White Paper
The Valuable Role of Routine Metabolic Assessment in Optimizing GLP-1 Receptor Agonist Therapy

Short Summary

Routine measurement of metabolism, specifically Resting Metabolic Rate (RMR) and Respiratory Quotient (RQ/RER), offers critical benefits for patients on GLP-1 RA drugs:

- **Personalised Care:** RMR provides precise caloric needs, moving beyond inaccurate estimations, while RQ reveals the body's primary fuel source (carbohydrates vs. fats). This objective data enables highly tailored nutritional and exercise plans to optimize fat loss and preserve lean body mass.
- **Combating Metabolic Adaptation:** Weight loss often triggers a metabolic slowdown (metabolic adaptation), leading to plateaus. Routine RMR measurement detects this early, allowing proactive adjustments to diet and activity to overcome stalled progress and prevent weight regain.
- **Optimizing Body Composition:** GLP-1 RAs can lead to significant lean body mass (LBM) loss. Monitoring RMR (which correlates with LBM) and RQ (to guide protein intake and fat oxidation) helps preserve crucial muscle mass, ensuring healthier and more sustainable weight loss outcomes.
- **Enhanced Adherence and Outcomes:** Providing patients with objective data on their unique metabolic response fosters understanding, motivation, and adherence to their treatment plan, leading to better long-term success.

About Metabolic Health Solutions (MHS)

Metabolic Health Solutions (MHS) is an award winning, medical technology and digital health company, commercialising low cost, metabolic measurement technology. MHS is an ISO13485 company with CE, TGA, and HSA Certification for its lead technology ECAL. MHS is the only metabolic health company vertically integrated from R+D and Manufacturing, through to the delivery of clinical services. This provides unique insights for both patients and providers and supports the provision of effective personalised metabolic health. METS_IQ™, delivers these insights at scale to meet the global health pandemic of obesity and weight related metabolic health disorders, particularly monitoring and supporting the new GLP1-ra therapeutics and in Bariatric care.

Executive Summary

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have profoundly transformed the therapeutic landscape for type 2 diabetes mellitus (T2DM) and obesity. These agents demonstrate remarkable efficacy in weight reduction, with reported losses ranging from 4% to 15% for liraglutide and semaglutide, and even more substantial reductions, up to 24%, observed with newer dual and triple agonists.[1] Beyond their impact on body weight and glycemic control, GLP-1 RAs confer significant cardiometabolic advantages, including a reduced incidence of cardiovascular mortality, myocardial infarction, and stroke.[1] Their primary mechanisms of action involve appetite suppression, delayed gastric emptying, and enhanced glycemic regulation.[1]

Despite these considerable benefits, GLP-1 RA therapy introduces specific clinical challenges. A notable concern is the potential for disproportionate lean body mass (LBM) loss, which can account for 20% to 50% of total weight reduction, a higher proportion than typically observed with conventional diet and exercise interventions.[9] Furthermore, the physiological phenomenon of metabolic adaptation, characterized by a greater-than-expected decrease in resting metabolic rate (RMR) during weight loss, can impede sustained progress and contribute to weight regain.[11] These factors highlight the necessity for a more precise, individualized approach to patient management.

This report posits that the routine measurement of RMR and Respiratory Quotient (RQ) through indirect calorimetry provides invaluable objective data to personalize nutritional and exercise interventions. Such measurements enable proactive management of metabolic adaptation, optimization of substrate utilization, and mitigation of adverse body composition changes. Therefore, the integration of RMR and RQ measurements is advocated as an indispensable component of comprehensive GLP-1 RA patient care, designed to enhance treatment efficacy, ensure long-term weight maintenance, and improve overall metabolic health.

Introduction: The Evolving Landscape of GLP-1 RA Therapy and Metabolic Health

Brief Overview of GLP-1 RAs

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are a class of medications that mimic the actions of the natural incretin hormone, GLP-1. This hormone plays a crucial role in glucose homeostasis by enhancing glucose-dependent insulin secretion, suppressing glucagon release, delaying gastric emptying, and promoting a sense of fullness or satiety.[1] Originally developed for the management of type 2 diabetes mellitus (T2DM), their therapeutic utility has significantly expanded to include chronic weight management for individuals with overweight and obesity.[1] Clinical trials have consistently demonstrated impressive weight loss outcomes with these agents. For instance, liraglutide and semaglutide have shown weight reductions ranging from 4% to 15% of initial body weight.[1] Newer dual agonists, such as tirzepatide, have achieved even greater weight loss, approaching 20.9%, while triple agonists like retatrutide have demonstrated reductions of up to 24.2%.[4]

Beyond their primary effects on weight and glycemic control, GLP-1 RAs offer a spectrum of significant cardiometabolic benefits. These include improvements in blood pressure and lipid profiles, alongside a notable reduction in major adverse cardiovascular events (MACE).[1] The benefits extend to conditions such as metabolic dysfunction-associated steatotic liver disease (MASLD) by reducing hepatic fat accumulation, inflammation, and oxidative stress, and enhancing insulin sensitivity and lipid metabolism.[19] Emerging research also suggests their potential in neurodegenerative diseases like dementias and Parkinson's disease, mediated by effects such as reduced neuroinflammation and improved nerve growth.[1]

Emerging Challenges in GLP-1 RA Therapy

Despite their profound efficacy, GLP-1 RA therapy is associated with certain challenges that warrant careful consideration. Common adverse effects primarily involve the gastrointestinal system, including nausea, vomiting, diarrhea, and constipation, which can affect up to 50% of patients and often necessitate slow dose titration.[1] While rare, more serious risks such as pancreatitis and thyroid cancer have also been identified.[1]

A significant clinical concern revolves around body composition changes, specifically the potential for disproportionate lean body mass (LBM) loss during the rapid weight reduction induced by these medications.[9] Studies indicate that LBM loss can constitute between 20% and 50% of the total weight lost with GLP-1 RAs, a proportion that is notably

higher than that typically observed with traditional diet and exercise interventions.[9] While a meta-analysis suggested that LBM loss (approximately 28% of total weight loss) falls within the expected range for non-pharmacological weight loss interventions (10-30%) [22], the preservation of muscle mass remains critical for long-term metabolic health and preventing sarcopenia.[10] The substantial and often rapid weight reduction observed with GLP-1 RAs inherently results in the loss of both adipose tissue and lean body mass (LBM).[10] This phenomenon is a common physiological response to any significant caloric deficit and subsequent weight loss, regardless of the intervention method. While the absolute reduction in LBM is a consideration, studies indicate that GLP-1 RA therapy can lead to an improved proportion of lean mass relative to fat mass, contributing to a more advantageous body composition overall.[16] Nevertheless, the preservation of LBM is of paramount importance for several physiological reasons. Muscle tissue is metabolically active and significantly contributes to an individual's resting metabolic rate.[24] Consequently, a substantial loss of LBM can lead to a decrease in RMR, thereby complicating long-term weight management and increasing the propensity for weight regain.[16] Furthermore, maintaining adequate muscle mass is critical for preserving physical function, strength, and preventing conditions such as sarcopenia, particularly relevant in aging populations or those with pre-existing muscle fragility.[10] This underscores that the objective of weight management extends beyond mere reduction in body weight; the *composition* of weight loss, prioritizing fat reduction while minimizing LBM depletion, is essential for durable health benefits and sustainable outcomes.
Another significant challenge is the body's adaptive response to reduced caloric intake, known as metabolic adaptation. This phenomenon leads to a greater-than-expected decrease in RMR, potentially causing weight loss plateaus and making sustained weight loss more difficult.[11] This physiological defense mechanism poses a considerable barrier to achieving and maintaining weight loss. Additionally, there is significant inter-individual variability in the weight loss response to GLP-1 RAs, which cannot be fully attributed to pharmacological response alone.[25]

Thesis: The Critical Need for Routine RMR and RQ Assessment

Current clinical guidelines for GLP-1 RA therapy primarily focus on managing glycemic control and overall weight loss, with limited specific guidance on comprehensive nutritional interventions or the monitoring of metabolic rate and substrate utilization.[9]

This report asserts that routine, objective measurement of RMR and RQ is essential for developing a truly personalised and optimized GLP-1 RA treatment strategy. These measurements can provide actionable data regarding individual metabolic responses, enabling clinicians to tailor diet, exercise, and potentially medication regimens. Such precision can maximize fat loss, preserve lean mass, help overcome weight plateaus, and ultimately facilitate sustainable long-term health outcomes.

Fundamentals of Metabolic Assessment: RMR and RQ

To effectively manage metabolic health, particularly in the context of GLP-1 RA therapy, a clear understanding of key metabolic parameters is essential. Resting Metabolic Rate (RMR) and Respiratory Quotient (RQ) are two such critical measurements that provide objective insights into an individual's energy expenditure and substrate utilization.

Resting Metabolic Rate (RMR)

RMR represents the energy required to sustain fundamental bodily functions and maintain homeostasis in an awake individual under resting, thermoneutral conditions.[24] It is the most substantial component of total 24-hour energy expenditure, typically accounting for 60% to 70% of the total calories burned daily.[24] Consequently, RMR serves as a potential indicator of future weight regain or maintenance challenges.[28]

RMR is highly individualized and influenced by a multitude of factors. These include body size, the amount of lean muscle tissue (which demands more energy for maintenance compared to adipose tissue), the quantity of body fat, sex (males generally exhibit a faster RMR due to larger body size and greater lean muscle mass, often linked to higher testosterone levels), age (RMR tends to decrease with advancing age, primarily due to a natural loss of muscle mass), race or ethnicity, and genetic predispositions.[24]

Furthermore, RMR can fluctuate significantly as a result of weight changes, illness, and other physiological factors.[29] Clinically, an accurate RMR measurement is paramount for establishing precise daily caloric targets necessary for achieving weight loss, promoting weight gain, or maintaining a stable body weight.[29] The body can adapt to prolonged low-calorie diets by reducing its RMR, a phenomenon that can lead to stalled weight loss progress.[11]

Respiratory Quotient (RQ)

The Respiratory Quotient (RQ) is defined as the ratio of carbon dioxide exhaled to oxygen

consumed (VCO2/VO2) during respiration.[13] This ratio directly reflects the type of macronutrient (substrate) the body is primarily oxidizing for energy.[11] The interpretation of RQ values provides valuable metabolic information: an RQ of 1.0 indicates a predominant reliance on carbohydrate oxidation (e.g., glucose); an RQ of approximately 0.7 suggests the body is primarily burning fat; and an RQ near 0.8 points to predominant protein oxidation.[30] Values exceeding 1.0 may indicate organic acid oxidation, while an RQ of 0 suggests partial oxidation, often seen when CO2 produced during respiration is consumed by photosynthesis in plants.[31]

Clinically, RQ offers insights into metabolic flexibility, which is the body's capacity to efficiently switch between utilizing carbohydrates and fats for energy.[16] In individuals with obesity, the body may exhibit a diminished ability to effectively utilize fat as an energy source.[11] Monitoring RQ helps clinicians understand an individual's current fuel utilization patterns and guide dietary adjustments to promote a more favorable fat-burning metabolism.[11]

Measurement Gold Standard: Indirect Calorimetry

Indirect calorimetry (IC) stands as the recognized gold standard technique for the accurate assessment of both RMR and RQ.[28] This method precisely measures oxygen consumption and carbon dioxide production to derive an individual's energy expenditure and the specific substrates being oxidized.[28]

A significant limitation of relying on commonly used predictive equations (e.g., Harris-Benedict) for RMR is their inherent inaccuracy. These equations are based on population averages and can substantially overestimate an individual's actual RMR, sometimes by as much as 1000 kcal per day, leading to erroneous caloric targets and potentially ineffective weight management strategies.[24] This highlights the critical necessity of direct measurement for truly individualized patient care.

For accurate RMR measurement, specific pre-test conditions must be met. Patients should be at complete rest, mentally and physically calm, in an awake state after a period of sleep, and have fasted for 12 to 14 hours since their last meal. The testing environment should be at a comfortable, thermoneutral temperature.[24] Prior to the appointment, patients are typically instructed to avoid exercise, caffeine, smoking, and certain medications to ensure reliable results.[29]

Table 2: Key Metabolic Parameters and Their Measurement Methods

Parameter	Definition	Physiological Significance	Gold Standard Measurement Method	Limitations of Predictive Equations	Supporting References
Resting Metabolic Rate (RMR)	Energy required to sustain basic functions at rest.	Accounts for 60-70% of total daily energy expenditure; indicator of future weight (re)gain.	Indirect Calorimetry (e.g., ECAL, Quark, ParvoTrueOne)	Overestimates RMR (e.g., by 1000 kcal/day); based on population averages, not individual.	[11]
Respiratory Quotient (RQ)	Ratio of CO2 exhaled to O2 consumed.	Reflects primary substrate utilization (carbohydrate vs. fat vs. protein oxidation).	Indirect Calorimetry (calculated from IC measurements)	Not applicable; RQ requires gas exchange measurement.	[11]

GLP-1 RAs: Impact on Energy Metabolism and Body Composition

Weight Loss and Appetite Regulation

GLP-1 RAs primarily induce weight loss by influencing appetite and satiety mechanisms. These medications reduce feelings of hunger, increase fullness, and delay gastric emptying, leading to a significant reduction in overall caloric intake.[1] Their action extends to the central nervous system, where they affect hunger centres and dopaminergic reward pathways, which may diminish cravings for less healthy food options.[1] Clinical trials have consistently demonstrated substantial weight loss, with liraglutide and semaglutide leading to reductions between 4% and 15% of body weight.[1] Newer dual agonists, such as tirzepatide, have shown even greater efficacy, with average weight loss around 20.9%, and the triple agonist retatrutide demonstrating reductions of approximately 24.2%.[4]

Body Composition Changes

While GLP-1 RAs are highly effective in reducing fat mass, particularly visceral fat, which is associated with higher cardiometabolic risk [16], a significant consideration is the accompanying loss of lean body mass (LBM).[9] Research indicates that 20% to 50% of the total weight lost with GLP-1 RAs may be LBM, a proportion that is higher than typically observed with traditional diet and exercise interventions.[9] A meta-analysis reported that approximately 28% of weight loss from GLP-1 RAs was LBM.[22]

The substantial and often rapid weight reduction observed with GLP-1 RAs inherently results in the loss of both adipose tissue and LBM.[10] This phenomenon is a common physiological response to any significant caloric deficit and subsequent weight loss, regardless of the intervention method. While the absolute reduction in LBM is a consideration, studies indicate that GLP-1 RA therapy can lead to an improved proportion of lean mass relative to fat mass, contributing to a more advantageous body composition overall.[16] Nevertheless, the preservation of LBM is of paramount importance for several physiological reasons. Muscle tissue is metabolically active and significantly contributes to an individual's resting metabolic rate.[24] Consequently, a substantial loss of LBM can lead to a decrease in RMR, thereby complicating long-term weight management and increasing the propensity for weight regain.[16] Furthermore, maintaining adequate muscle mass is critical for preserving physical function, strength, and preventing conditions such as sarcopenia, particularly relevant in aging populations or those with pre-existing muscle fragility.[10] This underscores that the objective of weight management extends beyond mere reduction in body weight; the *composition* of weight loss, prioritizing fat reduction while minimizing LBM depletion, is essential for durable health benefits and sustainable outcomes.

Influence on RMR and Metabolic Adaptation

While some preclinical studies suggest that GLP-1 RAs might increase energy expenditure [1], human studies involving single-agonist GLP-1 RAs (e.g., exenatide, liraglutide, semaglutide) generally indicate that weight loss is predominantly driven by reduced food intake, with no significant increase or even a decrease in resting energy expenditure.[8] Weight loss, irrespective of the method employed, typically triggers a physiological defence mechanism known as metabolic adaptation. This involves a decrease in RMR that is greater than what would be predicted solely by the changes in body composition.[12] This adaptive response presents a significant challenge to further weight loss and contributes

to the common issue of weight regain.[11]
However, novel dual GLP-1/glucagon receptor agonists (e.g., SAR425899, tirzepatide) show promise in attenuating this metabolic adaptation.[12] For example, studies with SAR425899 demonstrated a smaller reduction in body composition-adjusted sleeping metabolic rate (SMR) compared to placebo, even with greater overall weight loss, alongside increased fat oxidation.[12] This suggests that while weight loss generally leads to a metabolic slowdown, these dual agonists may offer a unique advantage by counteracting this adaptive response. The ability to mitigate metabolic adaptation could make weight loss more efficient and potentially more sustainable. Consequently, monitoring RMR becomes crucial to assess whether this beneficial attenuation of metabolic adaptation is occurring in individual patients, providing objective evidence of the drug's unique mechanism beyond appetite suppression.

Effects on Substrate Oxidation (RQ)
Research indicates that GLP-1 RAs, particularly dual agonists like tirzepatide, may preferentially promote fat oxidation.[13] A study involving tirzepatide reported a decrease in RQ, which signifies a shift towards greater fat utilization as the primary energy source.[13] The Respiratory Quotient (RQ) directly indicates the body's primary fuel source, distinguishing between carbohydrate and fat utilization.[11] Improved metabolic flexibility, defined as the body's capacity to efficiently switch between burning carbohydrates and fats for energy, is a key factor in long-term metabolic health.[16] GLP-1 therapy may enhance this flexibility by improving insulin sensitivity and promoting the utilization of stored fat as an energy source.[16] A decrease in RQ, moving closer to 0.7, directly signifies this beneficial shift towards increased fat oxidation.[13] Given that some GLP-1 RAs, such as tirzepatide, have been observed to decrease RQ, indicating increased fat oxidation [13], routine RQ measurement can confirm this desired metabolic shift in individual patients. This allows for precise fine-tuning of dietary recommendations, such as adjusting macronutrient ratios, to complement the drug's mechanism of action, potentially leading to more effective fat loss, especially in individuals who historically struggle to utilize fat as an energy source.[11]

The Argument for Routine RMR and RQ Measurement in GLP-1 RA Patients
The integration of routine RMR and RQ measurements into the clinical management of patients on GLP-1 RA therapy offers a robust, data-driven approach to optimize treatment

outcomes. These measurements provide granular, objective metabolic information that transcends the limitations of generalized guidelines and predictive models.

Personalised Nutritional and Exercise Prescriptions

Accurate RMR measurement provides the precise caloric needs for an individual at rest, moving beyond the inherent inaccuracies of predictive equations, which can lead to errors of up to 1000 kcal per day.[29] This objective data allows for the calculation of an accurate daily calorie target, essential for guiding weight loss, maintenance, or even gain.[29] Concurrently, RQ measurement provides real-time data on substrate utilization, indicating whether the body is primarily burning carbohydrates, fats, or proteins.[11] This information is critical for tailoring macronutrient intake, particularly protein, to preserve lean mass during significant weight loss.[4] For instance, if RQ is high, indicating a strong reliance on carbohydrate oxidation, dietary adjustments can be made to encourage a shift towards greater fat oxidation.[11] The data derived from RMR and RQ can also inform highly personalised exercise plans.[11] Resistance training is a well-established strategy to help preserve lean mass during weight loss.[4] Understanding a patient's metabolic profile can guide the intensity and type of physical activity to optimize fat burning and muscle retention.

GLP-1 RAs significantly reduce food intake, which can lead to a hypothesized prevalence of nutrient deficiencies.[9] Patient-centered nutritional guidance, informed by precise metabolic data, is therefore essential to optimize health outcomes and prevent unintended consequences.[9] A significant gap exists in current clinical practice, as there are limited specific Dietary Reference Intakes (DRIs) or medical nutrition therapy (MNT) guidelines tailored for individuals on GLP-1 RAs.[9] Routine RMR and RQ measurement provides objective data to bridge this gap, enabling clinicians to develop highly individualized MNT protocols, similar to the comprehensive guidance provided to bariatric surgery patients.[9] This objective metabolic data is precisely what is needed to create truly tailored nutritional interventions, allowing for precise calorie targets and macronutrient adjustments (e.g., ensuring adequate protein intake to combat LBM loss), moving beyond generic advice. This directly addresses the need for improved nutrition education and knowledge in this patient population.[9]

Proactive Management of Metabolic Adaptation and Weight Plateaus

As individuals lose weight, their RMR frequently decreases more than anticipated, a

phenomenon known as metabolic adaptation, which often leads to frustrating weight loss plateaus.[11] Routine RMR measurement can precisely detect this metabolic slowdown, enabling clinicians to make timely and appropriate adjustments to caloric intake or physical activity levels.[11] By understanding the dynamic changes in an individual's RMR, healthcare professionals can proactively modify diet and exercise plans to overcome plateaus and prevent weight regain.[11] This is particularly pertinent given the reported high rate of weight regain if GLP-1 RA therapy is discontinued.[10]

Relying on predictive equations for RMR is inherently prone to significant errors, leading to what can be termed "weight mismanagement" due to inaccurate caloric targets.[34] Direct measurement through indirect calorimetry eliminates this guesswork, providing precise and reliable data.[29] For patients on dual GLP-1/glucagon agonists, routine RMR measurement can objectively confirm if the expected attenuation of metabolic adaptation is occurring.[12] This provides tangible evidence of the drug's unique benefit beyond appetite suppression, guiding further therapeutic decisions and ensuring the patient is responding as anticipated. By accurately tracking RMR, clinicians can detect metabolic adaptation early, allowing for timely and precise adjustments to caloric intake and activity. This shifts the approach from reactive, trial-and-error management to a proactive, data-driven strategy, which is essential for navigating the complex physiological response of metabolic adaptation.

Optimizing Substrate Utilization

RQ measurement provides a direct indication of the body's fuel preference, distinguishing between carbohydrate and fat oxidation.[11] A lower RQ, closer to 0.7, signifies increased fat oxidation, which is a desirable metabolic state for effective fat loss.[11] If a patient's RQ indicates a persistent high reliance on carbohydrates, even while on GLP-1 RA therapy, this objective data can prompt specific dietary modifications, such as adjusting the carbohydrate-to-fat ratio, to encourage a metabolic shift towards greater fat burning.[11] GLP-1 therapy has been shown to improve metabolic flexibility by enhancing insulin sensitivity and promoting the utilization of stored fat as an energy source.[16] RQ serves as a direct, measurable indicator of this metabolic flexibility. Given that some GLP-1 RAs, such as tirzepatide, have been observed to decrease RQ, indicating increased fat oxidation [13], routine RQ measurement can confirm this desired metabolic shift in individual patients. This allows for the fine-tuning of diet to complement the drug's specific mechanism of action, potentially leading to more effective and targeted fat loss.

Monitoring RQ allows clinicians to verify if an individual patient is indeed shifting towards greater fat oxidation. If this shift is suboptimal, dietary and exercise interventions can be precisely adjusted to encourage this metabolic state, moving beyond assuming the drug's effect to confirming and optimizing it in the individual.

Mitigating Adverse Body Composition Changes

As previously discussed, GLP-1 RAs can lead to significant LBM loss, a concern for long-term health and metabolic function.[9] RMR is highly correlated with LBM, as muscle tissue is metabolically active.[24] A disproportionate drop in RMR relative to total weight loss could serve as an early warning sign of excessive LBM loss.

Monitoring RMR and RQ, in conjunction with direct body composition analysis (e.g., using devices like InBody 570 or DXA/DEXA, which have been employed in studies [6]), can guide targeted strategies to preserve LBM. These strategies include increasing protein intake, which has been shown to help retain lean mass during weight loss, [4] and implementing resistance training programs.[4] While body composition scans directly measure LBM, RMR provides a functional metabolic indicator of LBM health. If RMR drops more than expected for the fat loss achieved, it signals a potential for excessive LBM loss. RQ, in turn, can guide dietary protein adjustments to support muscle preservation. This allows for a data-driven approach to implementing LBM-preserving strategies, ensuring that the weight lost is predominantly fat, leading to healthier and more sustainable outcomes. Furthermore, rapid fat depletion, including facial fat pads, can lead to cosmetic concerns often termed "Ozempic face".[10] While primarily a consequence of fat loss, ensuring overall healthy body composition changes, guided by RMR and RQ, can contribute to a more balanced and sustainable outcome, potentially mitigating such undesirable effects.

Enhancing Patient Adherence and Outcomes

Providing patients with objective data on their RMR and RQ can significantly enhance their understanding of their unique metabolism and how their body is responding to therapy.[11] This concrete, individualized feedback can be highly motivating, fostering a greater sense of control and improving adherence to prescribed diet and exercise plans.[34] Regular monitoring allows for timely adjustments to the treatment plan, ensuring it remains optimized for the individual's evolving metabolic state.[5]

There is significant inter-individual variability in the weight loss response to GLP-1 RAs.[25] RMR and RQ measurements offer a powerful tool to understand and manage this

variability. When patients observe objective evidence of their metabolism changing—for instance, RMR stabilizing or even improving due to preserved LBM, or RQ shifting towards greater fat oxidation—it validates their efforts and reinforces adherence. This transforms the patient-provider dynamic into a more collaborative, data-informed partnership. This objective feedback can significantly boost motivation and adherence, leading to better long-term outcomes and potentially informing adjustments to medication (e.g., dosage titration based on metabolic response [5]).

Predicting and Refining Treatment Response

RMR and RQ, as integral components of a comprehensive metabolic phenotyping approach, can provide deeper insights into an individual's unique metabolic profile and their specific response to GLP-1 RA therapy.[13] This detailed metabolic understanding can aid in predicting who might be a better responder to therapy or identify those at higher risk for specific metabolic challenges, such as excessive LBM loss or pronounced metabolic adaptation.

RMR and total energy expenditure (TEE) are integrated into quantitative systems pharmacology (QSP) models, such as the Hall body composition model, to quantify and predict the effects of GLP-1 RAs on body weight changes, fat mass, and fat-free mass over time.[35] This mechanistic understanding can support drug development and optimize existing treatment strategies.[35] The ultimate goal extends beyond mere weight reduction to optimizing overall metabolic health, which RMR and RQ directly assess.[16] Combining RMR and RQ data with other patient-specific information, such as genetic polymorphisms [19], moves the practice of obesity management towards precision medicine. This allows for a more targeted selection of GLP-1 RA type, dosage, and adjunctive therapies (e.g., dual/triple agonists [2]), based on an individual's unique metabolic signature, rather than a one-size-fits-all approach. This enables clinicians to anticipate challenges like metabolic adaptation or disproportionate LBM loss and proactively adjust therapy, leading to more predictable and optimized outcomes for each patient.

Table 1: Clinical Utility of RMR and RQ in GLP-1 RA Therapy

Clinical Challenge/Goal in GLP-1 RA Therapy	How RMR Measurement Helps	How RQ Measurement Helps	Supporting References
Lean Body Mass Preservation	Identifies disproportionate RMR drop (signalling LBM loss).	Guides macronutrient adjustments to favour fat burning and protein intake.	9
Managing Metabolic Adaptation/Weight Plateaus	Detects metabolic slowdown/adaptation.	Not directly applicable but complements RMR data for overall metabolic picture.	11
Optimizing Substrate Utilization (Fat Oxidation)	Indirectly supports by informing overall energy balance.	Confirms shift towards fat oxidation; assesses metabolic flexibility.	11
Personalised Caloric and Macronutrient Prescription	Provides precise daily calorie target.	Informs dietary strategies to complement drug effects and optimize macronutrient ratios.	9
Enhancing Patient Adherence & Education	Offers objective feedback on metabolic changes.	Offers objective feedback on metabolic changes.	5
Predicting & Refining Treatment Response	Contributes to metabolic phenotyping for individualized response.	Contributes to metabolic phenotyping for individualized response.	13

Clinical Implementation and Future Directions

Practical Considerations for Integrating Indirect Calorimetry

The practical integration of indirect calorimetry into routine clinical practice for GLP-1 RA patients is feasible. Regulated clinical devices such as ECAL and Breezing Med , are available and capable of accurately measuring RMR and RQ within a short, typically 5 - 10-minute, test duration.[11] Adherence to standardized pre-testing instructions, including fasting and avoidance of exercise, caffeine, smoking, and certain medications, is crucial to ensure the accuracy and reliability of the results.[29] While there may be initial costs associated with acquiring these devices and the disposable components [5], the long-term benefits of optimized treatment, reduced complications, and improved patient outcomes may ultimately justify and outweigh these investments. Widespread adoption, however, necessitates increased accessibility of IC devices and comprehensive training for healthcare professionals on their proper use and interpretation.

The Role of a Multidisciplinary Team

Optimal GLP-1 RA therapy requires a multifaceted approach that extends beyond mere pharmacological intervention.[9] A collaborative multidisciplinary team is crucial for comprehensive patient care. This team should ideally include endocrinologists, bariatric physicians, registered dietitians (RDNs), exercise physiologists, and potentially mental health professionals.[6] RDNs, in particular, play a vital role in providing patient-centered nutritional guidance, especially given the current gaps in specific dietary recommendations for GLP-1 RA users.[9]

Current clinical management of cardiometabolic diseases is often fragmented across multiple specialties, leading to suboptimal outcomes, redundant diagnostic tests, and potentially conflicting medical advice.[39] Routine RMR and RQ measurement can serve as a central data point for an integrated care model, unifying the efforts of various specialists. This objective metabolic data provides a common language and framework for tailoring interventions across diet, exercise, and medication, fostering better collaboration and holistic patient management.[9] The objective, quantifiable metabolic data provided by RMR and RQ can be readily understood and utilized by all members of the multidisciplinary team, from physicians to RDNs and exercise physiologists. This shared metabolic "snapshot" allows for coherent, coordinated adjustments to treatment plans (diet, exercise, medication dosage), preventing conflicting advice and optimizing patient outcomes. This shifts the approach from a siloed practice to a truly collaborative one, with metabolic data serving as the unifying thread.

Current Gaps in Clinical Guidelines and the Need for Updated Recommendations

Despite the increasing popularity and proven efficacy of GLP-1 RAs, there remains limited evidence and a notable absence of specific Dietary Reference Intakes (DRIs) or MyPlate guidance for low-calorie diets or medical weight loss specifically tailored for this patient population.[9] Existing clinical guidance often focuses primarily on managing gastrointestinal side effects, with general nutrition recommendations based on broader weight loss literature rather than GLP-1 RA-specific metabolic considerations.[9] There is a clear and growing call for more integrated care plans that combine GLP-1 RAs with targeted diet and lifestyle modifications to enhance patient outcomes.[9]

Clinical guidelines are currently lagging behind the rapid advancements in GLP-1 RA therapy, particularly concerning comprehensive metabolic monitoring. The observed metabolic changes, such as LBM loss, metabolic adaptation, and shifts in RQ, necessitate the development of new, specific clinical guidelines that incorporate routine RMR and RQ measurement. These updated guidelines should provide clear protocols for interpreting results and translating them into actionable, personalised interventions. This proactive approach would ensure optimal long-term health outcomes and help prevent potential adverse effects, elevating the standard of care for GLP-1 RA patients.

Call for Further Research

To further refine GLP-1 RA therapy, several areas warrant additional robust research. More large-scale studies are needed to assess the replicability of findings regarding nutrient intake and long-term deficiencies in GLP-1 RA users.[9] Further investigation into the long-term effects of GLP-1 RAs on RMR specifically, and the potential for "resetting" the body's weight regulation system, is crucial.[16] Research on the predictive value of RMR and RQ in determining individual weight loss response and optimizing GLP-1 RA dosing and combination therapies is also critical.[25] Studies examining the synergistic effects of exercise, particularly resistance training, in conjunction with GLP-1 RA therapy and automated insulin delivery (AID) systems, are also needed.[27]

Despite extensive research, significant gaps remain in understanding the long-term metabolic adaptations and precise nutritional needs of GLP-1 RA patients. Future research should prioritize how RMR and RQ can be utilized not only to optimize current GLP-1 RA therapies but also to inform the development of next-generation weight loss agents. These future agents should specifically target metabolic adaptation and fat oxidation while preserving lean mass.[12] This research will be pivotal for advancing precision

medicine in obesity, leading to a more complete understanding of GLP-1 RA effects and enabling the creation of truly evidence-based, comprehensive, and sustainable treatment protocols.

Conclusion

The profound efficacy of GLP-1 RAs in weight management and cardiometabolic health is undeniable, marking a significant advancement in therapeutic options. However, their optimal utilization demands a nuanced understanding of individual metabolic responses. This report argues that the routine measurement of Resting Metabolic Rate (RMR) and Respiratory Quotient (RQ) via indirect calorimetry is not merely supplementary but an indispensable component of comprehensive, personalised GLP-1 RA patient care.
By providing objective, actionable metabolic data, RMR and RQ measurements empower clinicians to precisely tailor nutritional and exercise interventions. This precision enables proactive management of metabolic adaptation and weight plateaus, optimizes substrate utilization for maximal fat loss, and critically, helps mitigate the concerning loss of lean body mass. This data-driven approach fosters enhanced patient adherence, refines treatment efficacy, and ultimately paves the way for more sustainable weight management and superior long-term metabolic health outcomes for individuals undergoing GLP-1 RA therapy.

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