão-específica, Diabetes mellitus, Revisão de escopo.

INTRODUCTION

The understanding of tissue-specific insulin resistance (IR) has evolved over the years, with recent advances focusing on the intricate mechanisms underlying this condition.[1] Our concept of type 6 diabetes mellitus (T6DM) refers to the localized development of IR in specific organs, such as the brain, hypothalamus, pituitary gland, thyroid, lung, heart, liver, pancreas, kidneys, spleen, small intestine, large intestine, muscle, adipose tissue, vessels, ovaries, and testicles, independent of systemic insulin sensitivity[2].

Recent studies have highlighted the role of pro-inflammatory cytokines, adipokines, and lipotoxicity in promoting IR at the cellular level, contributing to the pathogenesis of T6DM[3] Furthermore, evidence suggests that genetic predisposition and epigenetic modifications may also play a significant role in the development of organ-specific IR, influencing the onset and progression of metabolic disorders[4].

The identification of novel therapeutic targets aimed at mitigating IR in isolated organs represents a promising approach for the treatment of this condition. Targeted interventions focused on modulating specific molecular pathways involved in tissue-specific insulin signaling hold great potential for improving metabolic health and reducing the risk of complications associated with IR[5]. Additionally, personalized medicine approaches that consider individual variations in genetic and environmental factors may enhance the efficacy of treatments targeting organ-specific IR in patients with metabolic disorders[6]. Thus, the concept of T6DM emphasizes the importance of exploring tissue-specific mechanisms of IR to develop targeted therapies for improving metabolic health and reducing its related complications.

A scoping review offers a comprehensive exploration of existing research on a particular topic, identifying key concepts, research gaps, and the extent of available evidence. Unlike systematic reviews, scoping reviews are more flexible in their methodology, accommodating a broader range of study designs. By providing a detailed overview of the literature, scoping reviews inform research agendas, policy development, and practice. For instance, a scoping review by Arksey and O'Malley[7] established a foundational framework for conducting these studies, outlining key steps such as identifying the research question, selecting studies, charting the data, and collating, summarizing, and reporting the results.

Our objective is to characterize T6DM as an organ- and system-specific IR through a scoping review, encompassing the central nervous system, endocrine glands (hypothalamus, pituitary, thyroid, and reproductive system), respiratory system, cardiovascular system, hepatobiliary system, gastrointestinal tract, hematopoietic system, musculoskeletal system, adipose tissue, and vasculature.

MATERIALS AND METHODS

Registration

To guarantee transparency and uphold methodological principles, review protocol was written prior to undertaking the review in the OSF Registries under the unique identifier https://doi.org/10.17605/OSF.IO/WRT8V. This publicly accessible record, available at https://archive.org/details/osf-registrations-wrt8v-v1 comprehensively details the search strategy.

Search Strategy

A scoping review was performed to explore the clinical significance of organ-specific IR. Following the methodological approach detailed by Arksey and

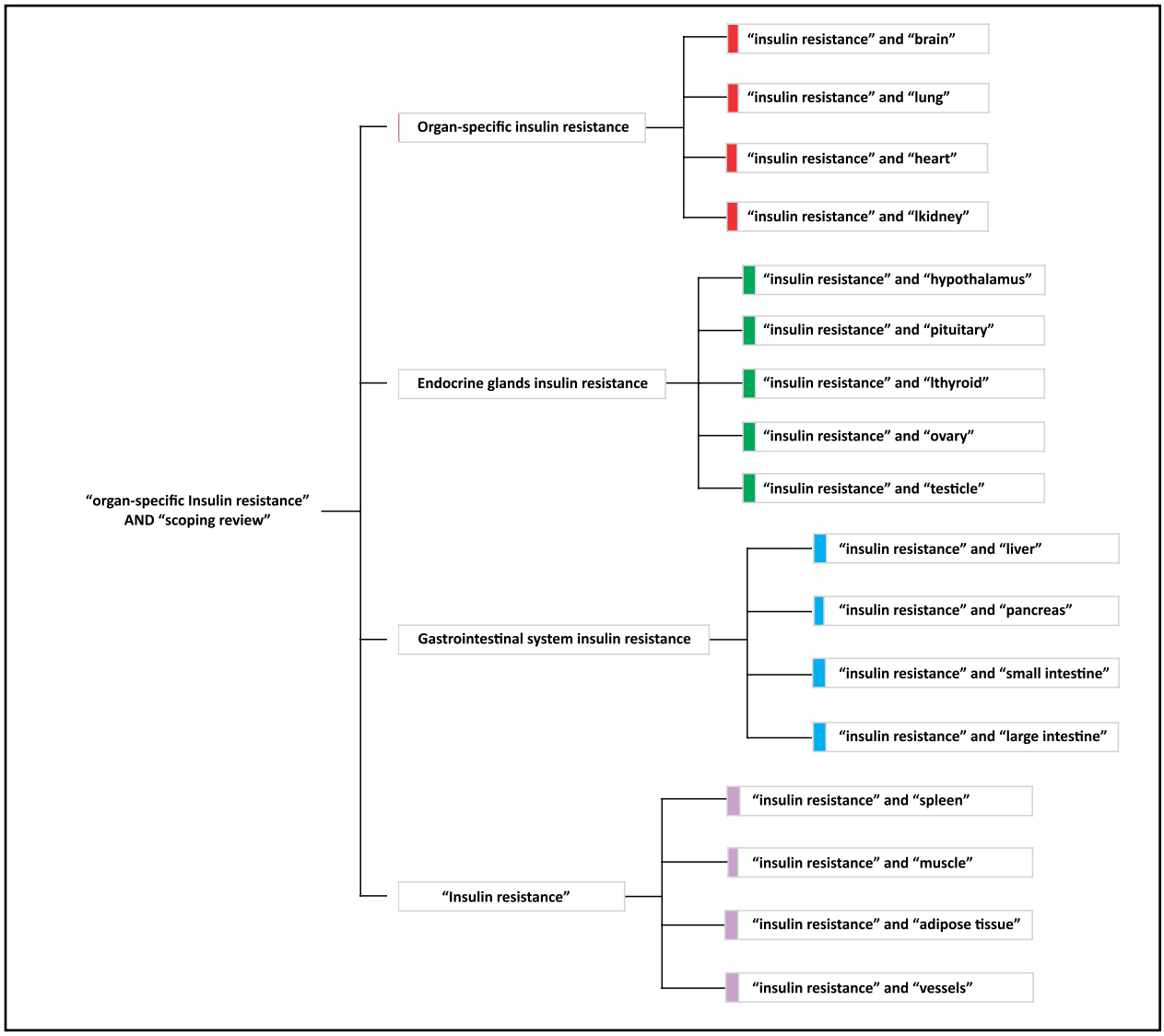
O'Malley[7], a comprehensive search of the PubMed literature was conducted to address the question: Can IR confined to individual organs, without systemic metabolic complications, be considered an in-situ manifestation of the diabetic state?

This scoping review adhered to the adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and its extension for scoping reviews (PRISMA-ScR),[8] to ascertain that the review encompassed all pertinent subject areas. The literature search encompassed the PubMed databases, focusing on articles published between January 1990 and October 2024. The search strategy included a combination of Medical Subject Headings (MeSH) terms and keywords, such as "insulin resistance", "organ-specific insulin resistance", and "brain", "hypothalamus", "pituitary", "thyroid", "lung", "heart", "liver", "pancreas", "kidney", "spleen", "small intestine", "large intestine", "muscle", "adipose tissue", "vessels", "ovary", "testicle". Data were extracted using a standardized data extraction form (**Figure 1**).

Inclusion and Exclusion Criteria

All articles within the research domain were meticulously examined. English-language studies explicitly addressing IR were included. Original research articles were considered if they reported IR at the organ or system level. Articles were excluded if they were not human-based studies or if they were published prior to 1990. Review papers, editorials, case studies, and opinion pieces were not included in this analysis.

Figure 1. Search strategy



RESULTS

A comprehensive literature search was conducted in PubMed using the keywords "insulin resistance" and "organ-specific insulin resistance." While "insulin resistance" yielded a vast number of results[123,764], "organ-specific insulin resistance" produced a significantly smaller dataset (8 results).

To explore specific organ-system associations, we further refined our search by combining "insulin resistance" with terms representing various organs and systems. We selected only articles that presented a significant association between the terms used.

The selection of articles for this review followed a four-stage process: Identification, Screening, Eligibility, and Inclusion (depicted **in Figure 2**).

During the identification phase, we identified a pool of potential records from relevant databases and excluded those that did not meet the initial criteria. During the screening stage, we reviewed each record in detail, excluding those deemed ineligible based on our inclusion and exclusion criteria. We then sought to retrieve the full texts of the remaining records, but were unable to obtain some for various reasons. Finally, we assessed the retrieved reports for eligibility and excluded those that did not meet the inclusion criteria. The inclusion stage represented the final set of studies included in the scoping review (**Table 1**).

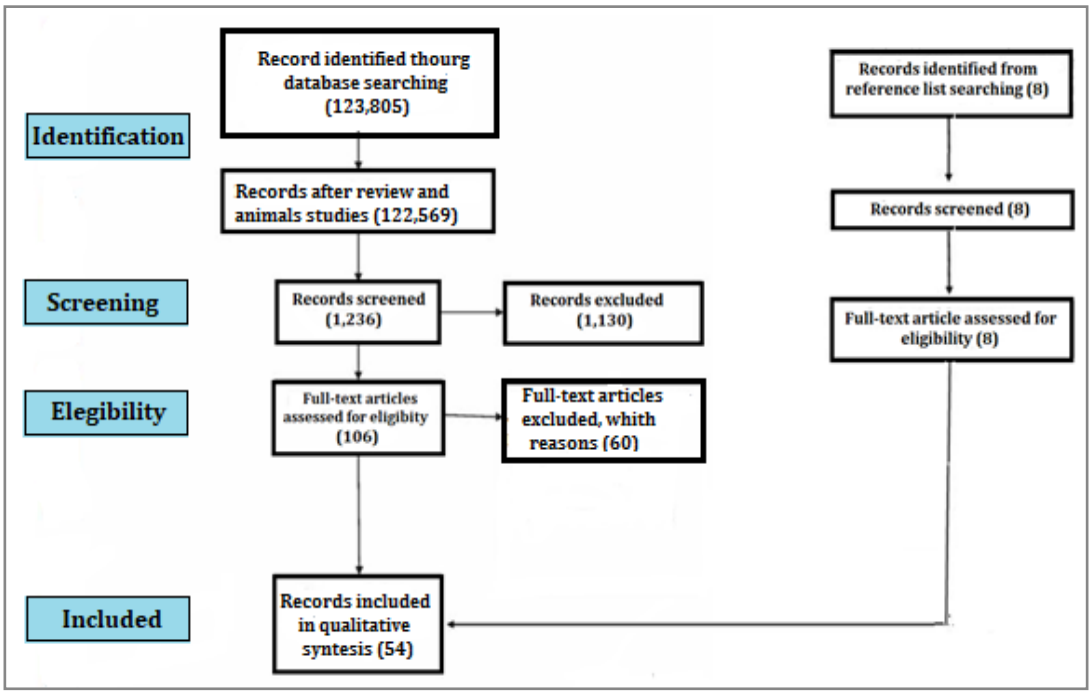
Brain insulin resistance

1. Kullmann S, et al. (2022)[9]: Objective: "To evaluate the effects of an exercise intervention on insulin sensitivity of the brain"; Study type: Clinical trial; Conclusion: "An 8-week exercise intervention in sedentary individuals can restore insulin action in the brain".
2. Mansur RB, et al. (2021)[10]: Objective: "To directly explore the potential role of neuronal insulin signaling using an innovative technique based on biomarkers derived from plasma extracellular vesicles enriched for neuronal origin"; Study type: Randomized, double-blind, placebo-controlled; Conclusion: "Brain insulin signaling is a target for further mechanistic and therapeutic investigations".
3. Nijssen KM, et al. (2024)[11]: Objective: "To investigate longer-term effects of mixed nuts on brain insulin sensitivity in older individuals with overweight/obesity" Study type: Randomized, single-blinded, controlled, crossover trial; Conclusion: "Longer-term mixed nut consumption affected insulin action in brain regions involved in the modulation of metabolic and cognitive processes in older adults with overweight/obesity".

Hypothalamic insulin resistance

4. Kullmann S, et al. (2022)[12]: Objective: "SGLT2 inhibition may be a pharmacological approach to

Figure 2. The Process of Selection.



ARTICLE Authors and Year	OBJECTIVE	STUDY TYPE	CONCLUSION
Brain Insulin Resistance			
Kullmann S, et al.[9] (2022)	Evaluate effects of exercise on brain insulin sensitivity	Clinical trial	Exercise can restore brain insulin action
Mansur RB, et al.[10] (2021)	Explore the role of neuronal insulin signaling	Randomized, double-blind, placebo-controlled	Brain insulin signaling is a potential therapeutic target
Nijssen KM, et al.[11] (2024)	Investigate long-term effects of nuts on brain insulin sensitivity	Randomized, single-blinded, controlled, crossover trial	Nut consumption affects insulin action in brain regions
Hypothalamic Insulin Resistance			
Kullmann S, et al.[12] (2022)	Evaluate the effect of SGLT2 inhibition on brain insulin resistance	Randomized, double-blind, placebo-controlled clinical trial	SGLT2 inhibition can restore hypothalamic insulin sensitivity
Pituitary Insulin Resistance			
Pascual-Corrales E, et al.[13] (2024)	Investigate the impact of pituitary surgery on glucose metabolism	National multicenter retrospective study	Pituitary surgery improves glucose metabolism and can lead to diabetes remission
Biagetti B, et al.[14] (2021)	Evaluate insulin resistance in acromegaly	Systematic review and meta-analysis	Insulin resistance is an early event in acromegaly
Kinoshita Y, et al.[15] (2011)	Identify factors involved in impaired glucose metabolism in acromegaly	Retrospective study	Insulin resistance impairs glucose metabolism in acromegaly
Thyroid Insulin Resistance			
Ferrannini E, et al.[16] (2017)	Evaluate the relationship between thyroid hormone levels and insulin resistance	Prospective study and metabolomic analysis	Thyroid hormone levels are associated with insulin resistance
Chuang TJ, et al.[17] (2021)	Evaluate the relationship between TSH and insulin resistance, glucose effectiveness, and insulin secretion	Cross-sectional study	TSH is positively related to insulin resistance, and negatively related to glucose effectiveness
Javed A, et al.[18] (2015)	Determine the relationship between TSH and insulin sensitivity, lipids, and adipokines in obese adolescents	Clinical trial	Sex-specific association between TSH and insulin sensitivity in obese adolescent males
Pulmonary Insulin Resistance			
Sagun G, et al.[19] (2015)	Determine the role of insulin resistance in lung function	Cross-sectional study	Insulin resistance contributes to decline in lung function
Bulcun E, et al.[20] (2012)	Investigate the frequency of glucose metabolism disorders and insulin resistance in sleep apnea	Cross-sectional study	Sleep apnea is associated with high frequency of glucose metabolism disorders
Huang T, et al.[21] (2022)	Examine the risk of developing sleep apnea based on insulin resistance and hyperglycemia	Prospective study	Insulin resistance may play a more important role than hyperglycemia in the pathogenesis of sleep apnea
Michalek-Zrabkowska M, et al.[22] (2021)	Assess the relationship between sleep apnea and insulin resistance	Cross-sectional study	Individuals with moderate to severe sleep apnea have a higher prevalence of insulin resistance

Myocardial Insulin Resistance			
Cook SA, et al.[23] (2010)	Determine the mechanisms of myocardial insulin resistance in non-insulin-dependent diabetes mellitus and left-ventricular dysfunction	Analytical study	Mechanisms differ between non-insulin-dependent diabetes mellitus and left-ventricular dysfunction
Iozzo P, et al.[24] (2002)	Investigate the association between type 2 diabetes and myocardial IR	Case-control study	Type 2 diabetes is associated with myocardial IR independent of coronary artery disease
Swan JW, et al.[25] (1997)	Assess insulin sensitivity in chronic heart failure (CHF) patients	Cross-sectional study	CHF is associated with marked insulin resistance
Lautamäki R, et al.[26] (2006)	Determine the manifestations of metabolic syndrome in different organs in patients with liver steatosis	Analytical study	Liver fat content is an independent indicator of myocardial insulin resistance
Liver Insulin Resistance			
Lecoultre V, et al.[27] (2014)	Assess the effect of chlorogenic acid-rich coffee on hepatic insulin resistance	Randomized, controlled, crossover trial	Coffee consumption attenuates hepatic insulin resistance
Fraenkel E, et al.[28] (2023)	Assess IGF-1 and IGFBP3 as markers of insulin resistance in prediabetes and T2DM	Observational clinical study	IGF-1 and IGFBP3 are potential markers of hepatic insulin resistance
Haus JM, et al.[29] (2010	Examine the effects of exercise/diet intervention on hepatic insulin resistance	Clinical Trial	Lifestyle interventions can reduce hepatic insulin resistance
Miyazaki Y, et al.[30] (2002)	Examine the relationship between peripheral/hepatic insulin sensitivity and fat distribution in T2DM	Clinical Trial	Visceral adiposity is associated with both peripheral and hepatic insulin resistance
Kotronen A, et al.[31] (2007)	Determine the effect of liver fat on insulin clearance and hepatic insulin sensitivity	Clinical Trial	Increased liver fat is associated with impaired insulin clearance and hepatic insulin resistance
Pancreatic insulin resistance			
Wagner R, et al.[32] (2020)	To investigate genotype × pancreatic fat interactions on insulin secretion	Observational study	The associations suggest that pancreatic steatosis only impairs beta-cell function in subjects at high genetic risk for diabetes. Genetically determined insulin resistance specifically renders pancreatic fat deleterious for insulin secretion.
Ladwa M, et al.[33] (2021)	To compare postprandial insulin secretion and the relationships between insulin secretion, insulin sensitivity and pancreatic fat in men of black West African (BA) and white European (WE) ancestry	Cross-sectional study	Ethnicity is an independent determinant of beta cell function in black and white men. In response to a meal, healthy BA men exhibit lower insulin secretion compared with their WE counterparts for their given insulin sensitivity.

Weng S, et al.[34] (2018)	To explore the prevalence of nonalcoholic fatty pancreas disease (NAFPD) in a Chinese adult population, and investigate factors associated with NAFPD aggravation	Cross-sectional study	The lipid metabolism disorder was the basis for the pathogenesis of NAFPD, and the resulting abnormal secretion of adipokines and ectopic fat deposition in other areas could interact to cause IR and glucose metabolism disorder, which resulted in T2DM.
Liang B, et al.[35] (2020)	To explore the effects of high T3 levels on β-cell line insulin resistance, as well as the roles of endoplasmic reticulum stress (ERS)	Analytical study	High T3 levels can induce insulin resistance in β-cell line by activating ERS and the apoptotic pathway.
Renal insulin resistance			
Becker B, et al.[36] (2005)	he relationship among insulin resistance, adiponectin, and cardiovascular (CV) morbidity in patients with mild and moderate kidney disease was investigated	Prospective study	In patients with chronic kidney diseases, a syndrome of insulin resistance is present even in the earliest stage of renal dysfunction, and several components of this syndrome are associated with CV events.
Landau M, et al.[37] (2011)	To assess whether the factors associated with insulin resistance (IR) were different in those with and without chronic kidney disease (CKD)	Analytical study	In Stage 3 CKD, kidney function is associated with IR; except for adiponectin, the correlates of IR are similar in those with and without CKD.
El-Aziza RA, et al.[38] (2018)	To assess spleen longitudinal diameter (SLD) in patients with metabolic syndrome (MS) and to investigate the possible factors affecting spleen size	Case-control study	Patients with MS had larger spleen size than healthy controls. SLD significantly correlated with waist circumference but not IL-10 in patients with MS.
Small intestine Insulin Resistance			
Urita Y, et al.[39] (2006)	To investigate non-invasively the incidence of absorption of carbohydrates in diabetic patients during an oral glucose tolerance test and to determine whether malabsorption may be associated with insulin secretion and insulin resistance	Cross-sectional study	Insulin resistance may be overestimated by using these markers if the patient has carbohydrate malabsorption, or that carbohydrate malabsorption may be present prior to the development of insulin resistance. Hence carbohydrate malabsorption should be taken into account for estimating insulin resistance and beta-cell function.
Angelini G, et al.[40] (2021)	To assess the role of jejunum in insulin resistance in humans and in experimental animals	Observational study	Proximal gut plays a crucial role in controlling insulin sensitivity through a distinctive metabolic signature involving hepatic gluconeogenesis and muscle insulin resistance. Bypassing the jejunum is beneficial in terms of insulin-mediated glucose disposal in obesity.

Lalande C, et al.[41] (2020)	To evaluate small intestine epithelial cell homeostasis in a cohort of men covering a wide range of adiposity and glucose homoeostasis statuses	Cross-sectional study	A decreased functional enterocyte mass and an increased enterocyte death rate in presence of metabolic alterations but emphasizes that epithelial cell homeostasis is especially altered in presence of severe insulin resistance and T2D. The marked changes in small intestine cellularity observed in obesity and diabetes are thus suggested to be part of gut dysfunctions, mainly at an advanced stage of the disease.
Large intestine insulin resistance			
Honka H, et al.[42] (2013)	To validate, using an animal model, the use of positron emission tomography (PET) in the estimation of intestinal glucose uptake (GU), and thereafter to test whether intestinal insulin-stimulated GU is altered in morbidly obese compared with healthy human participants	Clinical study	Intestinal GU can be quantified in vivo by [(18)F]FDG PET. Intestinal insulin resistance occurs in obesity before the deterioration of systemic glucose tolerance.
Gao C, et al.[43] (2022)	To investigate the effects of intestinal alkaline phosphatase (IAP) in controlled intestinal inflammation and alleviated associated insulin resistance (IR)	In vitro study	The IAP can be used as a natural anti-inflammatory agent to reduce intestinal inflammation-induced IR.
Muscle insulin resistance			
Magkos F, et al.[44] (2012)	To evaluate the relationship between the rate of release of free fatty acids (FFA) into plasma and skeletal muscle insulin sensitivity in human subjects	Clinical Trial	The data suggest that the correlation between FFA kinetics and muscle glucose metabolism is due to multiorgan insulin resistance rather than a direct effect of FFA itself on skeletal muscle insulin action and challenge the view that increased adipose tissue lipolytic rate is an important cause of insulin resistance.
Nowotny B, et al.[45] (2013)	To examine initial events occurring during the onset of insulin resistance upon oral high-fat loading compared with lipid and low-dose endotoxin infusion	Clinical Trial	The oral fat ingestion rapidly induces insulin resistance by reducing nonoxidative glucose disposal, which associates with muscle PKCθ activation and a rise in distinct myocellular membrane diacylglycerols, while endotoxin-induced insulin resistance is exclusively associated with stimulation of inflammatory pathways.
Abbasi F, et al.[46] (2000)	To evaluate the ability of insulin to regulate free fatty acid (FFA) concentrations in healthy nondiabetic subjects selected to be either insulin-resistant or -sensitive on the basis of insulin-mediated glucose disposal by muscle	Clinical Trial	The results demonstrate that the ability of insulin to regulate plasma FFA concentrations is impaired in healthy subjects with muscle insulin resistance, indicating that insulin-resistant individuals share defects in the ability of insulin to stimulate muscle glucose disposal and to inhibit adipose tissue lipolysis.

Krebs M, et al.[47] (2002)	To examine effects of short-term plasma amino acid (AA) elevation on whole-body glucose disposal and cellular insulin action in skeletal muscle	Clinical Trial	The plasma amino acid elevation induces skeletal muscle insulin resistance in humans by inhibition of glucose transport/phosphorylation, resulting in marked reduction of glycogen synthesis.
Kelley DE, et al.[48] (2001)	To examine the respective roles of plasma free fatty acids, regional adiposity, and other metabolic factors as determinants of the severity of skeletal muscle insulin resistance (IR) in type 2 diabetes mellitus (DM)	Clinical Trial	The severity of skeletal muscle IR in type 2 DM is closely related to the IR of suppressing lipolysis and that plasma fatty acids and visceral adipose tissue are key elements mediating the link between obesity and skeletal muscle IR in type 2 DM.
Adipose Tissue insulin resistance			
Halloun R, et al.[49] (2023)	To test whether adipose tissue insulin sensitivity predicts changes in the degree of obesity over time	Secondary analysis of an observational study	The adipose tissue insulin resistance is not protective from increases of the degree of obesity and skeletal muscle insulin resistance is not associated with increases of the degree of obesity.
Hazlehurst JM, et al.[50] (2013)	To determine whether glucocorticoids have tissue-specific effects on insulin sensitivity in vivo	Double-blind, randomized, placebo-controlled, crossover study	The human subcutaneous adipose insulin sensitization by glucocorticoids in vivo demonstrates tissue-specific actions of glucocorticoids to modify insulin action.
Cifarelli V, et al.[51] (2020)	To evaluate the potential influence of adipose tissue (AT) oxygenation on AT biology and insulin sensitivity in people	Clinical Trial	To reduce AT oxygenation in individuals with obesity contributes to insulin resistance by increasing plasma PAI-1 concentrations and decreasing AT branched-chain amino acid (BCAA) catabolism and thereby increasing plasma BCAA concentrations.
Jiang J, et al.[52] (2020)	To examine the association of different anatomical forms of obesity with adipose tissue insulin resistance and to assess the diagnostic value and contribution of obesity to adipose tissue insulin resistance	Cross-sectional study	Maintaining waist circumference in males and body mass index in females to a normal range could be an important strategy to significantly reduce the occurrence of adipose tissue insulin resistance and the subsequent metabolic diseases.
Ter Horst KW, et al.[53] (2017)	To validate simplified methods for the quantification of adipose tissue insulin resistance against the assessment of insulin sensitivity of lipolysis suppression during hyperinsulinemic-euglycemic clamp studies	Analytical study	sensitivity can be reliably quantified in overweight and obese humans by simplified index methods. The sensitivity and specificity of the Adipo-IR index and the fasting plasma insulin-glycerol product, combined with their simplicity and acceptable agreement, suggest that these may be most useful in clinical practice.

Wen J, et al.[54] (2020)	The degree of adipose tissue insulin resistance increases in obesity, prediabetes and type 2 diabetes, but whether it associates with prediabetes is unclear	Cross-sectional study	Adipose tissue insulin resistance is associated with prediabetes and should be considered for use in population studies.
Zhou Q, et al.[55] (2024)	To examine the association between adipose tissue-specific insulin resistance and atherosclerotic burden and plaques in intracranial, extracranial, and coronary arteries in community residents without diabetes	Clinical Trial	Adipose tissue-specific insulin resistance is associated with atherosclerotic burden and plaques in intracranial and coronary arteries in Chinese community nondiabetic residents.
Vascular insulin resistance			
Feldman RD, et al.[56] (1996)	To determine whether dietary salt restriction might affect vascular sensitivity to insulin	Prospective study	In these younger normotensive and hypertensive subjects, dietary salt restriction increases resistance to the vasodilating effects of insulin.
Wang N, et al.[57] (2020)	To examine whether GLP-1 recruits microvasculature and improves the action of insulin in obese humans	Clinical Trial	In obese humans with microvascular insulin resistance, GLP-1's vasodilatory actions are preserved in both skeletal and cardiac muscle microvasculature, which may contribute to improving metabolic insulin responses and cardiovascular outcomes.
Vinet A, et al.[58] (2015_	To assess the insulin vasoreactivity in metabolic syndrome (MetS), and to evaluate the effects of a lifestyle program	Case-control study	The local vasodilatory effects to insulin and its overall flow motion are impaired in MetS subjects in relation to inflammation. The lifestyle intervention reversed this insulin-induced vascular dysfunction in parallel to decreased inflammation level.
Love KM, et al.[59] (2024)	To elucidate the impact of elevated free fatty acids (FFAs) on insulin action across the arterial tree and define the relationship among insulin actions in the different arterial segments	Randomized crossover study	Clinically relevant elevation of plasma FFA concentrations induces pan-arterial insulin resistance, the vascular insulin resistance outcomes are interconnected, and insulin-mediated muscle microvascular perfusion associates with cardiovascular disease predictors. Our data provide biologic plausibility whereby a causative relationship between FFAs and cardiovascular disease could exist, and suggest that further attention to interventions that block FFA-mediated vascular insulin resistance may be warranted.

Ovarian insulin resistance			
Wu XK, et al.[60] (2003)	Insulin resistance is a common feature of both polycystic ovary syndrome (PCOS) and non-insulin-dependent diabetes mellitus (NIDDM); however, the persistent reproductive disturbances appear to be limited to the former, suggesting that insulin resistance in the ovary itself may confer this susceptibility	Prospective study	There is a selective defect in insulin actions in PCOS granulosa cells, which suggests ovarian insulin resistance, and this metabolic phenotype is associated with an enhanced IGF-1 mitogenic potential. Troglitazone could divergently alter expression of various IRS molecules and insulin actions and could be used as an ovarian insulin sensitizer and mitogen/steroidogenic inhibitor in PCOS.
Testicular insulin resistance			
Contreras PH, et al.[61] (2018)	To evaluate insulin sensitivity and testicular function in a cohort of adult males suspected of being insulin-resistant	Prospective study	Waist Circumference predicted both insulin resistance (>99 cm) and hypogonadism (>110 cm), suggesting that the first hit of abdominal obesity is insulin resistance and the second hit is male hypogonadism. Normal weight did not protect from insulin resistance, while a relevant proportion of obese subjects were non-insulin resistant.
Verit A, et al.[62] (2014)	To investigate the possible effect of insulin resistance (IR) on male reproductive system via evaluation of semen analysis, male sex hormones and serum lipid profiles, and testicular volumes	Prospective study	IR may be accused of causing detrimental effect on male infertility due to hyperinsulinemic state and being one of the components for MetS. Interestingly, due to our preliminary results, we do not found any inverse correlation between IR and male reproductive functions.

reverse brain insulin resistance?"; Study type: Randomized, double-blind, placebo-controlled clinical trial; Conclusion: "The results corroborate insulin resistance of the hypothalamus in humans with prediabetes. Treatment with empagliflozin for 8 weeks was able to restore hypothalamic insulin sensitivity, a favorable response that could contribute to the beneficial effects of SGLT2 inhibitors".

Pituitary insulin resistance

5. Pascual-Corrales E, et al. (2024)[13]: Objective: "To investigate the impact of pituitary surgery on glucose metabolism and to identify predictors of remission of diabetes after pituitary surgery in patients with acromegaly"; Study type: National multicenter retrospective study of patients with acromegaly undergoing transsphenoidal surgery; Conclusion: "Glucose metabolism improved in patients with acromegaly after surgery and 21% of the diabetic patients experienced diabetes remission".
6. Biagetti B, et al. (2021)[14]; Objective: "To exam whether the Homeostatic Model Assessment of Insulin Resistance is higher in Caucasian, adult, treatment-naïve patients with acromegaly than in the reference population independently of diabetes presence and to evaluate the impact of treatment on its assessment"; Study type: Systematic review and meta-analysis; Conclusion: "The study confirms that insulin resistance is an early event in acromegaly".
7. Kinoshita Y, et al. (2011)[15]; Objective: "To identify factors involved in the impairment of glucose metabolism in acromegaly, we evaluated clinical parameters before and immediately after surgical cure of the disease"; Study type: Retrospective study; Conclusion: "Insulin resistance impairs glucose metabolism in acromegaly".

Thyroid insulin resistance

8. Ferrannini E, et al. (2017)[16]; Objective: "To evaluate the relationship between thyroid hormone levels

within the normal range and insulin resistance"; Study type: Prospective study and metabolomic analysis; Conclusion: "We demonstrate that serum fT3 concentrations within the euthyroid range are independently associated with insulin resistance both cross-sectionally and longitudinally. This association is supported by a metabolite pattern that points at increased oxidative stress as part of the insulin resistance syndrome".

9. Chuang TJ, et al. (2021)[17]; Objective: "To evaluate the relationships between thyroid-stimulating hormone (TSH) and Increased insulin resistance (IR); decreased glucose effectiveness (GE); and both first-and second phase of insulin secretion (FPIS, SPIS) in adult Chinese"; Study type: Cross-sectional study; Conclusion: "The data showed that IR, FPIS, and SPIS were positively related to the TSH level in middle-aged Chinese, whereas GE was negatively related. In both genders, IR had the tightest association followed by GE, FPIS, and SPIS".
10. Javed A, et al. (2015)[18]; Objective: "To determine the relationship between TSH concentrations and insulin sensitivity, lipids, and adipokines in euthyroid, non-diabetic, obese adolescents"; Study type: Clinical Trial; Conclusion: "Study suggests a sex-specific association between TSH and insulin sensitivity in euthyroid, non-diabetic, obese adolescent males".

Pulmonary Insulin Resistance

11. Sagun G, et al. (2015)[19]; Objective: "To determine if insulin resistance plays a detrimental role in lung function in outpatients admitted to internal medicine clinics in adults from Turkey"; Study type: Cross sectional study; Conclusion: "Insulin resistance should also be considered amongst the contributing factors for decline in lung function".
12. Bulcun E, et al. (2012)[20]; Objective: "To investigate the frequency of disorders of glucose metabolism (DGM) and Insulin resistance in patients with obstructive sleep apnea syndrome and determining factors for these disorders"; Study type: Cross sectional study; Conclusion: "Obstructive sleep apnea syndrome is associated with high frequency of DGM".
13. Huang T, et al. (2022)[21]; Objective: "To examine the risk of developing obstructive sleep apnea (OSA) according to baseline concentrations of fasting insulin and hemoglobin A1c"; Study type: Prospective study; Conclusion: "Independent of obesity, insulin resistance may play a more important role than hyperglycemia in the pathogenesis of OSA".
14. Michalek-Zrabkowska M, et al. (2021)[22]; Objective: "The aim of this research was to assess the relationship between prevalence and severity of obstructive sleep apnea (OSA) and insulin resistance among patients with increased risk of OSA without diabetes mellitus"; Study type: Cross sectional study; Conclusion: "Individuals with moderate to severe OSA without diabetes mellitus had a higher prevalence of insulin resistance".

Myocardial insulin resistance

15. Cook SA, et al. (2010)[23]; Objective: "Whole body and myocardial insulin resistance are features of non-insulin-dependent diabetes mellitus (NIDDM) and left-ventricular dysfunction (LVD). We determined whether abnormalities of insulin receptor substrate-1 (IRS1), IRS1-associated PI3K (IRS1-PI3K), and glucose transporter 4 contribute to tissue-specific insulin resistance"; Study type: Analytical study; Conclusion: "The mechanisms of myocardial insulin resistance are different between NIDDM and LVD".
16. Iozzo P, et al. (2002)[24]; Objective: "To investigate whether type 2 diabetes is associated with myocardial IR independent of coronary artery disease (CAD)"; Study type: Case-control study; Conclusion: "Type 2 diabetes is specifically associated with myocardial insulin resistance (IR) that is independent of and nonadditive with angiographic CAD and proportional to skeletal muscle and whole-body IR".
17. Swan JW, et al. (1997)[25]; Objective: "To assess insulin sensitivity in patients with chronic heart failure (CHF) and its relation to disease severity"; Study type: Cross sectional study; Conclusion: "CHF is associated with marked insulin resistance, characterized by both fasting and stimulated hyperinsulinemia. Advanced heart failure is related to increased insulin resistance, but this is not directly mediated through ventricular dysfunction or increased catecholamine levels".
18. Lautamäki R, et al. (2006)[26]; Objective: "To determine the manifestations of metabolic syndrome in different organs in patients with liver steatosis"; Study type: Analytical study; Conclusion: "In patients with type 2 diabetes and coronary artery disease, liver fat content is a novel independent indicator of myocardial insulin resistance and reduced coronary functional capacity".

Liver insulin resistance

19. Lecoultre V, et al. (2014)[27]; Objective: "To assess whether the consumption of chlorogenic acid-rich coffee attenuates the effects of short-term fructose overfeeding, dietary conditions known to increase intrahepatocellular lipids (IHCLs), and blood triglyceride concentrations and to decrease hepatic insulin sensitivity in healthy humans"; Study type: Randomized, controlled, crossover trial; Conclusion: "Coffee consumption attenuates hepatic insulin resistance but not the increase of IHCLs induced by fructose overfeeding. This effect does not appear to be mediated by differences in the caffeine or chlorogenic acid content".
20. Fraenkel E, et al. (2023)[28]; Objective: "To assess insulin-like growth factor 1 (IGF-1) and IGF-binding protein 3 (IGFBP3) as markers of insulin resistance in patients with prediabetes and type 2 diabetes mellitus"; Study type: Observational clinical study; Conclusion: "The results demonstrate a fundamental role of IGF-1 and IGFBP3 in the patho-physiology of hepatic insulin resistance and suggest them as indirect indicators of the hepatic insulin resistance".
21. Haus JM, et al. (2010)[29]; Objective: "To examine the effects of an exercise/diet lifestyle intervention on free fatty acid (FFA)-induced hepatic insulin resistance in obese humans"; Study type: Clinical Trial; Conclusion: "Both lifestyle interventions are effective in reducing hepatic insulin resistance under basal and hyperinsulinemic conditions. However, the reversal of FFA-induced hepatic insulin resistance is best achieved with a combined exercise/caloric-restriction intervention".
22. Miyazaki Y, et al. (2002)[30]; Objective: "To examine the relationship between peripheral/hepatic insulin sensitivity and abdominal superficial/deep subcutaneous fat and intra-abdominal visceral fat in patients with type 2 diabetes mellitus (T2DM)"; Study type: Clinical Trial; Conclusion: "The visceral adiposity is associated with both peripheral and hepatic insulin resistance, independent of gender, in T2DM. In male but not female T2DM, deep subcutaneous adipose tissue also is associated with peripheral and hepatic insulin resistance".
23. Kotronen A, et al. (2007)[31]; Objective: "To determine the effect of liver fat on insulin clearance and hepatic insulin sensitivity"; Study type: Clinical Trial; Conclusion: "The increase liver fat is associated with both impaired insulin clearance and hepatic insulin resistance. Hepatic insulin sensitivity associates with liver fat content, independent of insulin clearance".

Pancreatic insulin resistance

24. Wagner R, et al. (2020)[32]; Objective: "To investigate genotype × pancreatic fat interactions on insulin secretion" Study type: Observational study; Conclusion: "The associations suggest that pancreatic steatosis only impairs beta-cell function in subjects at high genetic risk for diabetes. Genetically determined insulin resistance specifically renders pancreatic fat deleterious for insulin secretion".
25. Ladwa M, et al. (2021)[33]; Objective: "To compare postprandial insulin secretion and the relationships between insulin secretion, insulin sensitivity and pancreatic fat in men of black West African (BA) and white European (WE) ancestry"; Study type: Cross-sectional study; Conclusion: "Ethnicity is an independent determinant of beta cell function in black and white men. In response to a meal, healthy BA men exhibit lower insulin secretion compared with their WE counterparts for their given insulin sensitivity".
26. Weng S, et al. (2018)[34]; Objective: "To explore the prevalence of nonalcoholic fatty pancreas disease (NAFPD) in a Chinese adult population, and investigate factors associated with NAFPD aggravation"; Study type: Cross-sectional study; Conclusion: "The lipid metabolism disorder was the basis for the pathogenesis of NAFPD, and the resulting abnormal secretion of adipokines and ectopic fat deposition in other areas could interact to cause IR and glucose metabolism disorder, which resulted in T2DM".
27. Liang B, et al. (2020)[35]; Objective: "To explore the effects of high T3 levels on β-cell line insulin resistance, as well as the roles of endoplasmic reticulum stress (ERS)"; Study type: Analytical study; Conclusion: "High T3 levels can induce insulin resistance in β-cell line by activating ERS and the apoptotic pathway".

Renal insulin resistance

28. Becker B, et al. (2005)[36]; Objective: "The relationship among insulin resistance, adiponectin, and cardiovascular (CV) morbidity in patients with mild and moderate kidney disease was investigated"; Study type: Prospective study; Conclusion: "In patients with chronic kidney diseases, a syndrome of insulin resistance is present even in the earliest stage of renal dysfunction, and several components of this syndrome are associated with CV events".

29. Landau M, et al. (2011)[37]; Objective: "To assess whether the factors associated with insulin resistance (IR) were different in those with and without chronic kidney disease (CKD)"; Study type: Analytical study; Conclusion: "In Stage 3 CKD, kidney function is associated with IR; except for adiponectin, the correlates of IR are similar in those with and without CKD".

Spleen insulin resistance

30. El-Aziza RA, et al. (2018)[38]; Objective: "To assess spleen longitudinal diameter (SLD) in patients with metabolic syndrome (MS) and to investigate the possible factors affecting spleen size"; Study type: Case-control study; Conclusion: "Patients with MS had larger spleen size than healthy controls. SLD significantly correlated with waist circumference but not IL-10 in patients with MS".

Small intestine Insulin Resistance

31. Urita Y, et al. (2006)[39]; Objective: "To investigate non-invasively the incidence of absorption of carbohydrates in diabetic patients during an oral glucose tolerance test and to determine whether malabsorption may be associated with insulin secretion and insulin resistance"; Study type: Cross-sectional study; Conclusion: "Insulin resistance may be overestimated by using these markers if the patient has carbohydrate malabsorption, or that carbohydrate malabsorption may be present prior to the development of insulin resistance. Hence carbohydrate malabsorption should be taken into account for estimating insulin resistance and beta-cell function".
32. Angelini G, et al. (2021)[40]; Objective: "To assess the role of jejunum in insulin resistance in humans and in experimental animals"; Study type: Observational study; Conclusion: "Proximal gut plays a crucial role in controlling insulin sensitivity through a distinctive metabolic signature involving hepatic gluconeogenesis and muscle insulin resistance. Bypassing the jejunum is beneficial in terms of insulin-mediated glucose disposal in obesity".
33. Lalande C, et al. (2020)[41]; Objective: "To evaluate small intestine epithelial cell homeostasis in a cohort of men covering a wide range of adiposity and glucose homoeostasis statuses"; Study type: Cross-sectional study; Conclusion: "A decreased functional enterocyte mass and an increased enterocyte death rate in presence of metabolic alterations but emphasizes that epithelial cell homeostasis is especially altered in presence of severe insulin resistance and T2D. The marked changes in small intestine cellularity observed in obesity and diabetes are thus suggested to be part of gut dysfunctions, mainly at an advanced stage of the disease".

Large intestine insulin resistance

34. Honka H, et al. (2013)[42]; Objective: "to validate, using an animal model, the use of positron emission tomography (PET) in the estimation of intestinal glucose uptake (GU), and thereafter to test whether intestinal insulin-stimulated GU is altered in morbidly obese compared with healthy human participants"; Study type: Clinical study; Conclusion: "Intestinal GU can be quantified in vivo by [(18)F]FDG PET. Intestinal insulin resistance occurs in obesity before the deterioration of systemic glucose tolerance".
35. Gao C, et al. (2022)[43]; Objective: "To investigate the effects of intestinal alkaline phosphatase (IAP) in controlled intestinal inflammation and alleviated associated insulin resistance (IR)"; Study type: In vitro study; Conclusion: "The IAP can be used as a natural anti-inflammatory agent to reduce intestinal inflammation-induced IR".

Muscle insulin resistance

36. F, et al. (2012)[44]; Objective: "To evaluate the relationship between the rate of release of free fatty acids (FFA) into plasma and skeletal muscle insulin sensitivity in human subjects"; Study type: Clinical Trial; Conclusion: "The data suggest that the correlation between FFA kinetics and muscle glucose metabolism is due to multiorgan insulin resistance rather than a direct effect of FFA itself on skeletal muscle insulin action and challenge the view that increased adipose tissue lipolytic rate is an important cause of insulin resistance".
37. Nowotny B, et al. (2013)[45]; Objective: "To examine initial events occurring during the onset of insulin resistance upon oral high-fat loading compared with lipid and low-dose endotoxin infusion"; Study type: Clinical Trial; Conclusion: "The oral fat ingestion rapidly induces insulin resistance by reducing nonoxidative glucose disposal, which associates with muscle PKCθ activation and a rise in distinct myocellular membrane diacylglycerols, while endotoxin-induced insulin resistance is exclusively associated with stimulation of inflammatory pathways".
38. Abbasi F, et al. (2000)[46]; Objective: "To evaluate the ability of insulin to regulate free fatty acid (FFA)

concentrations in healthy nondiabetic subjects selected to be either insulin-resistant or -sensitive on the basis of insulin-mediated glucose disposal by muscle"; Study type: Clinical Trial; Conclusion: "The results demonstrate that the ability of insulin to regulate plasma FFA concentrations is impaired in healthy subjects with muscle insulin resistance, indicating that insulin-resistant individuals share defects in the ability of insulin to stimulate muscle glucose disposal and to inhibit adipose tissue lipolysis".

39. Krebs M, et al. (2002)[47]; Objective: "To examine effects of short-term plasma amino acid (AA) elevation on whole-body glucose disposal and cellular insulin action in skeletal muscle"; Study type: Clinical Trial; Conclusion: "The plasma amino acid elevation induces skeletal muscle insulin resistance in humans by inhibition of glucose transport/phosphorylation, resulting in marked reduction of glycogen synthesis".
40. Kelley DE, et al. (2001)[48]; Objective: "To examine the respective roles of plasma free fatty acids, regional adiposity, and other metabolic factors as determinants of the severity of skeletal muscle insulin resistance (IR) in type 2 diabetes mellitus (DM)"; Study type: Clinical Trial; Conclusion: "The severity of skeletal muscle IR in type 2 DM is closely related to the IR of suppressing lipolysis and that plasma fatty acids and visceral adipose tissue are key elements mediating the link between obesity and skeletal muscle IR in type 2 DM".

Adipose Tissue insulin resistance

41. Halloun R, et al. (2023)[49]; Objective: "To teste whether adipose tissue insulin sensitivity predicts changes in the degree of obesity over time" Study type: Secondary analysis of an observational study; Conclusion: "The adipose tissue insulin resistance is not protective from increases of the degree of obesity and skeletal muscle insulin resistance is not associated with increases of the degree of obesity".
42. Hazlehurst JM, et al. (2013)[50]; Objective: "To determine whether glucocorticoids have tissue-specific effects on insulin sensitivity in vivo"; Study type: Double-blind, randomized, placebo-controlled, crossover study; Conclusion: "The human subcutaneous adipose insulin sensitization by glucocorticoids in vivo demonstrates tissue-specific actions of glucocorticoids to modify insulin action".
43. Cifarelli V, et al. (2020)[51]; Objective: "To evaluate the potential influence of adipose tissue (AT) oxygenation on AT biology and insulin sensitivity in people"; Study type: Clinical Trial; Conclusion: "To reduce AT oxygenation in individuals with obesity contributes to insulin resistance by increasing plasma PAI-1 concentrations and decreasing AT branched-chain amino acid (BCAA) catabolism and thereby increasing plasma BCAA concentrations".
44. Jiang J, et al. (2020)[52]; Objective: "To examine the association of different anatomical forms of obesity with adipose tissue insulin resistance and to assess the diagnostic value and contribution of obesity to adipose tissue insulin resistance"; Study type: Cross-sectional study; Conclusion: "Maintaining waist circumference in males and body mass index in females to a normal range could be an important strategy to significantly reduce the occurrence of adipose tissue insulin resistance and the subsequent metabolic diseases".
45. Ter Horst KW, et al. (2017)[53]; Objective: "To validate simplified methods for the quantification of adipose tissue insulin resistance against the assessment of insulin sensitivity of lipolysis suppression during hyperinsulinemic-euglycemic clamp studies"; Study type: Analytical study; Conclusion: "Adipose tissue insulin sensitivity can be reliably quantified in overweight and obese humans by simplified index methods. The sensitivity and specificity of the Adipo-IR index and the fasting plasma insulin-glycerol product, combined with their simplicity and acceptable agreement, suggest that these may be most useful in clinical practice".
46. Wen J, et al. (2020)[54]; Objective: "The degree of adipose tissue insulin resistance increases in obesity, prediabetes and type 2 diabetes, but whether it associates with prediabetes is unclear"; Study type: Cross-sectional study; Conclusion: "Adipose tissue insulin resistance is associated with prediabetes and should be considered for use in population studies".
47. Zhou Q, et al. (2024)[55]; Objective: "To examine the association between adipose tissue-specific insulin resistance and atherosclerotic burden and plaques in intracranial, extracranial, and coronary arteries in community residents without diabetes"; Study type: Clinical Trial; Conclusion: "Adipose tissue-specific insulin resistance is associated with atherosclerotic burden and plaques in intracranial and coronary arteries in Chinese community nondiabetic residents".

Vascular insulin resistance

48. Feldman RD, et al. (1996)[56]; Objective: "To determine whether dietary salt might affect vascular

sensitivity to insulin"; Study type: Prospective study; Conclusion: "In these younger normotensive and hypertensive subjects, dietary salt restriction increases resistance to the vasodilating effects of insulin".

49. Wang N, et al. (2020)[57]; Objective: "To examine whether GLP-1 recruits microvasculature and improves the action of insulin in obese humans"; Study type: Clinical Trial; Conclusion: "In obese humans with microvascular insulin resistance, GLP-1's vasodilatory actions are preserved in both skeletal and cardiac muscle microvasculature, which may contribute to improving metabolic insulin responses and cardiovascular restriction outcomes".
50. Vinet A, et al. (2015)[58]; Objective: "To assess the insulin vasoreactivity in metabolic syndrome (MetS), and to evaluate the effects of a lifestyle program"; Study type: Case-control study; Conclusion: "The local vasodilatory effects to insulin and its overall flow motion are impaired in MetS subjects in relation to inflammation. The lifestyle intervention reversed this insulin-induced vascular dysfunction in parallel to decreased inflammation level".
51. Love KM, et al. (2024)[59]; Objective: "To elucidate the impact of elevated free fatty acids (FFAs) on insulin action across the arterial tree and define the relationship among insulin actions in the different arterial segments"; Study type: Randomized crossover study; Conclusion: "Clinically relevant elevation of plasma FFA concentrations induces pan-arterial insulin resistance, the vascular insulin resistance outcomes are interconnected, and insulin-mediated muscle microvascular perfusion associates with cardiovascular disease predictors. Our data provide biologic plausibility whereby a causative relationship between FFAs and cardiovascular disease could exist, and suggest that further attention to interventions that block FFA-mediated vascular insulin resistance may be warranted".

Ovarian insulin resistance

52. Wu XK, et al. (2003)[60]; Objective: "Insulin resistance is a common feature of both polycystic ovary syndrome (PCOS) and non-insulin-dependent diabetes mellitus (NIDDM); however, the persistent reproductive disturbances appear to be limited to the former, suggesting that insulin resistance in the ovary itself may confer this susceptibility" Study type: Prospective study; Conclusion: "There is a selective defect in insulin actions in PCOS granulosa cells, which suggests ovarian insulin resistance, and this metabolic phenotype is associated with an enhanced IGF-1 mitogenic potential. Troglitazone could divergently alter expression of various IRS molecules and insulin actions and could be used as an ovarian insulin sensitizer and mitogen/steroidogenic inhibitor in PCOS".

Testicular insulin resistance

53. Contreras PH, et al. (2018)[61]; Objective: "To evaluate insulin sensitivity and testicular function in a cohort of adult males suspected of being insulin-resistant"; Study type: Prospective study; Conclusion: "Waist Circumference predicted both insulin resistance (>99 cm) and hypogonadism (>110 cm), suggesting that the first hit of abdominal obesity is insulin resistance and the second hit is male hypogonadism. Normal weight did not protect from insulin resistance, while a relevant proportion of obese subjects were non-insulin resistant".
54. Verit A, et al. (2014)[62]; Objective: "To investigate the possible effect of insulin resistance (IR) on male reproductive system via evaluation of semen analysis, male sex hormones and serum lipid profiles, and testicular volumes"; Study type: Prospective study; Conclusion: "IR may be accused of causing detrimental effect on male infertility due to hyperinsulinemic state and being one of the components for MetS. Interestingly, due to our preliminary results, we do not found any inverse correlation between IR and male reproductive functions".

DISCUSSION

Given the novelty of the term "In-Situ Diabetes Mellitus" and the proposed "Type 6 Diabetes Mellitus," it was imperative to ensure that the objectives of our study aligned with the existing body of diabetes research, clinical practices, and potential implications. Our concept of T6DM refers to the localized development of IR in specific organs, such as the brain, hypothalamus, pituitary gland, thyroid, lung, heart, liver, pancreas, kidneys, spleen, small intestine, large intestine, muscle, adipose tissue, vessels, ovaries, and testicles, independent of the systemic insulin sensitivity. We evaluated organ- and system-specific IR, which was characterized as T6DM. The scoping review presented in this study provides an overview of the existing literature on organ-specific IR, a condition characterized by the development of IR in individual organs indepen-

dent of systemic metabolic disturbances. Our results highlight the complex nature of this condition, involving a wide range of tissues and organs.

IR manifests through various mechanisms that differ across tissues, yet several critical signaling pathways are frequently impaired. These impairments often involve a reduction in the activity of insulin receptor tyrosine kinases, changes in the phosphorylation of IRS, and the dysregulation of downstream signaling components, including phosphatidylinositol 3-kinase (PI3K), and protein kinase B (Akt). Additionally, chronic inflammation may worsen IR by activating inflammatory signaling pathways, particularly those associated with tumor necrosis factor alpha (TNF-α) and nuclear factor-κB. In this regard, each organ or tissue can be considered a potential locus of IR, with the degree of severity and the specific molecular mechanisms influenced by factors such as genetic predisposition, environmental conditions, and the presence of comorbidities[8].

Recent studies have delved into the relationship between exercise, diet, and brain-IR. Kullmann et al.[9] demonstrated that a modest 8-week exercise program can effectively restore brain insulin action in sedentary individuals. Mansur et al.[10] employed innovative techniques to explore the direct role of neuronal insulin signaling, highlighting its potential as a therapeutic target. Nijssen et al.[11] investigated the long-term impact of nut consumption on brain-IR in older adults with overweight/obesity, revealing positive effects on brain regions involved in metabolic and cognitive processes. These findings collectively underscore the importance of lifestyle interventions and dietary choices in maintaining optimal brain health and function. The brain once thought to be insulin-impervious, has been shown to possess insulin receptors and utilize insulin signaling for neuronal function[63]. Based on the evidence presented in our review, it is evident that brain-IR closely aligns with the pathophysiological characteristics of T2DM, suggesting a potential analogy to "brain in- situ diabetes mellitus."

Studies have explored the potential of SGLT2 inhibitors in addressing hypothalamic-IR. Kullmann et al.[12] investigated the effects of empagliflozin on hypothalamic-IR in individuals with prediabetes. Their randomized, double-blind, placebo-controlled trial demonstrated that 8-week treatment with empagliflozin successfully restored hypothalamic insulin sensitivity. The pathogenesis of hypothalamic-IR involves complex mechanisms, including chronic inflammation, nutrient overload, and endoplasmic reticulum stress[64]. Thus, our review suggests that this condition would imply that the hypothalamus itself would be experiencing a form similar to T2DM, characterized by impaired glucose uptake and utilization.

Studies have been conducted on the impact of pituitary dysfunction on glucose metabolism and insulin sensitivity. In our review, we found three studies that met the inclusion criteria: Pascual-Corrales et al.[13] demonstrated that pituitary surgery in patients with acromegaly could improve glucose metabolism and lead to diabetes remission, Biagetti et al.[14] confirmed that IR is an early feature of acromegaly, independent of the diabetes status, and Kinoshita et al.[15] further elucidated the role of IR in impairing glucose metabolism in acromegaly patients, highlighting the importance of addressing pituitary dysfunction to improve metabolic control. Mechanisms concerning to pituitary IR include inflammation, oxidative stress, and dysregulation of insulin signaling pathways[65], but the diagnosis remains challenging and often relies on a combination of clinical evaluation, biochemical tests, and imaging studies. Thus, the phenomenon of pituitary-IR, which could be conceptualized as "pituitary in-situ diabetes mellitus", represents a substantial research frontier within the field of endocrinology.

It has been investigated the association between thyroid hormone levels and IR. Ferrannini et al.[16] demonstrated a positive association between serum free T3 levels and IR. Chuang et al.[17] found that elevated TSH levels were associated with increased IR, impaired glucose effectiveness, and reduced insulin secretion in middle-aged Chinese individuals. Javed et al.[18] reported a sex-specific association between TSH levels and IR in obese adolescents, suggesting potential sex differences in the effect of thyroid hormones on insulin metabolism. These results highlight the interplay between thyroid function and IR, and emphasize the importance of maintaining optimal thyroid hormone levels for metabolic health. Thyroid dysfunction and IR are closely linked, with each condition potentially exacerbating the others. Thyroid hormones influence glucose metabolism by regulating glucose transporters and key metabolic enzymes[66]. These findings highlight the importance of comprehensive assessment and management of thyroid function in individuals with IR, particularly those with obesity and thyroid nodules.

We selected four studies that correlated the association between IR and lung function. Sagun et al.[19] found that IR contributes to lung function decline, Bulcun et al.[20] identified a high frequency of glucose metabolism disorders, including IR, in patients with obstructive sleep apnea syndrome (OSA), Huang et al.[21] revealed that IR, independent of obesity, is a

major risk factor for the development of OSA, and Michalek-Zrabkowska et al.[22] confirmed that individuals with moderate to severe OSA have a higher prevalence of IR. Pulmonary-IR has emerged as a critical focus in respiratory research. The presence of insulin receptors in the lungs indicates a direct influence of insulin on pulmonary function, although the underlying mechanisms of pulmonary-IR remain elusive. Chronic inflammation and oxidative stress are key factors in the pathogenesis of pulmonary-IR, interfering with insulin signaling pathways[67]. The identification of insulin receptors in pulmonary tissue has revealed a link between metabolic health and respiratory function[68]. Thus, the evidence presented underscores the relationship between IR and pulmonary function. The identification of insulin receptors in the lungs, coupled with the elucidation of mechanisms such as inflammation and oxidative stress, establishes IR as a significant contributor to pulmonary dysfunction.

Myocardial-IR is a significant factor in the development of cardiovascular complications. Cook et al.[23] demonstrated distinct mechanisms of myocardial-IR between T2DM and left ventricular dysfunction, Iozzo et al.[24] established a strong association between T2DM and myocardial-IR, independent of coronary artery disease, Swan et al.[25] highlighted the association between chronic heart failure and insulin resistance, emphasizing its role in disease progression, and Lautamäki et al.[26] identified liver fat content as a novel independent indicator of myocardial-IR in patients with T2DM and coronary artery disease. Myocardial-IR is a condition that contributes to cardiac dysfunction. While often associated with systemic IR, myocardial-IR can develop independently[69]. The heart is a responsive tissue to insulin action, and studies have consistently demonstrated a high prevalence of myocardial-IR in heart failure patients, even in those with well-controlled diabetes[70]. Although frequently associated with systemic IR, myocardial-IR can develop independently and contribute to the pathogenesis of various cardiovascular diseases. While the heart is a highly insulin-sensitive tissue, the mechanisms underlying myocardial-IR vary and involve alterations in multiple signaling pathways.

This review investigated the factors that contribute to hepatic IR. The studies of: Lecoultre et al.[27] demonstrated that coffee consumption can attenuate hepatic insulin resistance induced by fructose overfeeding, Fraenkel et al.[28] highlighted the role of IGF-1 and IGFBP-3 as potential markers of hepatic-IR, Haus et al.[29] showed that lifestyle interventions, including exercise and calorie restriction, can effectively reduce hepatic-IR, Miyazaki et al.[30], and Kotronen et al.[31] identified a strong association between visceral adiposity and liver fat content with impaired hepatic insulin sensitivity, underscoring the importance of addressing these factors in the management of metabolic disorders. Hepatic-IR is a complex metabolic disorder that leads to increased hepatic glucose production and reduced glucose uptake, thereby contributing to hyperglycemia and dyslipidemia. The consequences of hepatic-IR extend beyond the liver, affecting systemic glucose regulation and lipid metabolism[71]. Therefore, hepatic-IR emerges as a complex pathophysiological process that is central to the development of T2DM and associated metabolic disturbances.

Pancreatic-IR is a complex metabolic disorder that contributes to impaired insulin secretion and the development of T2DM. Wagner et al.[32] demonstrated that pancreatic steatosis can impair β-cell function, particularly in individuals with a genetic predisposition to diabetes; Ladwa et al.[33] highlighted ethnic differences in β-cell function, with Black West African men exhibiting lower insulin secretion compared to White European men; Weng et al.[34] and Liang et al.[35] emphasized the role of lipid metabolism disorders, adipokine dysregulation, and endoplasmic reticulum stress in the pathogenesis of pancreatic insulin resistance and the subsequent development of T2DM. Genetic factors, hormonal imbalances, and chronic inflammation contribute to the pathogenesis of pancreatic-IR[72]. The interplay between peripheral and pancreatic-IR exacerbates the metabolic dysfunction associated with T2DM. The clinical consequences of pancreatic-IR are indispensable for the development of efficacious therapeutic interventions.

Renal-IR is a complex metabolic disorder that contributes to the progression of chronic kidney disease (CKD). Becker et al.[36] demonstrated the presence of IR in patients with early-stage CKD, highlighting its association with cardiovascular events. Landau et al.[37] further investigated the factors associated with renal-IR in patients with CKD and identified kidney function as a key determinant. Renal-IR is a complex metabolic disorder that contributes to the development of diabetic nephropathy and other kidney-related complications. Renal-IR can lead to increased renal glucose production and impaired glucose reabsorption, exacerbating hyperglycemia. The mechanisms underlying renal-IR involve multiple factors, including oxidative stress, inflammation, and dysregulation of key signaling pathways such as the PI3K/Akt pathway. The renin-angiotensin-aldosterone and sympathetic nervous systems also play significant roles in the development and progression of renal IR[73]. Although substantial progress

has been achieved in unraveling the complexities of the existence of selective IR in the kidney, numerous questions remain unanswered.

El-Aziza et al.[38] investigated the association between metabolic syndrome (MS) and spleen size. The study found that patients with MS had significantly larger spleen sizes compared to healthy controls. While spleen size correlated with waist circumference, it did not correlate with IL-10 levels in MS patients. These findings suggest a potential link between metabolic dysfunction and splenomegaly in individuals with MS. The spleen plays a fundamental role in the development of IR by regulating monocyte trafficking and differentiation into inflammatory macrophages. Splenectomy has been shown to protect against IR, particularly in obese individuals, by limiting the availability of inflammatory monocytes[74]. Excessive caloric intake induces inflammatory signaling and endoplasmic reticulum stress, leading to IR in various tissues, including the hypothalamus, muscle, and liver. The spleen, as a reservoir of monocytes, contributes to the worsening of IR by releasing inflammatory macrophages into adipose tissue[75]. The complex between physiological and pathological factors in spleen-IR underscores the spleen's important function in maintaining systemic glucose balance.

The small intestine plays an important role in glucose metabolism and insulin sensitivity. Urita et al.[39] demonstrated that carbohydrate malabsorption can impact insulin resistance and beta-cell function, Angelini et al.[40] highlighted the importance of the jejunum in regulating insulin sensitivity, suggesting that bypassing the jejunum can improve insulin-mediated glucose disposal, and Lalande et al.[41] revealed alterations in small intestinal epithelial cell homeostasis in individuals with obesity and T2DM, suggesting a link between gut dysfunction and metabolic disorders. The small intestine by secreting incretin hormones like GLP-1 and GIP, which stimulate insulin secretion and enhance glucose uptake in peripheral tissues[76]. While the small intestine's primary function is nutrient absorption, it may also contribute to the development of IR. Imbalances in GLP-1 and GIP signaling can lead to persistently elevated blood glucose levels and the onset of IR[77]. Investigating the mechanisms implicit in the small intestine-IR represents a analytical step towards effectively managing metabolic disorders and improving overall health outcomes.

The gut microbiome participates in regulating systemic metabolism, including insulin sensitivity. Honka et al.[42] demonstrated that intestinal IR precedes systemic glucose intolerance in obesity, suggesting a potential early role of the gut in the development of metabolic disorders. Gao et al.[43] highlighted the importance of intestinal alkaline phosphatase in modulating intestinal inflammation and improving insulin sensitivity. These studies underscore the relationship between gut health, inflammation, and systemic metabolic regulation. Changes in gut microbiota composition, such as dysbiosis, can lead to increased intestinal permeability, inflammation, and altered short-chain fatty acid production, contributing to the development of IR[78]. Additionally, insulin signaling within the colon is essential for maintaining glucose balance. Disruptions in this signaling pathway can impair glucose uptake and utilization by colonic epithelial cells, further exacerbating IR. Investigations into large intestinal-IR have revealed a complex interplay between the gut and metabolic conditions. By delving into the molecular pathways underlying large intestinal-IR, we can identify novel therapeutic targets aimed at enhancing colonic insulin sensitivity. Consequently, focusing on large intestinal-IR presents a promising avenue in metabolic research, with the potential to develop strategies for addressing and managing metabolic disorders.

The mechanisms implicit in skeletal muscle-IR are complex and multifactorial. Magkos et al.[44] demonstrated that the relationship between free fatty acid and muscle glucose metabolism is likely due to multi-organ IR rather than a direct effect of fatty acids on muscle insulin action. Nowotny et al.[45] revealed that oral fat ingestion induces IR by activating specific signaling pathways in muscle cells. Abbasi et al.[46] and Krebs et al.[47] highlighted the role of IR in regulating plasma free fatty acid concentrations and muscle glucose uptake, respectively. Kelley et al.[48] emphasized the importance of plasma fatty acids and visceral adipose tissue in mediating the link between obesity and skeletal muscle-IR. In the 1960s, Randle et al.[79] proposed one of the earliest theories to explain muscle-IR mechanisms. They determined that a sudden rise in muscle fatty acid oxidation results in citrate buildup, which hinders phosphofructokinase, a crucial glycolysis enzyme. A key mechanism implicit muscle-IR involves the disruption of mitochondrial and endoplasmic reticulum interactions, leading to reduced insulin-stimulated glucose uptake[80]. Additionally, alterations in insulin receptor signaling pathways, particularly IRS1 phosphorylation, contribute to Muscle IR[81]. Oxidative stress, inflammation, and amino acid imbalances play significant roles in the development of Muscle IR. The activation of kinases like IKK and JNK, as well as the role of Toll-like receptors, have been implicated in the pathogenesis of Muscle IR[82].

Adipose tissue-IR plays a relevant role in the development of metabolic disorders. Halloun et al.[49] demonstrated that adipose tissue-IR is not protective against obesity progression. Hazlehurst et al.[50] showed that glucocorticoids can have tissue-specific effects on insulin sensitivity, including adipose tissue. Cifarelli et al.[51] highlighted the role of adipose tissue oxygenation in regulating insulin sensitivity. Jiang et al.[52] emphasized the importance of maintaining a healthy body weight to reduce adipose tissue-IR. Ter Horst et al.[53], Wen et al.[54], and Zhou et al.[55] further established the association between adipose tissue-IR and the development of metabolic disorders, including prediabetes, T2DM, and atherosclerosis. Pioneering studies in the 1990's first established the link between inflammation and adipose tissue-IR[83]. Macrophages play a key role in adipose tissue inflammation and IR. Adipose tissue dysfunction, characterized by adipocyte hypertrophy and macrophage infiltration, contributes to systemic inflammation and impaired glucose homeostasis[84]. Both visceral and subcutaneous adipose tissue can contribute to IR, with visceral adipose tissue being particularly detrimental. Brown adipose tissue, through its thermogenic properties, can positively impact metabolic health. This effect is attributed to the presence of uncoupling protein 1 in brown adipocytes, which is a crucial target in the battle against diabetes and the reduction of body fat mass. However, the accumulation of white adipose tissue and the associated inflammatory environment can exacerbate IR[85].

IR can impair vascular function, contributing to cardiovascular disease. Feldman et al.[56] demonstrated that dietary salt restriction can exacerbate vascular-IR, Wang et al.[57] showed that GLP-1 can improve microvascular insulin action in obese individuals, Vinet et al.[58] found that lifestyle interventions can reverse insulin-induced vascular dysfunction in metabolic syndrome, and Love et al.[59] highlighted the role of elevated free fatty acids in inducing pan-arterial IR and its association with cardiovascular disease risk. IR impacts both arteries and arterioles affecting the endothelial and smooth muscle layers. This vascular-IR is significant in the development of vascular and related diseases. Impaired insulin signaling in vascular endothelial cells can lead to endothelial dysfunction, promoting atherogenesis and inflammation[86]. Vascular-IR is implicated in the pathogenesis of diabetes by hindering insulin delivery to tissues and affecting insulin secretion[87]. Nitric oxide, a key vasodilator, is impaired in vascular-IR, leading to reduced vascular barrier integrity and increased macrophage infiltration[88].

IR in the ovary is a key feature of polycystic ovary syndrome (PCOS). Wu XK et al.[60] demonstrated a selective defect in insulin action in PCOS granulosa cells, suggesting that ovarian-IR contributes to the reproductive disturbances observed in PCOS. These findings highlight the potential therapeutic role of insulin-sensitizing agents in the management of PCOS. The long-term consequences of IR in individuals with PCOS encompass metabolic irregularities, a heightened risk of T2DM, hypertension, cardiovascular diseases, and endometrial cancer. In polycystic ovaries, the insulin-induced stimulation of androgens in thecal cells remains intact and is even enhanced through the direct activation of insulin receptors, while the insulin-mediated uptake of glucose in granulosa cells is significantly compromised[60]. Several proteins, including adiponectin, apelin, and resistin, have been implicated in the pathogenesis of PCOS and IR[89]. Insulin plays a substantial role in ovarian steroidogenesis by stimulating androgen, estrogen, and progesterone production[90].

IR can impair male reproductive function. Contreras et al.[61] found that abdominal obesity is associated with both IR and hypogonadism, suggesting a sequential relationship between these conditions. Verit et al.[62] investigated the potential impact of IR on male fertility, but did not find a clear correlation between IR and semen parameters. Testosterone plays a significant role in the formation of both muscular and visceral adipose tissue, affecting the differentiation of pluripotent stem cells and suppressing the maturation of preadipocytes. Moreover, testosterone exerts a protective influence on pancreatic β cells, likely through mechanisms involving androgen receptors and the modulation of inflammatory cytokines. A deficiency in testosterone is linked to a higher occurrence of metabolic syndrome components, particularly the accumulation of visceral adipose tissue and the development of IR[91]. Insulin signaling plays a crucial role in testicular function, promoting sperm production and maturation[92]. IR in the testes can impair these processes, leading to reduced sperm quality and testosterone levels[93]. Consequently, testicular-IR may adversely affect male reproductive health by disrupting testicular function and playing a role in the onset of metabolic syndrome.

This scoping review has some limitations that should be acknowledged. Firstly, the relatively small number of studies focusing specifically on organ-specific IR compared to the vast literature on systemic IR indicates a need for further research in this area. Secondly, the heterogeneity of study designs and methodologies used in the included studies makes it challenging to draw definitive conclusions about the

prevalence and clinical significance of organ-specific IR across different populations. Finally, the focus on English-language studies may have excluded relevant research conducted in other languages. Despite these limitations, the findings of this scoping review provide a valuable foundation for future research on organ-specific IR, and the concept of "in-situ diabetes mellitus" or "T6DM" offers a promising framework for understanding the heterogeneity of diabetes and guiding future investigations.

Finally, there are 17 tissues that can induce insulin resistance, and there are also 17 mechanisms that can be activated to trigger insulin resistance. The consequences of living with insulin resistance can lead to cognitive alterations, endocrine system disorders, fatty liver and pancreatic disease, cardiovascular system dysfunctions, alterations in homeostasis and coagulation, cancer, among others. Thus, once insulin resistance is established, a subclinical inflammatory process occurs, characterized by hyperinsulinemia, activation of signaling pathways, and endoplasmic reticulum stress. Some of the consequences of insulin resistance mentioned above are a result of hyperinsulinemia or alterations in the metabolism itself or the sum of these factors.

CONCLUSION

The findings suggest that investigating organ-specific IR in the context of T2DM is a promising avenue for future research to deepen our understanding of disease pathophysiology. Thus, this scoping review answers the following question "In-Situ Insulin Resistance - Localized Type 2 Diabetes Mellitus or Type 6 Diabetes Mellitus?", emphasizing the need for targeted investigations into localized manifestations of IR and their implications for DM management strategies.

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