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PRECISION ENDOCRINOLOGY AND INSULIN RESISTANCE - ADVANCES IN BIOMARKERS AND PERSONALIZED THERAPIES: SYSTEMATIC REVIEW WITH A META ANALYSIS APPROACH

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ABSTRACT

Insulin resistance constitutes a central pathophysiological axis of type 2 diabetes mellitus, obesity, metabolic syndrome, and various cardiometabolic conditions. With the advancement of precision endocrinology, it has become possible to understand this condition as a heterogeneous phenotype, influenced by clinical, molecular, metabolomic, and therapeutic factors. The present study aimed to systematically analyze advances in biomarkers and personalized therapies applied to insulin resistance, using a subgroup meta-analysis approach. A systematic literature review was conducted in recognized scientific databases, including studies on precision medicine, metabolic subclassification, classical biomarkers, metabolomic and molecular biomarkers, as well as personalized therapeutic interventions.Thirty-three studies were included, organized into four main areas: precision medicine and phenotypic subtyping; classical biomarkers such as HOMA-IR, QUICKI, Matsuda index, and TyG index; emerging biomarkers including branched-chain amino acids, **α**-hydroxybutyrate, metabolomic signatures, and microRNAs; and personalized therapies such as intensive weight loss, metabolic surgery, GLP-1 agonists, dual GIP/GLP-1 agonists, and SGLT2 inhibitors. The results demonstrated that the subgroup approach is methodologically more appropriate given the heterogeneity of studies, populations, biomarkers, and interventions. Classical biomarkers remain useful for screening and initial stratification, while omic markers show potential for prognostic refinement and early identification of metabolic risk. Therapeutic interventions were shown to be more relevant when targeted to the patient's clinical and metabolic profile.It is concluded that precision endocrinology applied to insulin resistance represents a promising frontier for early diagnosis, therapeutic personalization, prevention of type 2 diabetes, and reduction of cardiometabolic complications.

Keywords:insulin resistance; precision endocrinology; biomarkers; personalized therapies.

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INTRODUCTION

Insulin resistance constitutes one of the main pathophysiological axes of contemporary metabolic diseases, being directly associated with the development of type 2 diabetes mellitus, obesity, metabolic syndrome, metabolic dysfunction-associated steatotic liver disease, atherogenic dyslipidemia, arterial hypertension, and increased cardiovascular risk. Traditionally understood as a reduction in the biological response of peripheral tissues to the action of insulin, especially in skeletal muscle, adipose tissue, and liver, this condition has come to be recognized not only as an isolated biochemical alteration but as a systemic, multifactorial, and heterogeneous phenotype, influenced by genetic predisposition, body composition, low-grade chronic inflammation, mitochondrial function, dietary profile, gut microbiota, lipid metabolism, pancreatic insulin secretion, and individual variability in therapeutic response [1-5].

In recent decades, the advancement of precision endocrinology has progressively modified the clinical understanding of insulin resistance. The conventional model, based on broad diagnostic categories and interventions standardized, has been replaced by a more individualized approach, guided by the integration of clinical characteristics, laboratory biomarkers, metabolomic signatures, genetic variables, adiposity phenotypes, and pharmacological response. In this context, precision medicine in diabetes and metabolic diseases proposes that prevention, diagnosis, prognostic stratification, and treatment be adapted to the biological and clinical particularities of each individual [1,2]. This perspective is especially relevant because patients classified under the same diagnosis, such as type 2 diabetes or metabolic syndrome, may present distinct pathophysiological mechanisms, varying degrees of insulin resistance, different levels of beta-pancreatic dysfunction, and heterogeneous therapeutic responses [3-7].

The subclassification of metabolic phenotypes has become a central field in precision endocrinology. Cluster analysis-based studies have demonstrated that adults with recent-onset diabetes can be grouped into distinct subtypes, with differences in insulin resistance, insulin deficiency, body mass index, glycemic control, and risk of

microvascular and macrovascular complications [5]. These findings indicate that insulin resistance should not be interpreted uniformly, but rather as part of a metabolic spectrum that can vary according to age, visceral adiposity, beta-pancreatic reserve, systemic inflammation, and cardiometabolic risk. Recent systematic reviews reinforce that the subclassification of type 2 diabetes and metabolic disorders can aid in the identification of subgroups with a higher risk of progression, a greater likelihood of complications, and a potential differentiated response a interventions pharmacological and non-pharmacological [3,4].

Despite this conceptual advancement, the clinical application of precision endocrinology still depends on the consolidation of reliable, accessible, and clinically useful biomarkers. The hyperinsulinemic-euglycemic clamp remains considered the reference method for assessing insulin sensitivity, but its high cost, operational complexity, and low applicability in clinical routine limit its use on a large scale. For this reason, different surrogate indices have been developed to estimate insulin resistance or sensitivity from more laboratory variables simple. Among the classical markers, HOMA-IR, HOMA-**β**, QUICKI, Matsuda index, and triglyceride-glucose index, known as TyG [8-13], stand out. These instruments have enabled significant advances in epidemiological studies, clinical trials, and population assessments, although they present limitations related to methodological variability, ethnic differences, glycemic status, medication use, and the absence of universally applicable cutoff points [9, 13].

HOMA-IR, derived from fasting glucose and insulin concentrations, has established itself as one of the most widely used measures for estimating insulin resistance in clinical and population studies [8,9]. QUICKI, also based on fasting parameters, was proposed as a simple and accurate alternative for assessing insulin sensitivity [10]. The Matsuda index, in turn, uses data from the oral glucose tolerance test, allowing a more dynamic assessment of the insulin response during glycemic stimulus [11]. The TyG index, calculated from fasting triglycerides and glucose, has gained prominence for its simplicity, low cost, and potential applicability in clinical settings with less availability of insulin dosage

[12, 13]. Together, these markers represent relevant tools for screening and metabolic stratification, but they still do not fully capture the molecular complexity of insulin resistance.

With the expansion of omics technologies, especially metabolomics, proteomics, transcriptomics, and microRNA analysis, new possibilities have emerged for the identification of early biomarkers and molecular signatures associated with insulin resistance. Metabolomic studies have demonstrated that alterations in branched-chain amino acids, acylcarnitines, lipid metabolites, **α**-hydroxybutyrate, and other metabolic intermediates may precede or accompany the development of insulin resistance and type 2 diabetes [14-21]. These metabolic signatures not only broaden the pathophysiological understanding of the disease but also offer potential for risk stratification, progression monitoring, and selection of individualized therapeutic strategies.

Among emerging biomarkers, branched-chain amino acids have received special attention. Metabolomic evidence indicates that elevated concentrations of leucine, isoleucine and valine, as well as metabolites derived from their degradation, are associated with obesity, insulin resistance and increased risk of developing type 2 diabetes [14, 16,20,21]. Similarly, **α**-hydroxybutyrate has been described as an early marker of metabolic dysfunction and glucose intolerance, suggesting its potential usefulness in identifying individuals in the early stages of deterioration of insulin sensitivity [19]. These findings reinforce the transition from a metabolic assessment based only on glucose, insulin and traditional lipids to a more refined approach, capable of capturing biochemical changes prior to the full clinical manifestation of the disease.

In addition to circulating metabolites, microRNAs have been investigated as post-transcriptional regulators involved in insulin resistance, inflammation, adipogenesis, muscle function and intracellular insulin signaling [22,24]. These small non-coding RNAs can modulate pathways related to glucose transport, insulin sensitivity in skeletal muscle, mitochondrial function and inflammatory response. Although there are still challenges related to

standardization methodological, reproducibility and clinical validation, microRNAs represent a promising frontier for precision endocrinology, especially for their potential use as diagnostic, prognostic, and therapeutic biomarkers [22-24].

In the therapeutic field, the personalization of treatment for insulin resistance and type 2 diabetes has advanced significantly. Intensive weight loss interventions have demonstrated the potential to induce remission of type 2 diabetes, especially when applied in the early stages of the disease and accompanied by sustained weight loss maintenance [25-27]. Studies such as DiRECT reinforce that structured weight loss can profoundly modify the metabolic course of the disease, reducing the need for medications and favoring sustained glycemic improvement in specific patient subgroups [25-27]. These results indicate that the proper selection of candidates, considering diabetes duration, beta-pancreatic reserve, degree of adiposity, and adherence to follow-up, is essential to maximize clinical benefits.

Metabolic surgery has also established itself as a high-impact intervention for individuals with obesity and type 2 diabetes, demonstrating superiority over conventional clinical therapy in outcomes such as glycemic remission, medication reduction, and sustained improvement in metabolic control [28,29]. However, not all patients respond in the same way, and the magnitude of the benefit may vary according to body mass index, duration of diabetes, residual beta-pancreatic function, body fat distribution, and presence of comorbidities. Thus, metabolic surgery represents a clear example of an intervention whose indication should be guided by clinical and metabolic stratification, aligning with the principles of precision endocrinology.

In parallel, therapies modern pharmacological therapies, such as glucagon-like peptide-1 receptor agonists, dual GIP/GLP-1 agonists, and sodium-glucose cotransporter-2 inhibitors, have substantially expanded the possibilities of treatment personalized. Semaglutide has demonstrated significant effects on weight reduction in adults with overweight or obesity [30]. Tirzepatide, due to its action

combined in incretin pathways, showed relevant reductions in glycated hemoglobin and body weight in individuals with type 2 diabetes and obesity [31,32]. Empagliflozin, in addition to its glycemic effect, demonstrated cardiovascular benefits in patients with type 2 diabetes and high cardiovascular risk [33]. These findings show that the therapeutic choice must go beyond isolated glycemic control, incorporating adiposity, cardiovascular risk, renal function, metabolic profile, and individual probability of response.

Despite the accelerated growth of evidence, there are still relevant gaps in the integration between insulin resistance biomarkers and personalized therapeutic decisions. Some studies focus on isolated biomarkers, while others evaluate interventions without refined metabolic stratification. Furthermore, the heterogeneity of methodological designs, populations, outcomes, and measurement methods makes direct comparison between findings difficult.

In this scenario, a systematic review with a subgroup meta-analysis approach becomes methodologically appropriate to critically organize the literature, identify response patterns, compare biomarkers, and evaluate the impact of different therapeutic strategies in distinct clinical and metabolic subgroups.

Thus, the present study aims to systematically analyze the advances in precision endocrinology applied to insulin resistance, with emphasis on classical, metabolomic and molecular biomarkers, as well as personalized therapies aimed at improving insulin sensitivity, glycemic control, weight loss, metabolic remission and reduction of cardiometabolic risk. Additionally,

we seek to synthesize the available evidence by intervention subgroups and biomarker profile, offering a critical view on the current clinical applicability and future perspectives of precision medicine in the management of

insulin resistance.

METHODOLOGY

The present study was designed as a systematic review with a subgroup meta-analysis approach, developed with the objective of analyzing

critically evaluate the available scientific evidence on precision endocrinology applied to insulin resistance, with emphasis on classical biomarkers, metabolomic biomarkers and molecular biomarkers, metabolic subclassification, and personalized therapies. The methodological framework was guided by international recommendations for systematic reviews and meta-analyses, with organization of the identification, screening, eligibility, and inclusion process of studies according to the principles of the PRISMA protocol, adapted to the scope of the investigation and the editorial standards of the Revista Científica Ipedss.

The guiding question was structured based on the PICO strategy, considering as the population adults with insulin resistance, obesity, metabolic syndrome, prediabetes, or type 2 diabetes mellitus; as intervention or exposure, the use of clinical, laboratory, metabolomic, molecular or genetic biomarkers associated with insulin resistance, as well as personalized pharmacological, surgical, or behavioral therapies; as comparators, conventional methods of metabolic assessment, usual clinical treatment, placebo, alternative interventions, or absence of stratification by biomarkers; and as primary outcomes, changes in insulin resistance, insulin sensitivity, HOMA-IR, QUICKI, Matsuda index, TyG index, glycated hemoglobin, fasting blood glucose, body weight, type 2 diabetes remission, therapeutic response, cardiometabolic risk and prognostic markers.

The literature search was conducted in internationally recognized scientific databases, including PubMed/MEDLINE, PubMed Central, Scopus, Web of Science, Embase, Cochrane Library, Nature Portfolio, ScienceDirect and specialized journals in endocrinology, metabolism, diabetes and translational medicine. Priority was given to indexed, traceable studies with identifiable authorship, recognized scientific journals, available DOI or bibliographic record, and direct alignment with the review topic. The search strategy combined controlled descriptors and free terms in English, including: "precision endocrinology", "precision medicine", "insulin resistance", "type 2 diabetes", "metabolic syndrome", "biomarkers", "HOMA-IR", "QUICKI", "Matsuda index", "triglyceride-glucose index", "TyG index", "metabolomics", "branched-chain amino acids", "microRNAs", "personalized therapy",

GLP-1 receptor agonists", "GIP/GLP-1 receptor agonist", "SGLT2 inhibitors", "bariatric surgery", "metabolic surgery" and " diabetes remission". The Boolean operators AND and OR were used to broaden or restrict the search sensitivity according to the thematic combination analyzed.

Studies published in peer-reviewed scientific journals, in English, Portuguese, or Spanish, that presented a direct relationship with precision endocrinology, insulin resistance, metabolic biomarkers, or personalized therapies in metabolic diseases were considered eligible. Scientific consensuses, systematic reviews, meta-analyses, cohort studies, cross-sectional studies, methodological studies for biomarker validation, metabolomic analyses, phenotypic clustering studies, randomized clinical trials, and longitudinal follow-up studies were included. The final selection prioritized evidence with greater translational relevance, methodological robustness, clinical applicability, and potential contribution to the construction of a systematic review with subgroup analysis.

Duplicate studies, publications without access to information were excluded essential bibliographic references, isolated reports without analytical value for the review's objective, studies with exclusively pediatric populations without possibility of extrapolation to adult metabolism adult, studies

exclusively experimental in vitro or animal models without clinical validation, editorial comments without original data or methodological synthesis, publications without direct alignment with insulin resistance or precision medicine, and articles whose primary focus was restricted to endocrine diseases unrelated to glycemic metabolism, adiposity, insulin sensitivity, or cardiometabolic risk.

The study selection process occurred in sequential stages. Initially, potentially relevant publications were identified through reading titles and abstracts. Subsequently, pre-selected articles were evaluated for eligibility through full reading or detailed analysis of available bibliographic information. In the final stage, 33 studies considered compatible with the review's scope were selected, distributed across four main thematic axes: precision medicine and metabolic subclassification metabolic;

classic biomarkers ofresistance to

insulin; omic, metabolomic, and molecular biomarkers; and personalized therapies aimed at metabolic improvement, weight loss, diabetes remission, or reduction of cardiometabolic risk.

Data extraction was performed using a standardized matrix, including author and year of publication, country or consortium of origin when available, study design, evaluated population, biomarker or intervention analyzed, primary outcomes, relevant results, and applicability for qualitative or quantitative synthesis. For biomarker studies, information was extracted on the type of marker evaluated, measurement method, relationship with insulin resistance, discriminatory capacity, clinical applicability, and methodological limitations. For intervention studies, data related to the type of treatment, population, comparator, follow-up duration, changes in body weight, glycated hemoglobin, blood glucose, type 2 diabetes remission, therapeutic response and outcomes cardiometabolic.

The qualitative analysis was organized in a narrative and integrative manner, considering the heterogeneity of methodological designs and the types of biomarkers evaluated. The classic biomarkers, such as HOMAIR, HOMA-β , QUICKI, Matsuda index and TyG index, were analyzed for their clinical applicability, operational simplicity, limitations and relationship with reference methods for assessing insulin sensitivity . The metabolomic and molecular biomarkers and molecular biomarkers, including branched-chain amino acids, α-hydroxybutyrate, acylcarnitines, metabolic signatures and microRNAs, were discussed regarding their potential for risk stratification, early diagnosis, prediction of metabolic progression and future integration into precision endocrinology models.

The meta-analysis approach was planned by subgroups, considering the methodological impossibility of indiscriminately combining studies with very different populations, interventions and outcomes. Thus, the studies were grouped according to clinical and methodological similarity. The first subgroup comprised intensive weight loss and metabolic remission interventions, focusing on studies derived from the DiRECT program. The second subgroup included trials

clinical trials of metabolic or bariatric surgery compared to conventional or intensive clinical therapy. The third subgroup included modern incretin therapies, especially GLP-1 receptor agonists and dual GIP/GLP-1 agonists, evaluating effects on body weight, glycated hemoglobin, and metabolic parameters. The fourth subgroup was reserved for the analysis of surrogate biomarkers of insulin resistance, considering studies that compared indices such as HOMA-IR, QUICKI, Matsuda, and TyG with reference methods or with clinically relevant metabolic outcomes.

For the quantitative synthesis, the planned continuous outcomes included mean change in glycated hemoglobin, body weight, fasting blood glucose, HOMA-IR, estimated insulin sensitivity, and other metabolic parameters, when available in a comparable way among the studies. For dichotomous outcomes, type 2 diabetes remission, occurrence of a clinically relevant therapeutic response, reduction or discontinuation of antidiabetic medications, and the presence of major cardiometabolic outcomes were considered. When the data were sufficiently homogeneous, the planned measure of effect for continuous variables would be the difference mean or standardized mean difference, while for dichotomous variables, relative risk, odds ratio, or risk ratio would be used, with respective 95% confidence intervals.

Heterogeneity between studies was anticipated as a relevant component of the analysis, due to differences in populations, methods of measuring insulin resistance, follow-up duration, study designs, diagnostic criteria, and types of intervention. For this reason, the random effects model was considered the most appropriate for subgroup meta-analysis, especially in sets of studies with significant clinical and methodological variability. A statistical heterogeneity would be assessed using Cochran's Q test and the I^2 statistic, considering higher I^2 values as indicative of greater inconsistency among results. In situations of substantial heterogeneity, the interpretation of quantitative findings would be complemented by narrative analysis, avoiding overly generalizing conclusions.

The assessment of methodological quality and risk of bias was planned according to the type of study included. For clinical trials

randomized, would be considered domains related to the generation of the randomization sequence, allocation concealment, blinding, follow-up losses, incomplete outcome data, and selective reporting. For observational studies, aspects such as population selection, exposure definition, outcome measurement, control of confounding factors, and adequacy of statistical analyses would be evaluated. Systematic reviews and consensuses were used primarily as conceptual and contextual support, not as main units for quantitative meta-analysis.

The final synthesis of results was planned to integrate quantitative and qualitative findings, preserving the distinction between biomarker validation evidence, phenotypic stratification studies, and therapeutic trials. This organization allows for evaluating not only which biomarkers are associated with insulin resistance but also how such markers can contribute to the identification of clinical subgroups with greater likelihood of response to specific interventions. The subgroup approach therefore seeks to align the methodological analysis with the very principle of precision endocrinology, in which the biological and clinical heterogeneity of patients should guide the interpretation of evidence and therapeutic decision-making.

As this is a systematic review based exclusively on previously published secondary data, there was no need for submission to a Research Ethics Committee. Nevertheless, principles of scientific integrity, traceability of sources, fidelity to original findings, and transparency in the selection and interpretation of studies were observed. The adopted methodology aims to provide a robust basis for the critical analysis of advances in biomarkers and personalized therapies in insulin resistance, contributing to the consolidation of a translational and internationally aligned of precision endocrinology.

RESULTS

The literature search and selection resulted in the inclusion of 33 studies scientific directly related to precision endocrinology, resistance to

insulin, metabolic biomarkers, and personalized therapies. The included studies were organized into four main axes of analysis: precision medicine and metabolic subclassification, classical biomarkers of insulin resistance, metabolomic and molecular biomarkers, and personalized therapeutic interventions. This organization allowed for structuring the results in a manner compatible with a systematic review with a subgroup meta-analysis approach, considering the clinical, methodological, and statistical heterogeneity of the evaluated studies.

From the total set of studies, 7 studies focused on precision medicine, metabolic subclassification, and individualized therapeutic response were identified, 6 studies related to classical biomarkers of insulin resistance, 11 studies on metabolomic, molecular, and omic biomarkers, and 9 studies focusing on personalized therapeutic interventions, including intensive weight loss, metabolic surgery, modern incretin therapies, and SGLT2 inhibitors. The thematic distribution of the sample highlights the translational breadth of the field, in which insulin resistance is analyzed not only as a pathophysiological marker but also as an axis for clinical, prognostic, and therapeutic stratification.

Table 1 - Distribution of included studies according to thematic axis and applicability in the review

Thematic axis	**Studies included**	**Number of studies**	**Main applicability**
Precision medicine and metabolic subclassification	[1-7]	7	Conceptual foundation, phenotypical Stratification and individualized therapeutic response
Classic biomarkers of insulin resistance	[8-13]	6	Evaluation of HOMA-IR, HOMA-**β**, QUICKI, Matsuda index, and TyG index
Biomarkers metabolomics and molecular	[14-24]	11	Identification of metabolic signatures, BCAA, **α**-hydroxybutyrate, microRNAs and Emerging biomarkers
Personalized therapies and metabolic interventions	[25-33]	9	Analysis of intensive weight loss, metabolic surgery, incretins, GIP/GLP-1 and SGLT2i

The analysis of precision medicine studies demonstrated that insulin resistance behaves as a heterogeneous phenotype, whose clinical interpretation depends on the integration between adiposity, beta-pancreatic function, glycemic control, cardiometabolic profile, risk of complications, and therapeutic response.

International consensuses on precision medicine in diabetes have highlighted that the individualization of care should involve prevention, diagnosis, treatment, and prognosis, with the progressive use of biomarkers and predictive models [1, 2]. The systematic review on type 2 diabetes subclassification reinforced that different models of phenotypic clustering can identify subgroups with distinct clinical trajectories [3]. The study by Ahlqvist et al. demonstrated that adults with recent-onset diabetes can be classified into five metabolic subgroups, with relevant differences in insulin resistance, deficiency of insulin, obesity, glycemic control, and risk of complications [5].

The analysis of therapeutic response studies also showed that clinical markers of insulin resistance can influence the effect of different pharmacological classes. Studies conducted in the context of precision medicine in diabetes indicated that individuals with distinct metabolic profiles may present different responses to DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors [4,6,7]. This finding supports the proposal that insulin resistance should not be used only as a diagnostic marker, but also as an element for therapeutic guidance.

Table 2 - Summary of studies on precision medicine, metabolic subclassification and therapeutic response

Studies	Type of evidence	Main focus	Contribution to the review
Chung et al. [1]	ADA/EASD Consensus	Precision medicine in diabetes	Defines the pillars of individualized prevention, diagnosis, treatment and prognosis
Tobias et al. [2]	International consensus	Clinical translation of precision medicine	Identifies gaps for clinical application and biomarker validation
Misra et al.[3]	Systematic review	Type 2 diabetes subclassification	Evaluates phenotypic stratification models and clinical applicability
Young et al. [4]	Systematic review	Therapeutic response heterogeneity	Supports the need for therapeutic subgroup analysis
Ahlqvist et al. [5]	Cluster analysis	Adult diabetes subgroups	Demonstrates distinct phenotypes associated with different clinical risks
Dennis et al. [6]	Therapeutic response study	Markers of insulin resistance and DPP-4i	Relates clinical biomarkers to glycemic response
Dennis [7]	Predictive modeling	Individualized treatment selection	Proposes the use of predictive models for therapeutic optimization

In studies of classical biomarkers, it was observed that HOMA-IR remains the most widely used index for estimating insulin resistance in clinical and epidemiological studies. Its main advantage is operational simplicity, as it uses fasting glucose and insulin. However, its interpretation depends on the population context, glycemic status, medication use, and laboratory standardization [8,9]. QUICKI, also based on fasting data, proved useful as a simple index of insulin sensitivity, while the Matsuda index stood out for incorporating information from the oral glucose tolerance test, allowing for a more dynamic assessment of the metabolic response.

[10, 11]. The TyG index was identified as a promising surrogate biomarker because it uses only fasting triglycerides and glucose, expanding its applicability in clinical and population contexts where insulin measurement is not available [12, 13].

These findings indicate that classical biomarkers are useful for screening and initial stratification, but present significant limitations for precision endocrinology when used in isolation. The absence of universal cutoff points, the influence of ethnic and metabolic factors, and the variability between laboratory methods reinforce the need to integrate these indices with emerging biomarkers, clinical data, and predictive models.

Table 3 - Classical biomarkers of insulin resistance identified in the review

Biomarker	Studies related	Variables used	Advantages	Limitations
HOMA-IR	[8,9]	Glucose and insulin Fasting	Simple, widely used, applicable in Large populations	Sensitive to laboratory variations, absence of a universal cutoff point
HOMA-β	[8,9]	Glucose and insulin Fasting	Estimates beta cell function pancreatic	Does not replace dynamic assessment of insulin secretion
QUICKI	[10]	Simple index of glucose and insulin Fasting	insulin sensitivity	Less routine clinical use compared to HOMA-IR
Matsuda index	[11]	Glucose and insulin during OGTT	Assesses sensitivity insulin in a dynamic	Requires an oral glucose tolerance test
TyG index	[12,13]	Triglycerides and	Low cost, does not require	May be influenced by

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Biomarker	Studies related	Variables used	Advantages	Limitations
		fasting glucose	insulin dosage, applicable in clinical routine	lipid alterations not directly related to insulin resistance

A analysis of the studies metabolomic and molecular demonstrated significant progress in the identification of biomarkers associated with insulin resistance. Branched-chain amino acids, especially leucine, isoleucine and valine, have been repeatedly associated with obesity, a worse metabolic profile, insulin resistance and future risk of type 2 diabetes [14, 16,20,21]. These findings indicate that dysfunction in amino acid metabolism may represent not only a consequence of insulin resistance, but also an active component in the progression of metabolic dysfunction.

Broad metabolomic signatures have also been linked to insulin resistance in population-based and prospective studies. Würtz et al. identified metabolic patterns associated with insulin resistance in more than seven thousand young adults, reinforcing the usefulness of metabolomics for early risk stratification [15]. Wang et al. and Floegel et al. demonstrated that specific profiles of Metabolites may predict future risk of type 2 diabetes, suggesting that biochemical alterations precede the clinical diagnosis of the disease [16, 17]. Palmer et al. also identified metabolomic profiles associated with both insulin resistance and conversion to diabetes in a longitudinal cohort [18]. **α**-hydroxybutyrate was described as an early marker of insulin resistance and glucose intolerance, expanding the spectrum of potential biomarkers for subclinical detection of metabolic dysfunction [19].

MicroRNAs have been identified as emerging molecular biomarkers, especially for their role in the post-transcriptional regulation of pathways involved in insulin sensitivity, inflammation, mitochondrial function, and muscle metabolism [22,24]. Although not yet established in clinical practice, these markers show potential for composing future models of molecular stratification in precision endocrinology.

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Table 4 - Metabolomic and molecular biomarkers associated with insulin resistance

Category of biomarker	Related studies	Principal findings	Potential clinical application
Branched-chain amino acids	[14,20,21]	Association with obesity, insulin resistance, and worse metabolic health	Metabolic risk stratification and identification of high-risk phenotypes Early prediction, progression monitoring, and risk models
Broad metabolomic signatures	[15-18]	Metabolic profiles associated with insulin resistance and diabetes risk	
α-hydroxybutyrate	[19]	Early biomarker of insulin resistance and glucose intolerance Relationship with mitochondrial dysfunction, incomplete fatty acid oxidation, and energy metabolism Regulation of pathways related to insulin signaling and muscle metabolism	Subclinical detection of metabolic dysfunction
Lipid metabolites and acylcarnitines	[14-18]		Integration with advanced metabolic phenotyping
microRNAs	[22,24]		Diagnostic biomarkers and possible future therapeutic targets
Integrated biomarkers of sensitivity/resistance	[23]	Comparative assessment of markers for predicting metabolic response	Support for selection personalized therapeutic

Regarding personalized therapeutic interventions, studies were grouped into subgroups according to clinical and methodological similarity. The first subgroup included intensive weight loss interventions, represented mainly by the DiRECT program and its follow-ups. These studies demonstrated that structured weight loss in primary care can induce remission of type 2 diabetes, especially when weight reduction is significant and maintained over time [25-27]. Longitudinal analysis reinforced that maintaining weight loss is decisive for the durability of metabolic remission, indicating that behavioral interventions can have a disease-modifying effect in selected subgroups.

The second subgroup included studies of metabolic or bariatric surgery compared to conventional or intensive clinical therapy. The trials demonstrated the superiority of metabolic surgery in glycemic outcomes and remission of type 2 diabetes in individuals with obesity and diabetes, supporting its role as a highly effective intervention in selected patients

[28,29]. The magnitude of the response, however, depends on clinical characteristics such as duration of diabetes, beta-pancreatic reserve, body mass index, and severity of metabolic dysfunction.

The third subgroup included modern incretin therapies. Semaglutide showed significant weight reductions in adults with overweight or obesity [30]. Tirzepatide, a dual GIP/GLP-1 agonist, demonstrated robust effects on body weight and glycated hemoglobin in patients with type 2 diabetes and obesity [31,32]. These results reinforce that modern pharmacological interventions can be interpreted within a logic of precision endocrinology, especially when therapeutic selection considers adiposity, glycemic control, cardiometabolic risk and probability of individual response.

The fourth subgroup included empagliflozin, a representative of SGLT2 inhibitors with robust evidence of cardiovascular benefit in patients with type 2 diabetes and high cardiovascular risk [33]. Although its direct effect on insulin resistance is less central than its hemodynamic, renal, and cardiometabolic impact, its inclusion reinforces that therapeutic personalization in diabetes should consider not only glycemic reduction but also cardiovascular and renal protection.

Table 5 - Proposed therapeutic subgroups for meta-analysis

Meta-analysis subgroup	Included studies	Primary intervention	Priority outcomes	Expected interpretation
Subgroup 1: loss intensive weight	[25-27]	Structured weight loss and weight maintenance program	Diabetes remission, body weight, HbA1c, medication use	Assess the impact of sustained weight loss on metabolic reversal
Subgroup 2: surgery metabolic	[28,29]	Surgery bariatric/metabolic versus clinical therapy	Diabetes remission, HbA1c, body weight, medication reduction	Evaluate the superiority of surgical intervention in phenotypes with obesity and diabetes
Subgroup 3: therapies incretin[30-32]-based		Semaglutide and tirzepatide	Body weight, HbA1c, blood glucose, metabolic response	Evaluate the impact of modern therapies on adiposity and glycemic control Integrate cardiovascular risk into personalization
Subgroup 4: cardiometabolic therapy with SGLT2i	[33]	Empagliflozin	Cardiovascular events, mortality, control	

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Subgroup d metals lipids	Study	I t principle function	D sf h priority	p tation of
Subgroup 5: surrogate biomarkers	[8-13]	HOMA-IR, QUICKI, Matsuda and TyG	metabolic Correlation with insulin resistance, clinical applicability, metabolic discrimination	therapeutic Assess the usefulness of indices in metabolic stratification

The subgroup meta-analysis approach proved more appropriate than a single global meta-analysis due to the wide heterogeneity among the included studies. The studies differed in terms of population type, presence or absence of diabetes, degree of obesity, duration of the disease, biomarkers evaluated, follow-up time, type of intervention, and outcomes analyzed. For this reason, aggregating data into subgroups allows for preserving clinical and methodological coherence, reducing the risk of inadequate interpretations.

Table 6 - Eligible outcomes for quantitative synthesis by subgroup

D f h	Subg up pli áv is	Tip d v iá l	P sí l m did d f it
Remission of type 2 diabetes	Intensive weight loss, metabolic surgery	Dichotomous	Relative risk or odds ratio
HbA1c reduction	Weight loss, metabolic surgery, incretins	Continuous	Mean difference or Standardized mean difference
Body weight reduction	Weight loss, metabolic surgery, incretins	Continuous	Mean difference
Fasting blood glucose	Weight loss, incretins, classical biomarkers	Continuous	Mean difference
HOMA-IR	Biomarkers, metabolic interventions	Continuous	Standardized mean difference
Estimated insulin sensitivity	QUICKI, Matsuda, TyG	Continuous or Correlational	Correlation, difference Mean or area under the curve
Cardiovascular events	SGLT2i and therapies Cardiometabolic	Dichotomous	Relative risk or hazard ratio
Medication reduction or discontinuation	Weight loss and metabolic surgery	Dichotomous	Relative risk or odds ratio

The synthesis of findings allowed for the identification that classical biomarkers remain useful for screening and initial classification of insulin resistance, but their ability to guide individualized therapeutic decisions is limited when used in isolation. On the other hand,

metabolomic biomarkers and molecular biomarkers offer greater potential for phenotypic refinement, especially to identify individuals at risk of progression to type 2 diabetes or with more aggressive metabolic profiles. However, these markers still require broader clinical validation before their routine incorporation into endocrinological practice.

In the therapeutic component, the results indicated that interventions with a greater impact on weight loss, metabolic function, and cardiometabolic risk are more relevant for precision endocrinology. Intensive weight loss demonstrated the potential for metabolic remission in selected subgroups [25-27]. Metabolic surgery showed a superior effect to conventional clinical treatment in individuals with obesity and type 2 diabetes [28,29]. Modern incretin therapies demonstrated a significant impact on body weight and glycemic control [30-32]. Empagliflozin reinforced the need to integrate cardiovascular risk into personalized therapeutic decision-making [33].

In an integrated manner, the results of this review indicate that precision endocrinology applied to Insulin resistance should be understood as a multidimensional strategy. This strategy involves identifying clinical phenotypes, selecting appropriate biomarkers, assessing cardiometabolic risk, and choosing interventions compatible with the patient's individual profile. Subgroup analysis has shown that different interventions respond to different metabolic profiles, reinforcing the need to overcome uniform therapeutic models and advance towards approaches based on phenotypic stratification, biomarkers, and individualized clinical response.

DISCUSSION

The findings of this systematic review with a subgroup meta-analysis approach reinforce that insulin resistance should be understood as a heterogeneous, dynamic, and multifactorial metabolic condition, whose clinical interpretation requires more than simply identifying hyperglycemia, hyperinsulinemia, or obesity. The analyzed literature demonstrates that precision endocrinology has advanced by proposing an integrated reading between clinical phenotype, laboratory biomarkers, metabolomic signatures, molecular markers, and response

individualized therapy. In this context, insulin resistance ceases to be merely a pathophysiological marker and begins to occupy a strategic position in risk stratification, prognostic definition, and the selection of personalized interventions [1-7].

One of the main results identified was the consolidation of precision medicine as an emerging axis in metabolic care. International consensuses reinforce that the personalized approach in diabetes and metabolic diseases should encompass prevention, diagnosis, treatment, and prognosis, considering biological, clinical, and environmental differences among individuals [1,2]. This paradigm is particularly relevant in insulin resistance, as patients with similar degrees of hyperglycemia may present distinct pathophysiological mechanisms, including a predominance of peripheral resistance, hepatic dysfunction, visceral adiposity, systemic inflammation, inadequate insulin secretion, or progressive beta-pancreatic failure. Thus, therapeutic individualization depends on the ability to identify these subphenotypes in a reproducible and clinically applicable manner.

The metabolic subclassification of type 2 diabetes represents an important advance in this direction. The study by Ahlqvist et al. demonstrated that adults with recently diagnosed diabetes can be grouped into subtypes with significant differences in insulin resistance, insulin deficiency, obesity, glycemic control, and risk of complications [5]. This perspective challenges the traditional model of classifying type 2 diabetes as a single, homogeneous entity. Instead, it suggests that insulin resistance should be interpreted within a phenotypic spectrum, in which different combinations of adiposity, beta-pancreatic function, age, laboratory markers, and cardiometabolic risk determine distinct clinical trajectories.

The systematic review by Misra et al. also supports this interpretation by demonstrating that subclassification models can offer clinical value in organizing metabolic profiles, although there are still challenges for their routine adoption [3]. Among these challenges are the need for external validation in different populations, standardization of classification criteria, incorporation of longitudinal data, and demonstration of real impact on clinical decisions. Therefore,

although subclassification represents a promising tool for precision endocrinology, its usefulness depends on its ability to improve concrete outcomes, such as glycemic control, complication prevention, metabolic remission, and reduction of cardiovascular events.

Another relevant point refers to the heterogeneity of therapeutic response. Analyzed studies indicate that clinical markers of insulin resistance may be associated with differentiated responses to certain drug classes [4,6,7]. This finding is essential for endocrinological practice, as it reinforces that therapeutic choice should not be guided exclusively by standardized algorithms based on glycated hemoglobin. Patients with a predominant phenotype of obesity and insulin resistance may benefit more intensely from interventions with an impact on weight loss and improvement of insulin sensitivity, while individuals with higher risk

cardiovascular or renal may require therapies with proven cardiometabolic benefit. Thus, personalized therapy must integrate glycemic control, body weight, visceral adiposity, cardiovascular risk, function

renal, lipid profile, tolerability, and individual probability of response.

The classic biomarkers

continue to play an important role in the assessment of insulin resistance, especially in studies

epidemiological and in clinical contexts where more complex methods are not available. HOMA-IR remains one of the most widely used indices due to its simplicity and applicability on a large scale [8,9]. QUICKI, the Matsuda index, and the TyG index broaden the assessment possibilities, allowing different ways to estimate insulin sensitivity or resistance from accessible variables [10-13]. However, the joint analysis of these studies reveals significant limitations. These indices do not fully capture the complexity of insulin resistance, are influenced by population and laboratory variables, and do not always have universally applicable cut-off points.

The TyG index deserves attention for its potential clinical applicability in lower complexity settings. By using only fasting triglycerides and glucose, it can be easily incorporated into care practice and population screening [12, 13]. This

This characteristic makes it especially relevant for healthcare systems with restricted access to insulin dosage or dynamic methods of metabolic assessment. However, its interpretation must consider that triglyceride levels can be influenced by diet, medication use, liver diseases, alcohol consumption, and other metabolic factors. Thus, the TyG should be understood as a useful surrogate marker, but not as an absolute equivalent of the hyperinsulinemic-euglycemic clamp.

The main limitation of classical biomarkers is their low capacity to discriminate underlying molecular mechanisms. Two individuals with high HOMA-IR, for example, may present distinct pathophysiologies: one may have a predominance of visceral adiposity and inflammation, while another may present muscular mitochondrial dysfunction, altered amino acid metabolism, or greater hepatic impairment. This limitation reinforces the need for integration between traditional markers and emerging biomarkers, especially in clinical prediction models aimed at precision medicine.

In this sense, the metabolomic studies included in this review demonstrate a substantial advance in the molecular understanding of insulin resistance. The association between branched-chain amino acids, obesity, and insulin resistance was recurrent in the analyzed studies [14,20,21]. The elevation of leucine, isoleucine, and valine may reflect alterations in amino acid catabolism, mitochondrial dysfunction, energy overload and impairment of metabolic oxidation. These markers may contribute to the identification of metabolically more vulnerable individuals, even before the development of manifest type 2 diabetes.

In addition to branched-chain amino acids, the broad metabolomic signatures identified in population and prospective studies demonstrate that metabolic alterations precede the clinical manifestation of the disease [15-18]. This is particularly relevant for precision endocrinology, as it allows shifting the focus from late treatment to early risk identification. Circulating metabolites associated with insulin resistance can function as signaling markers of subclinical metabolic dysfunction, allowing

preventive interventions before the establishment of persistent hyperglycemia or pancreatic beta-cell failure.

α-hydroxybutyrate also emerges as a biomarker relevant, especially due to its association with insulin resistance and glucose intolerance in non-diabetic individuals [19]. Its presence suggests that metabolic dysfunction can be detected in early stages, when reversibility is still more likely. This characteristic is fundamental for preventive and personalized medicine strategies, in which the goal is not only to treat established diabetes but to prevent or delay its progression.

MicroRNAs further expand the complexity of the discussion, as they act as post-transcriptional regulators of pathways involved in insulin sensitivity, inflammation, adipogenesis, and muscle metabolism [22,24]. Although their clinical application is still in its early stages, these markers have dual potential: they can be used both as diagnostic and prognostic biomarkers and as possible future therapeutic targets. However, the translation of microRNAs into clinical practice requires standardization of collection, processing, quantification, and interpretation methods, in addition to validation in large and diverse populations.

The analysis of therapeutic subgroups reinforces that treatment personalization should consider the predominant mechanism of metabolic dysfunction. In the intensive weight loss subgroup, studies derived from DiRECT demonstrated that structured weight reduction interventions can induce remission of type 2 diabetes, especially in patients with shorter disease duration and greater potential for functional recovery of beta cells [25-27]. This finding has great clinical relevance, as it shows that type 2 diabetes, in certain subgroups, can be partially reversible when the intervention effectively targets excess adiposity and metabolic overload.

The durability of remission, however, depends on maintaining weight loss over time [26,27]. This point is crucial for interpreting the subgroup meta-analysis, as the metabolic effects of behavioral interventions should not be evaluated only in the short term. Weight regain can compromise remission and reduce sustained metabolic benefit sustained. Therefore, strategies

customized must include longitudinal follow-up, support nutritional, monitoring behavioral and interventions adaptive for maintenance of results.

In the metabolic surgery subgroup, the analyzed studies demonstrate the superiority of surgical intervention compared to conventional or intensive clinical therapy in individuals with obesity and type 2 diabetes [28,29]. Metabolic surgery acts through multiple mechanisms, including significant weight loss, intestinal hormonal changes, improved insulin sensitivity, reduced lipotoxicity, and modulation of incretin secretion. However, its indication should be individualized, considering surgical risk, body mass index, duration of diabetes, beta-pancreatic reserve, comorbidities, adherence to follow-up, and patient preferences.

Metabolic surgery also illustrates a central principle of precision endocrinology: high-efficacy interventions are not necessarily universal, but can be extremely relevant when targeted to the appropriate profile. Patients with significant obesity, shorter-duration diabetes, and preserved beta-pancreatic function tend to have a higher probability of remission, while those with long-standing disease and advanced pancreatic failure may achieve metabolic improvement, but a lower chance of complete remission. Thus, biomarkers of beta-pancreatic function, insulin resistance, and visceral adiposity may be useful for selecting candidates with greater expected benefit.

Modern incretin therapies, represented mainly by semaglutide and tirzepatide, have demonstrated a significant impact on body weight and glycemic control [30-32]. These drugs hold a strategic position in contemporary endocrinology for acting simultaneously on satiety mechanisms, glucose-dependent insulin secretion, glycemic control, and weight reduction. Tirzepatide, in particular, by combining GIP/GLP-1 agonism, represents a therapeutic advance aligned with the concept of multi-target modulation of metabolic dysfunction [31,32].

The interpretation of these studies within a subgroup meta-analysis approach allows us to recognize that the

The efficacy of incretin therapies may vary according to the patient's phenotype. Individuals with obesity, greater visceral adiposity, inadequate glycemic control, and significant insulin resistance may experience substantial benefits. However, therapeutic response, tolerability, cost, availability, and adherence are factors that influence real-world effectiveness. Thus, personalization should consider not only pharmacological potency but also the patient's clinical and socioeconomic context.

Empagliflozin, included in the subgroup of cardiometabolic therapies, demonstrates that therapeutic personalization in diabetes should not be restricted to glycemic control or insulin resistance alone [33]. Patients with type 2 diabetes have an increased risk of events

cardiovascular and renal, and the therapeutic choice should consider target organ protection. In this way, SGLT2 inhibitors may be prioritized in individuals with high cardiovascular risk, heart failure, or chronic kidney disease, even when their direct effect on insulin resistance is not the

primary mechanism of benefit.

The organization of studies into subgroups revealed that a single global meta-analysis could generate methodologically fragile interpretations due to the heterogeneity of populations, interventions, and outcomes. Subgroup analysis, on the other hand, preserves clinical coherence and allows for the comparison of interventions within more homogeneous contexts. This design is particularly suitable for precision medicine themes, in which heterogeneity should not be treated merely as a statistical limitation, but as a central biological characteristic of the phenomenon under study.

The heterogeneity observed among the studies also points to a significant gap: many therapeutic trials still do not incorporate advanced biomarkers for the prior stratification of participants. Although metabolomics and molecular biomarker studies reveal promising signatures, there is still a gap between biomarker discovery and its application in interventional clinical trials. The future of precision endocrinology will require studies designed from the outset to test whether certain biomarker profiles better predict response to intensive weight loss, surgery

metabolic, incretin-based therapies, SGLT2 inhibitors, or therapeutic combinations.

Another critical point concerns applicability in different populations. Many biomarker studies and clinical trials have been conducted in specific populations, often with a predominance of certain ethnic groups, age ranges, or socioeconomic contexts. Since insulin resistance is influenced by genetics, environment, diet, healthcare access, body composition, and social determinants, the generalization of findings must be done with caution. The validation of biomarkers in diverse populations is essential to prevent precision medicine from widening inequalities rather than reducing them.

The integration between classical biomarkers and omics technologies appears to be the most promising path. In current clinical practice, indices such as HOMA-IR, TyG, QUICKI, and Matsuda can function as initial screening and stratification tools. In contexts of greater complexity or translational research, metabolomic signatures, microRNAs, and predictive models can refine the assessment and identify subgroups at higher risk or with a greater likelihood of therapeutic response. This integration may enable a tiered endocrinology, in which simple biomarkers are widely used and advanced tools are applied in situations of greater clinical need.

From a methodological standpoint, this review is relevant for proposing a framework compatible with the topic's complexity. The subgroup meta-analysis approach allows for separate analysis of biomarkers, behavioral interventions, metabolic surgery, incretin therapies, and cardiometabolic therapies. This organization prevents the inappropriate merging of heterogeneous studies and strengthens the interpretative validity of the results. Furthermore, the division into subgroups facilitates the identification of specific gaps, such as the need for more studies comparing biomarkers with each other, trials with metabolomic stratification, and therapeutic prediction analyses based on metabolic phenotypes.

However, some limitations must be considered. The first relates to the heterogeneity of the designs of the included studies, which ranged from consensus statements and systematic reviews to observational studies, analyses

metabolomic and randomized clinical trials. Although this diversity is consistent with the translational nature of precision endocrinology, it limits the possibility of uniform quantitative synthesis. The second limitation involves the variability of the analyzed outcomes, including laboratory markers, surrogate indices, diabetes remission, weight loss, cardiovascular events, and therapeutic response. The third limitation is related to the lack of universal standardization for insulin resistance biomarkers, especially in the case of surrogate indices and emerging omic markers.

It is also necessary to recognize that promising biomarkers do not always achieve immediate clinical relevance. The discovery of metabolomic or molecular associations does not, by itself, guarantee diagnostic or therapeutic applicability. For a biomarker to be incorporated into clinical practice, it needs to demonstrate analytical validity, clinical validity, clinical utility, reproducibility, cost-effectiveness, and the ability to modify therapeutic decisions. This is one of the main challenges for the translation of precision endocrinology.

Despite these limitations, the results of this review support that insulin resistance should be addressed through a multidimensional model. The combination of classical markers, biomarkers emerging, Phenotypic subclassification and therapeutic response analysis allows for a more precise view of metabolic dysfunction. This approach can favor early diagnosis, prevention of progression to type 2 diabetes, more rational therapeutic choice, individualized monitoring, and reduction of cardiometabolic complications.

Thus, the main contribution of this review is to demonstrate that precision endocrinology applied to insulin resistance is not just a technological trend, but a clinical necessity given the metabolic heterogeneity of patients. Subgroup analysis shows that different therapeutic strategies have greater or lesser relevance depending on the individual's clinical and biomarker profile. Intensive weight loss interventions, metabolic surgery, incretin therapies, and cardiometabolic therapies should be understood as complementary tools, whose ideal selection depends on the integration between

pathophysiology, risk, prognosis, and expected response.

In summary, the discussion of the findings confirms that the future of insulin resistance management will combine clinical accessibility and molecular sophistication. Simple indices such as HOMAIR and TyG will continue to be relevant for screening and monitoring, while biomarkers metabolomic,

microRNAs and predictive models may improve stratification in specialized contexts. The consolidation of this model will depend on prospective studies, clinical trials stratified by biomarkers and validation in diverse populations. In this way, precision endocrinology can advance from a conceptual promise to an effective clinical practice, capable of personalizing interventions and improving metabolic outcomes in individuals with insulin resistance.

CONCLUSION

This systematic review with a subgroup meta-analysis approach demonstrated that insulin resistance should be understood as a heterogeneous metabolic condition, multifactorial and progressive, whose evaluation requires integration between clinical parameters, laboratory biomarkers, metabolomic signatures, molecular markers, and individualized therapeutic response. The analyzed findings demonstrate that precision endocrinology represents a relevant advancement in the understanding and management of insulin resistance, by allowing patients with distinct metabolic phenotypes to be evaluated more specifically, surpassing traditional models based solely on broad diagnostic categories.

Classic biomarkers, such as HOMA-IR, HOMA-**β**, QUICKI, Matsuda index, and TyG index, remain useful tools for screening, epidemiological evaluation, and initial stratification of insulin resistance. However, their isolated use presents significant limitations, especially in the face of the pathophysiological complexity of metabolic dysfunction. In this sense, emerging biomarkers, such as branched-chain amino acids, **α**-hydroxybutyrate, signatures

metabolomic, acylcarnitines, and microRNAs, expand the possibility of early identification of individuals at risk, prognostic refinement, and the construction of more predictive models

aligned with the principles of precision medicine.

Subgroup analysis demonstrated that different therapeutic strategies have distinct relevance depending on the patient's clinical and metabolic profile. Intensive weight loss interventions showed potential to induce metabolic remission in selected subgroups, especially when associated with sustained weight loss maintenance. Metabolic surgery had a significant impact on individuals with obesity and type 2 diabetes, reinforcing its role in phenotypes with greater metabolic impairment. Modern incretin therapies, including GLP-1 agonists and dual GIP/GLP-1 agonists, demonstrated a relevant effect on body weight and glycemic control, while SGLT2 inhibitors reinforced the importance of considering cardiovascular and renal protection in therapeutic personalization.

The results also indicate that subgroup meta-analysis is methodologically more appropriate for this field, since the heterogeneity between studies, populations, biomarkers, interventions, and outcomes makes a single quantitative synthesis unfeasible without loss of coherence.

single quantitative without loss of coherence

clinic. Insulin resistance, in this context, should be analyzed as a spectrum of metabolic changes that may require different assessment and intervention strategies, depending on adiposity, beta-pancreatic function, cardiovascular risk, biochemical profile, and probability of therapeutic response.

Despite the observed advances, there are still significant gaps for the consolidation of precision endocrinology in clinical practice. Many emerging biomarkers still require external validation, methodological standardization, definition of cutoff points, cost-effectiveness evaluation, and proof of real clinical utility. Furthermore, future clinical trials should incorporate prior stratification by biomarkers and metabolic phenotypes, allowing the assessment of whether certain individual profiles predict better response to behavioral, pharmacological, surgical, or combined interventions.

Precision endocrinology applied to insulin resistance represents a promising and clinically necessary scientific frontier. The integration between classical biomarkers, omic technologies, metabolic subclassification, and personalized therapies can

favoring earlier diagnosis, prevention of progression to type 2 diabetes, more rational therapeutic selection, and reduction of complications cardiometabolic complications. Thus, the future of insulin resistance management should depend on integrated models, capable of combining clinical accessibility, scientific robustness, and evidence-based therapeutic personalization.

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