Perspectum

WHITEPAPER

Imaging Metabolic Inflammation in Obesity:

Unlocking Multi-Organ Endpoints for Cardiometabolic Drug Development

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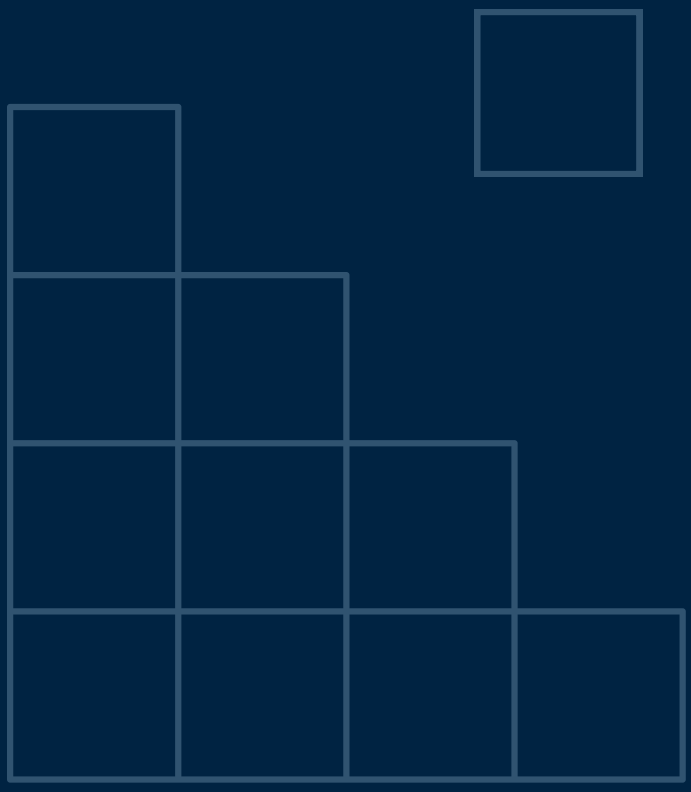

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Clinical obesity is a chronic, systemic illness characterised by alterations in the function of tissues, *organs*...

— The Lancet Diabetes & Endocrinology Commission on Clinical Obesity

Executive Summary

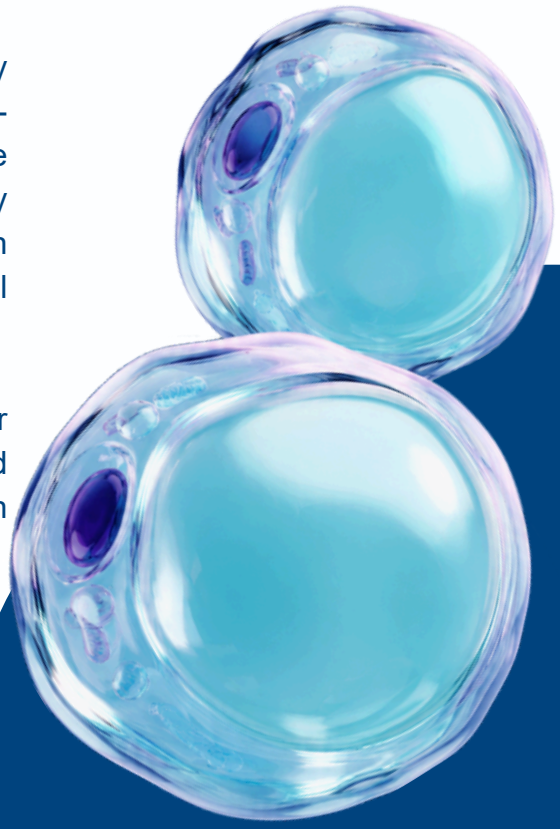
Organ-level imaging endpoints are redefining obesity clinical trials, enabling sponsors to measure metabolic inflammation, demonstrate disease modification, and differentiate therapies beyond weight loss.

Obesity is now recognised as a chronic, systemic inflammatory disease that affects the liver, heart, kidneys, pancreas, and skeletal muscle. Yet many development programmes still rely on endpoints that do not capture organ-level inflammatory activity and fail to reflect the biological processes driving disease progression and therapeutic response.

The obesity drug development landscape is rapidly expanding beyond weight management into a multi-indication cardiometabolic ecosystem. As sponsors pursue label expansion in a market projected to reach $95B by 2030, the ability to demonstrate organ-level effects on metabolic inflammation is becoming a meaningful differentiator in both regulatory and commercial strategy.

Multiparametric MRI-derived inflammatory biomarkers offer reproducible, organ-specific measures of tissue injury and dysfunction. These biomarkers can enable earlier detection of therapeutic effect, improve risk stratification, and generate stronger evidence of disease modification.

Perspectum's multi-organ imaging platform brings these biomarkers into clinical trials at scale, enabling robust assessment of organ-level therapeutic effects and supporting more efficient development, regulatory positioning, and lifecycle strategy across expanding cardiometabolic indications.



1. Obesity as a Multi-Organ Inflammatory Disease: The Commercial Opportunity

The obesity therapeutic landscape is rapidly evolving beyond weight management toward a broader cardiometabolic disease modification paradigm encompassing type 2 diabetes (T2D), chronic kidney disease (CKD), dysfunction–associated steatohepatitis (MASH), heart failure with preserved ejection fraction (HFpEF), and cardiovascular outcomes. This shift reflects growing recognition that **obesity is fundamentally a chronic, systemic inflammatory disease** rather than simply a disorder defined solely by excess body weight.

Anti-obesity therapies alone are projected to reach approximately **$95B1 by 2030**

As incretin-based therapies expand into multiple cardiometabolic indications, the commercial opportunity has grown substantially. Anti-obesity therapies alone are projected to reach approximately $95B [1]by 2030, with the broader cardiometabolic market expected to expand further as therapies move into cardiovascular, renal, and liver indications. Increasingly, the value of therapeutic assets is determined by not only their ability to reduce body weight, but by their capacity to demonstrate tissue remodelling, organ-level disease modification, and improved clinical outcomes across multiple systems (Figure 1).

This shift is changing clinical development strategy, sponsors now require evidence that therapies influence the biological processes driving disease progression, including inflammatory activity, ectopic fat deposition, fibrosis, and organ dysfunction. In parallel regulatory pathways are increasingly supporting earlier approval based on intermediate or surrogate endpoints, increasing the importance of

demonstrating mechanistic and tissue-level effects prior to clinical outcomes occurring. As a result, organ-level biomarkers are becoming increasingly important for differentiation, lifecycle expansion, and regulatory positioning in obesity and metabolic disease programs.

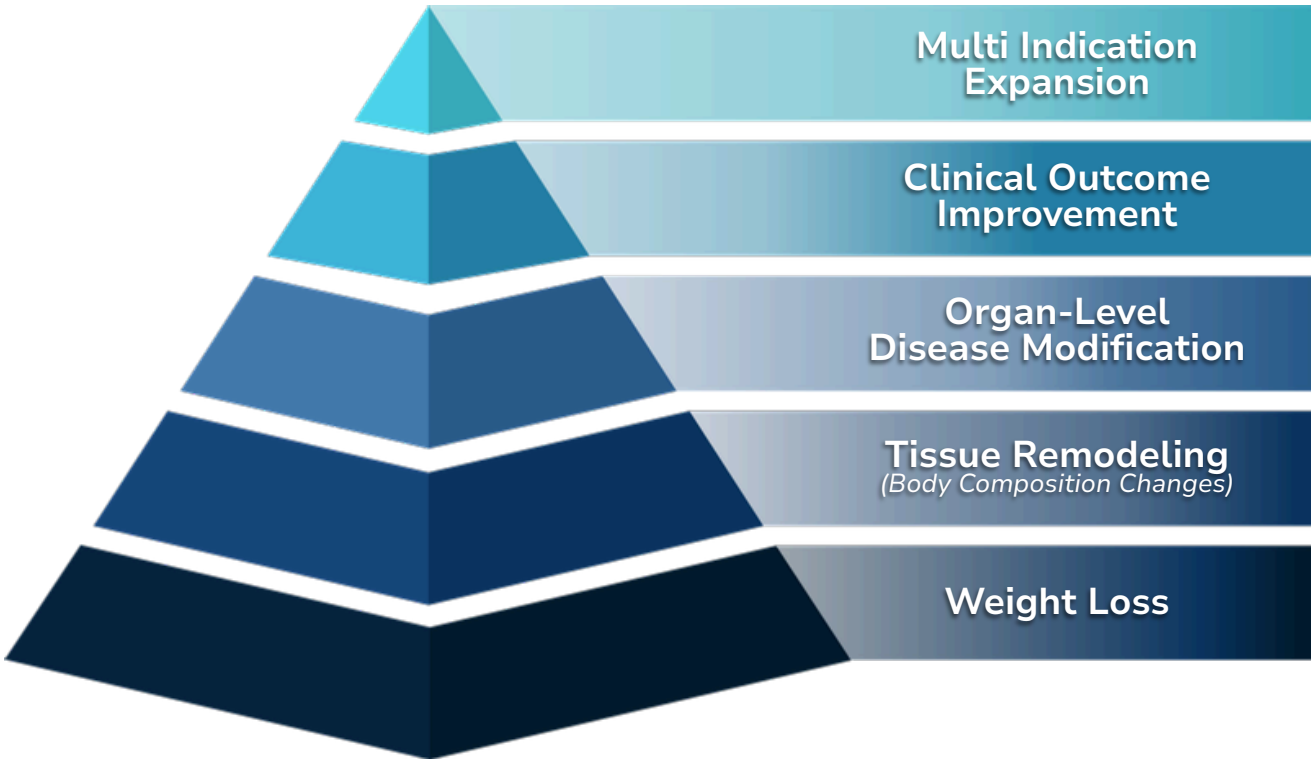


Figure 1: Hierarchy of therapeutic value in obesity drug development. Conceptual framework showing the progression from weight loss to tissue remodelling, organ-level disease modification, clinical outcome improvement, and ultimately multi-indication expansion across cardiometabolic diseases.

1.1 Metabolic Inflammation as the Driver of Organ Dysfunction

Obesity is increasingly understood as a state of chronic, low-grade metabolic inflammation arising through converging pathways including adipocyte hypertrophy, lipotoxicity, hypoxia, innate immune activation, and dysregulated inflammatory signalling. Mechanisms involving the NLRP3 inflammasome activation, toll-like receptor signalling, and altered nuclear receptor pathways such as PPAR and THR-β contribute to persistent inflammatory activity and progressive organ dysfunction.

Importantly, not all obesity carries the same metabolic risk. Individuals with similar BMI may exhibit different patterns of visceral adiposity, ectopic fat deposition, inflammatory burden, and organ injury, resulting in different cardiometabolic disease trajectories. Circulating inflammatory markers such as C-reactive protein, TNF-α, and IL-6 vary among individuals with similar adiposity, indicating that inflammatory profile, rather than body weight alone is a key determinant of metabolic health[6] (Figure 2).

This biological heterogeneity has important implications for therapeutic development. Weight reduction does not necessarily reflect resolution of inflammatory disease activity, and some therapies may produce meaningful organ-level benefit independent of substantial weight change. As a result, conventional endpoints centred on body weight provide an incomplete assessment of therapeutic response and disease modification.

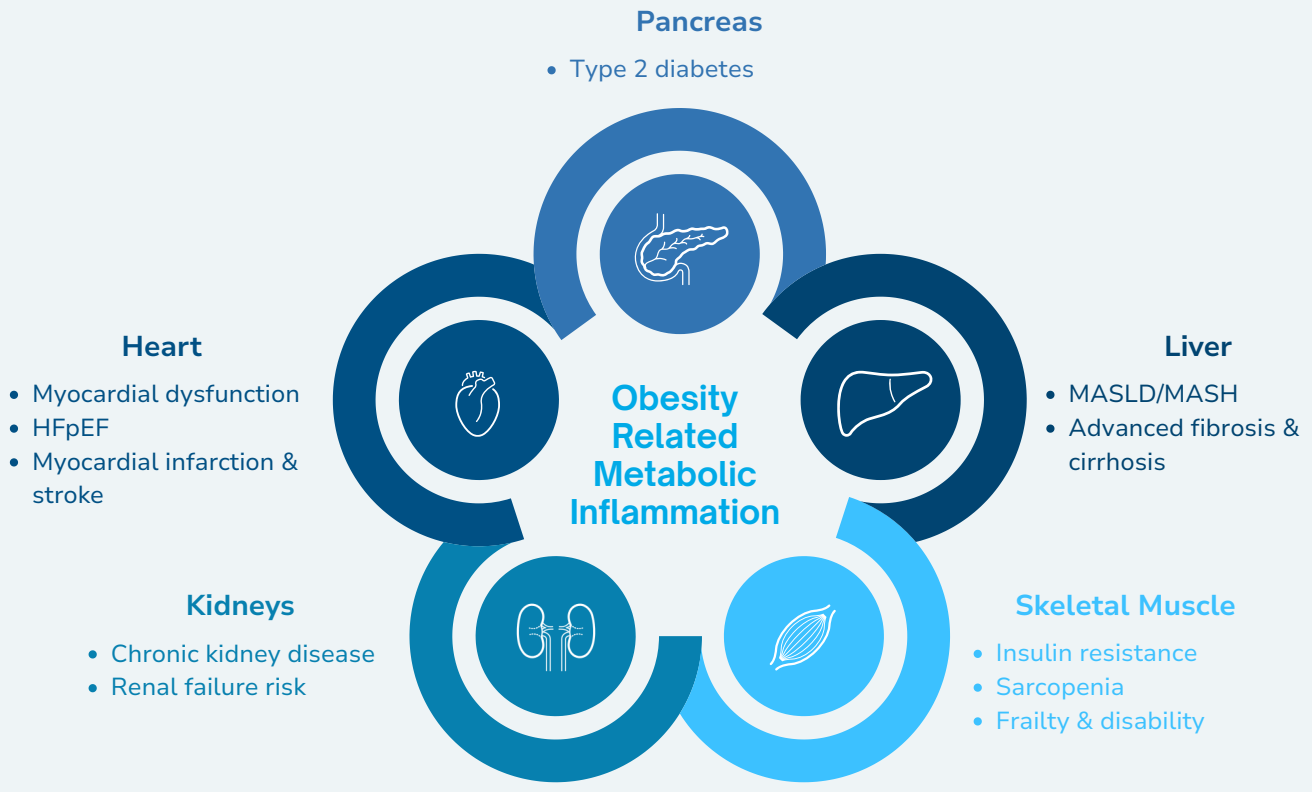


Figure 2. Multi-organ impact of metabolic inflammation in obesity. Obesity-related metabolic inflammation contributes to progressive dysfunction of the liver, heart, kidneys, pancreas, and skeletal muscle, driving MASLD/MASH, cardiovascular disease, chronic kidney disease, type 2 diabetes, and sarcopenia.

1.2 Multi-Organ Consequences of Metabolic Inflammation

Metabolic inflammation is systemic and drives dysfunction throughout the cardiometabolic system.

MRI-derived biomarkers of inflammation can therefore help distinguish individuals with relatively preserved metabolic health from those with high-risk obesity by directly assessing whole-body and organ-specific impairment.

For example, a recent multi-organ MRI study of adults with type 2 diabetes, demonstrated that nearly 90% of study participants living with overweight or obesity showed substantial steatosis and inflammation in the liver, pancreas, and kidneys,7 illustrating the systemic nature of metabolic disease.

In the liver, chronic inflammatory injury promotes progression from simple steatosis to metabolic dysfunction–associated steatohepatitis (MASH), to advanced fibrosis, increasing the risk of cirrhosis, liver failure, and liver-related mortality. In the heart, obesity-related metabolic and inflammatory stress contribute to myocardial fibrosis, vascular dysfunction, and HFpEF, now the dominant type of heart failure in people living with obesity. The adipokine hypothesis proposes that in obesity epicardial adipose tissue shifts from a protective energy depot to a pro-inflammatory phenotype, that directly contributes myocardial dysfunction.8

Similar inflammatory processes affect the kidneys and pancreas. Where metabolic stress contributes to CKD progression, albuminuria, declining renal function, beta cell dysfunction, and worsening glycaemic control. Skeletal muscle is also increasingly recognized as an important site of metabolic injury. Inflammation and myosteatosis, characterized by pathological fat infiltration within muscle tissue, contribute to insulin resistance, sarcopenia, frailty, and progressive decline in physical function.9

Together, these findings demonstrate that obesity-related metabolic dysfunction is fundamentally a multi-organ disease process. Therefore, demonstrating a therapy's ability to improve inflammatory activity and organ health across multiple systems is likely to be increasingly important for clinical differentiation, regulatory strategy, and label expansion across multiple indications.

1.3 Implications for Drug Development in Obesity

The growing recognition of obesity as a heterogeneous, multi-organ inflammatory disease has important implications for therapeutic development and clinical trial design. As therapies increasingly target tissue remodelling, inflammatory signalling, and organ protection, conventional endpoints centred on body weight and BMI may not fully capture all biologically meaningful treatment effects.

Importantly, therapies with similar effects on weight loss may also produce substantially different effects on inflammatory activity, organ injury, and long-term cardiometabolic risk. Conversely, some mechanisms may improve organ health independently of major changes in body weight. This creates a growing need for development strategies which prioritize the characterization of organ-level disease activity and therapeutic response more directly.

2. From Weight Loss to Disease Modification: Rethinking Endpoints in Obesity Drug Development

The rapid expansion of obesity therapeutics into broader cardiometabolic indications is fundamentally changing how therapeutic benefit is defined in clinical development.

Historically, obesity drug development has focused primarily on weight reduction and late-stage clinical outcomes. However, emerging therapies increasingly target inflammatory signalling, tissue remodelling, and organ protection before irreversible damage occurs.

This shift reflects growing recognition that obesity-related morbidity is driven not only by excess adiposity, but by downstream inflammatory and metabolic consequences which impact multiple organs simultaneously. The implications for clinical development are substantial. Therapeutic differentiation increasingly depends on demonstrating improvement across organ systems, particularly as Sponsor pursue expansion into MASH, HFpEF, CKD, and other cardiometabolic indications. This has resulted in increased interest in biomarkers capable of capturing inflammatory activity, tissue remodelling, and organ-specific therapeutic response earlier and more directly than conventional endpoints alone.

2.1 Anti-Inflammatory and Organ Directed Therapeutic Strategies

Modern obesity therapeutics increasingly extend beyond appetite suppression and weight reduction toward mechanisms targeting inflammatory and tissue-level disease biology. Incretin-based therapies have already demonstrated substantial improvements in weight, glycaemic control, cardiovascular outcomes, and liver disease activity, supporting the concept that obesity therapies can modify broader cardiometabolic risk.

Semaglutide 2.4 mg demonstrated mean weight reductions of 15–17% in large clinical trials10, while tirzepatide 15 mg achieved approximately 21% weight reduction.11 Importantly, recent evidence demonstrates that the therapeutic effect of these agents extends beyond adiposity reduction alone. In the phase 3 ESSENCE trial, semaglutide demonstrated improvements in MASH-related liver inflammation and fibrosis, supporting accelerated approval in this indication 12. Similarly, tirzepatide reduced cardiovascular death and worsening heart failure events in individuals with obesity-related HFpEF in the SUMMIT trial33.

At the same time, newer therapeutic classes are increasingly targeting key inflammatory signalling pathways more directly. NLRP3 inflammasome inhibitors, for example, aim to suppress upstream inflammatory signalling known to drive obesity-related organ damage across the heart, vasculature, liver, and kidneys. In a recent Phase 2 study, VTX3232 demonstrated meaningful reductions in systemic inflammatory markers, such as CRP, IL-6, and liver cT1, an MRI biomarker of which quantifies inflammatory and fibrotic liver disease activity despite limited changes in body weight.15

Similar principles are emerging in insulin-sensitising therapies. Pan-PPAR agonists, such as lanifibranor, have demonstrated improvements in hepatic and peripheral insulin sensitivity despite modest weight gain24, reinforcing that favourable tissue remodelling and metabolic improvement may occur independently of weight reduction. Together, these findings support a broader shift from weight-centric therapies towards direct evaluation of tissue health, inflammatory activity, and organ protection.

Table 1 Therapeutic classes and MRI endpoint strategy in obesity drug development.

Therapeutic classes	Target Indications	Relevant MRI Endpoints	Differentiation Value
GLP-1/Incretin-based therapies	Obesity, MASH, HFpEF, CKD, T2D	Body composition (adiposity, muscle volume and muscle fat fraction); multi-organ fat, inflammation and fibrosis, cardiac and renal function	Support expansion across cardiometabolic indications by demonstrating whether weight loss translates into multi-organ disease modification
Dual agonists	Obesity, MASH	Body composition (adiposity, muscle volume and muscle fat fraction), liver and cardiac fat, inflammation and fibrosis, cardiac function	Strengthens MASH positioning by confirming that fat reduction is accompanied by reduction in inflammatory disease activity
NLRP3 inflammasome inhibitors	Obesity with cardiometabolic risk, HFpEF, MASH	Body composition (adiposity, muscle volume and muscle fat fraction), cardiac and liver fibrosis and inflammation, cardiac function	Enables clear mechanistic differentiation by demonstrating anti-inflammatory effects independent of weight or fat change
Pan-PPAR agonists	MASH, T2D	Body composition (adiposity, muscle volume and muscle fat fraction), multi-organ inflammation and fibrosis	Captures metabolic improvement independent of weight change
Muscle-targeting therapies	Obesity, sarcopenic obesity, T2D	Body composition (adiposity, muscle volume and muscle fat fraction)	Addresses regulatory concerns on lean mass and quality of weight loss by demonstrating selective fat loss with muscle preservation

Summary of key therapeutic classes, their target indications, and corresponding MRI endpoints, highlighting how multiparametric imaging enables differentiation of treatment effects through assessment of adiposity, inflammation, fibrosis, and organ function.

2.2 Limitations of Current Endpoints in Obesity Trials

Despite this therapeutic evolution, many obesity and cardiometabolic clinical trials still rely on body weight, BMI, circulating biomarkers, and late-stage clinical outcomes. While these measures remain clinically important, they may result in an incomplete characterisation of the biological heterogeneity and organ-level disease activity underlying metabolic dysfunction.

Circulating inflammatory biomarkers such as IL-6, TNF-α, and CRP provide a measure of systemic inflammation but lack tissue specificity and cannot localise disease activity to individual organs.

Multi-organ MRI studies have demonstrated steatosis and inflammatory tissue injury across the liver, pancreas, kidneys, and skeletal muscle even in individuals with relatively unremarkable circulating biomarkers, highlighting the limitations of relying on blood-based measures alone. 7

Similarly, body composition tools such as DXA can estimate lean and fat mass, but cannot distinguish healthy muscle from fat-infiltrated or inflamed tissue, nor can they quantify ectopic fat accumulation within organs.16,17 Ultrasound-based techniques are limited by operator dependence and reduced accuracy in individuals with higher adiposity, limiting reproducibility for longitudinal assessment in trials where participants are living with obesity. These approaches also largely remain restricted to single organs or isolated pathological features.

2.3 The Strategic Value of Imaging Endpoints

Multiparametric, multi-organ MRI provides a quantitative and mechanistically grounded approach for assessing tissue health across multiple organs simultaneously.

Strategic Benefit of Inflammatory imaging endpoints in clinical trials

Early Go/No Go Decisions

Imaging biomarkers typically demonstrate low placebo variability. Early detection of tissue-level change enables confident proof-of-concept decisions and more efficient portfolio prioritisation.

Statistical Power & Trial Efficiency

Quantitative MRI reduces measurement variability and provides more sensitive endpoints, enabling more efficient trial design with smaller sample sizes and potentially shorter trial duration than with weight-based or event-driven endpoints.

Phase-Specific Utility

In early-phase trials, imaging biomarkers function as sensitive decision tools. In later phases, they serve as primary or co-primary endpoints and as enrichment strategies to identify patients most likely to benefit.

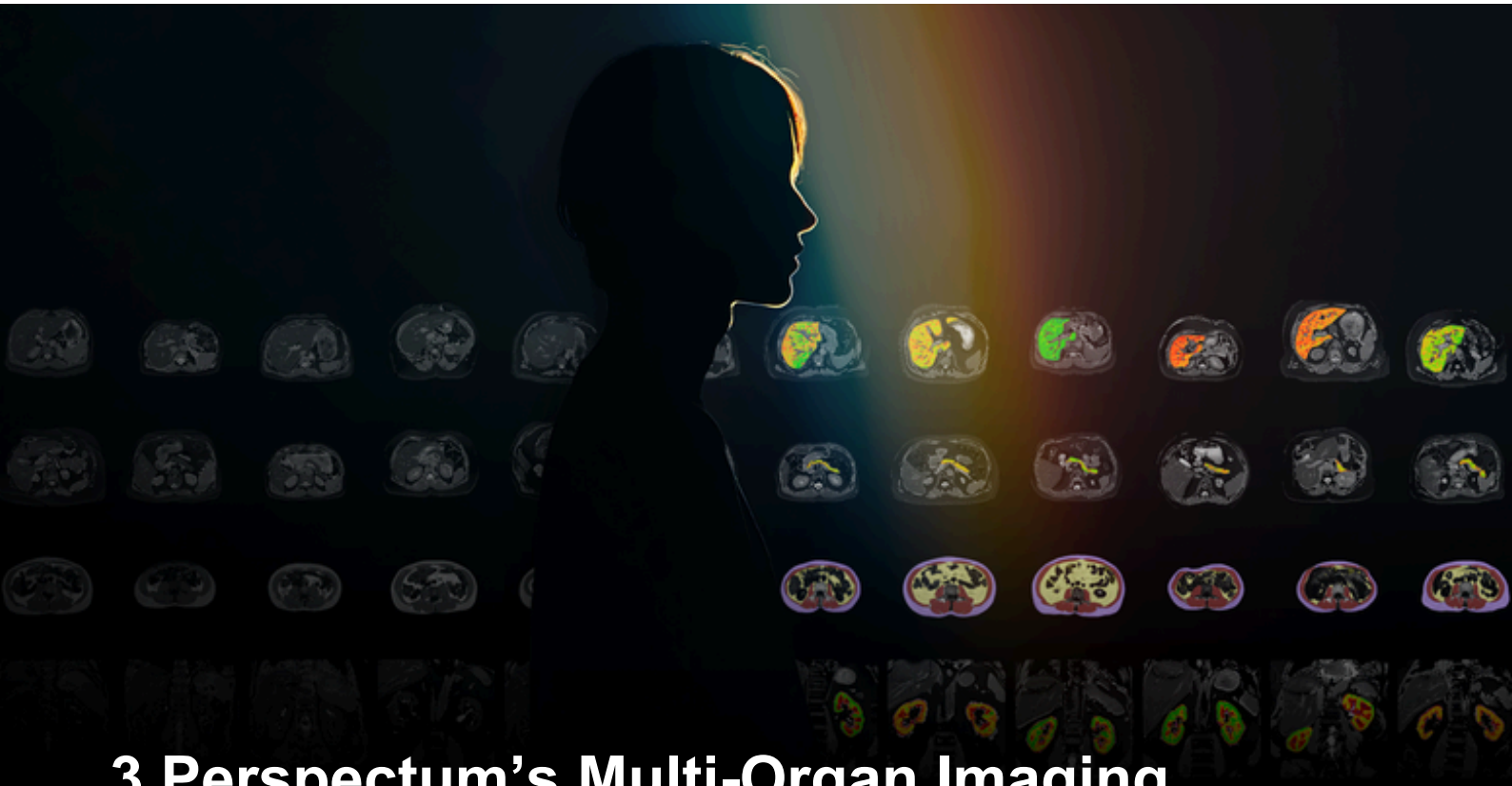
Accelerated Label Claim Identification

Imaging endpoints provide early, organ-specific evidence of therapeutic benefit beyond weight loss, strengthening support for regulatory label expansion into MASH, HFpEF, CKD, and related cardiometabolic indications.

By directly measuring inflammation-associated tissue injury, ectopic fat deposition, fibrosis, and structural remodelling, imaging biomarkers can detect therapeutic response earlier and more specifically than weight-based or systemic measures alone.

These capabilities have important implications for clinical development strategy. Sensitive imaging biomarkers may enable earlier proof-of-concept assessment, improve enrichment of high-risk populations, and reduce variability in longitudinal monitoring, supporting more efficient trial design and more confident go/no-go decision-making. Importantly, imaging endpoints can also help characterise weight-independent therapeutic effects, differentiating therapies that modify inflammatory disease activity from those producing adiposity reduction alone.

As obesity therapeutics expand across cardiometabolic indications, integrated imaging approaches are becoming increasingly valuable for generating coherent, organ-level evidence packages spanning liver disease, cardiovascular dysfunction, renal impairment, pancreatic inflammation, and body composition. This supports not only mechanistic understanding and pharmacodynamic assessment, but also broader regulatory positioning and lifecycle expansion across interconnected metabolic diseases.



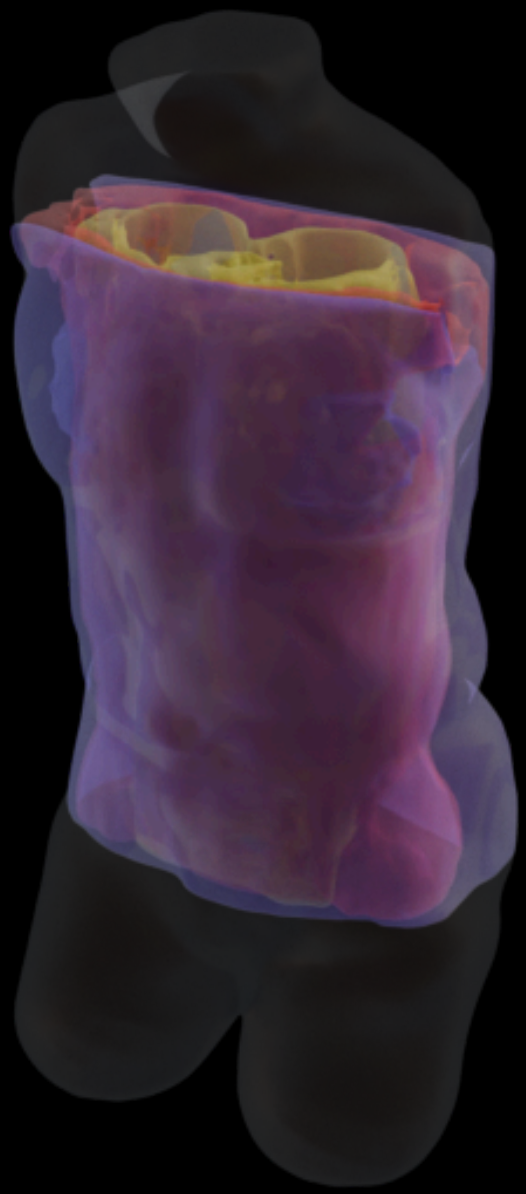
3 Perspectum's Multi-Organ Imaging Solution

Clinical development in obesity and metabolic disease increasingly requires coordinated assessment of adiposity, tissue remodelling, inflammatory activity, and organ function across multiple systems simultaneously.

Perspectum's multiparametric MRI platform integrates quantitative imaging biomarkers across the liver, heart, kidneys, pancreas, skeletal muscle, and adipose tissue within a standardised framework designed for longitudinal assessment and multi-centre clinical trials.

Capturing inflammatory activity by imaging offers an important point of differentiation for modern obesity therapies

By combining body composition analysis with organ-specific tissue characterisation, the platform enables comprehensive evaluation of metabolic disease biology within a single imaging session, supporting pharmacodynamic assessment, patient stratification, and detection of organ-level therapeutic response.



3.1 Body Composition: MRI Assessment Beyond Weight

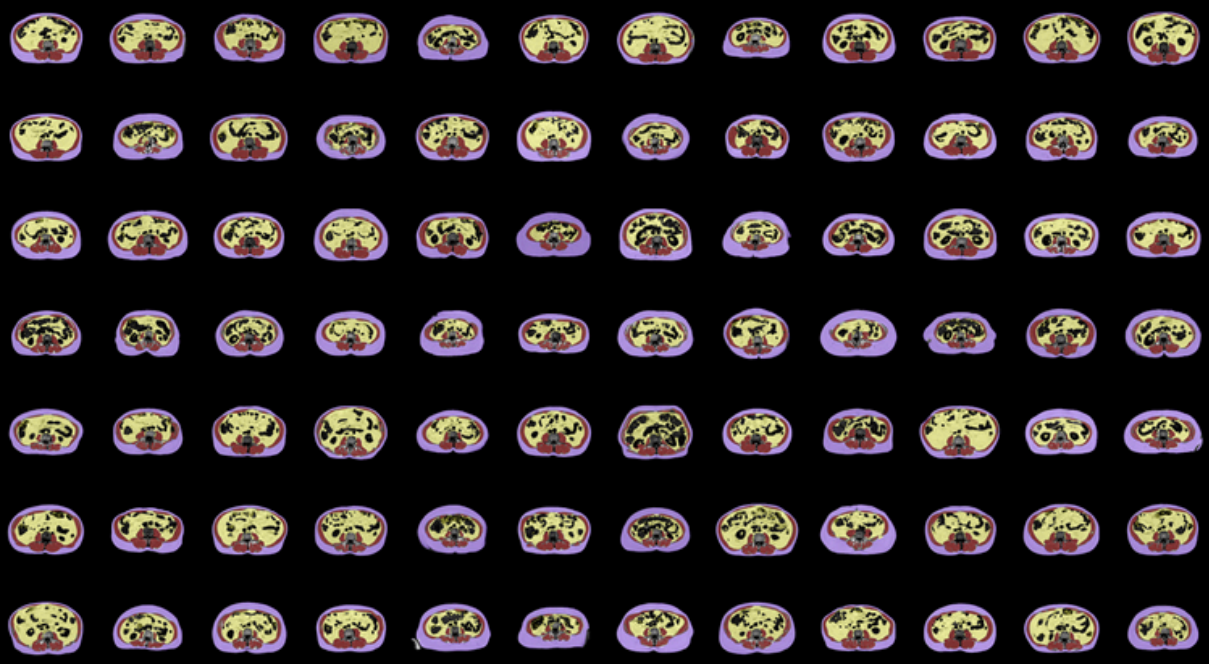
Body weight alone provides limited insight into metabolic health.

The biological consequences of obesity are determined not only by the quantity of adipose tissue, but also by its distribution, inflammatory activity, and infiltration into skeletal muscle and abdominal organs.

MRI enables simultaneous quantification of visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), ectopic fat deposition, skeletal muscle volume, muscle fat infiltration within a single examination, providing a more comprehensive assessment of metabolic tissue remodelling than weight-based measures alone.

Visceral and ectopic fat depots are particularly important in cardiometabolic diseases as they are inherently more pro-inflammatory and metabolically active than subcutaneous fat. Increased visceral adiposity and ectopic fat accumulation are associated with insulin resistance, dyslipidaemia, T2D, cardiovascular disease, and liver injury independently of BMI.18 19–21 Similarly, muscle quality is increasingly recognised as an important determinant of metabolic health. Myosteatosis, characterised by pathological fat infiltration within skeletal muscle, contributes to insulin resistance, sarcopenic decline, frailty, and impaired physical function, even in the presence of preserved muscle mass 25. As a result, recent FDA draft guidance for obesity drugs encourages monitoring both fat and lean tissue during weight-loss trials.4

These distinctions are increasingly relevant for obesity drug development. Therapies producing similar weight reduction may have markedly different effects on fat distribution, muscle preservation, and tissue quality. Conversely, metabolically favourable tissue remodelling may occur despite relatively modest changes in body weight.



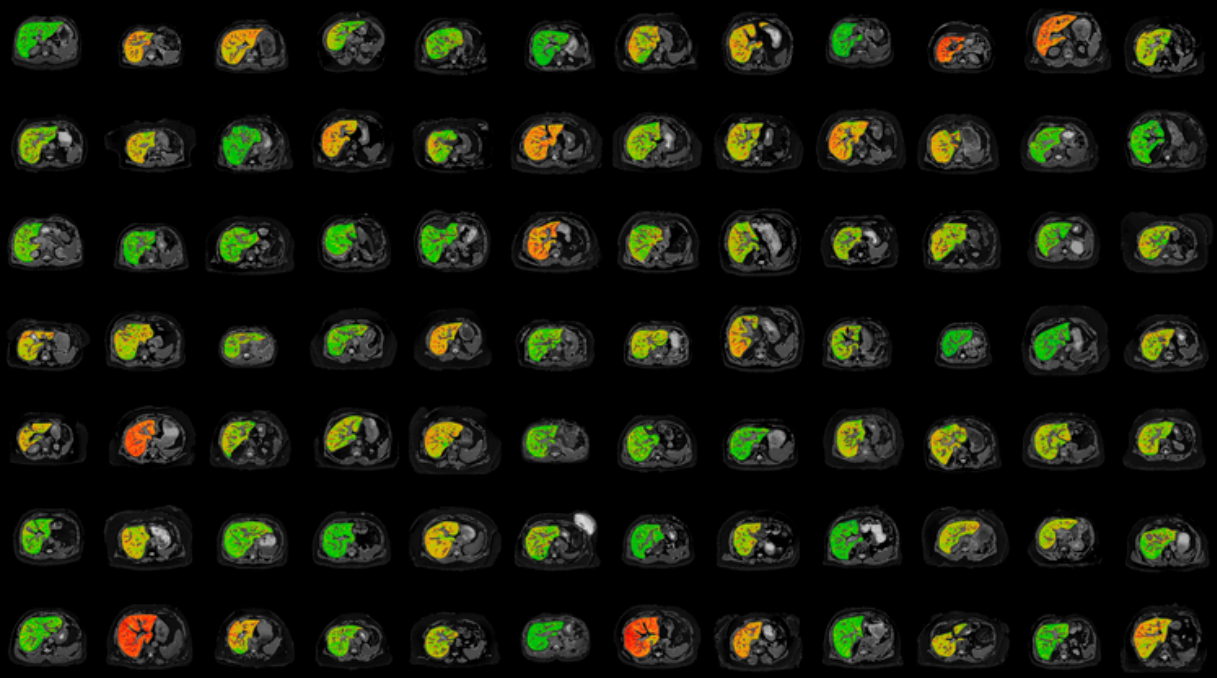
In a phase 2 trial, bimagrumab demonstrated selective fat loss with preservation of lean mass alongside significant metabolic improvements, despite comparatively modest changes in body weight.23 Similarly, in a phase 4 trial liraglutide demonstrated that reductions in fat mass rather than total weight loss were associated with improved cardiovascular risk.22 Together, these trials show that meaningful metabolic benefit can occur without large changes in body weight, highlighting the limitations of relying on body weight alone to assess therapeutic benefit.

Perspectum’s MRI-based body composition platform enables reproducible quantification of VAT, SAT, ectopic fat deposition across organs, and muscle composition in a single standardised assessment26–28, enabling reliable longitudinal assessment of treatment response and metabolic tissue remodelling in clinical trials

3.2 Liver cT1:
Inflammatory and Disease Progression Biomarker

In metabolic liver disease, steatosis alone does not determine clinical risk. Disease progression is driven by inflammatory injury and fibrotic remodelling that develop on top of fat accumulation, making assessment of inflammatory disease activity increasingly important for therapeutic evaluation and risk stratification.

Corrected T1 (cT1) is a quantitative MRI biomarker that captures tissue alterations associated with inflammatory and fibrogenic disease activity, while MRI PDFF (proton density fat fraction) quantifies hepatic steatosis. Importantly, these biomarkers capture distinct aspects of liver disease biology.

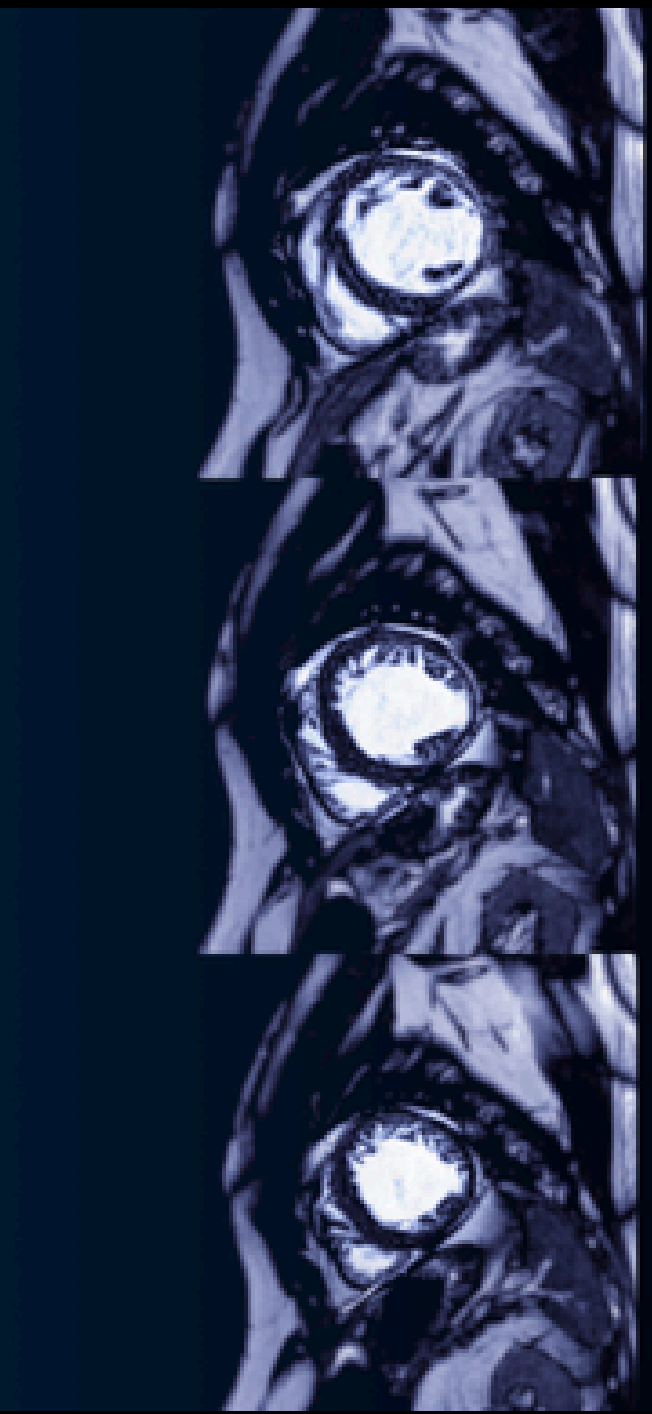


Large-scale population data demonstrate that elevated cT1 is not only associated with liver disease severity, but also with broader cardiometabolic risk, including cardiovascular events, liver outcomes, and all-cause mortality29. Real-world evidence further suggests that inflammatory disease activity identified by cT1 may predict liver disease progression even in individuals without advanced fibrosis, supporting its value for identifying high-risk populations earlier in disease evolution31.

Therapeutic studies illustrate the importance of distinguishing steatosis reduction from broader improvements in inflammatory activity. In the SYNERGY-NASH trial, tirzepatide demonstrated dose-dependent improvements in MASH resolution and fibrosis on histology, alongside reductions in cT1 consistent with reduced inflammatory disease activity32.

Similarly, pemvidutide resulted in large, sustained reductions in cT1, together with improvements in other non-invasive markers of liver inflammation and fibrosis.14 Both of these drugs also demonstrated significant reductions in liver fat as measured by MRI PDFF. Conversely, the NLRP3 inflammasome inhibitor VTX3232 reduced cT1 without corresponding reductions in liver fat,15 demonstrating that inflammatory activity and steatosis may respond differently depending on therapeutic mechanism.

These findings support the growing importance of inflammation-sensitive imaging biomarkers for assessing liver disease modification, pharmacodynamic response, and mechanistic differentiation in obesity and cardiometabolic drug development.

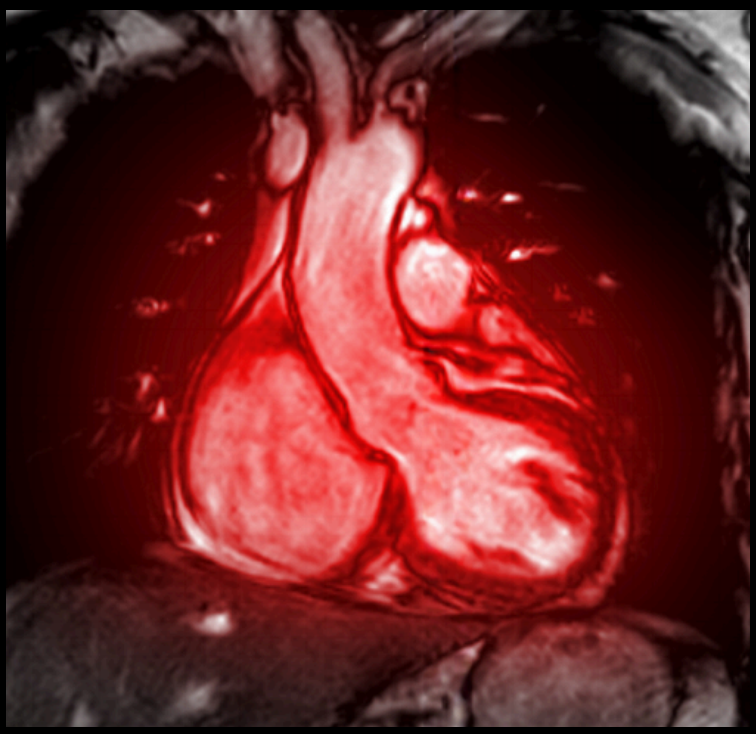


3.3 Cardiac: Imaging from Inflammation to HFpEF

Heart failure with preserved ejection fraction (HFpEF) has emerged as one of the most important cardiovascular complications of obesity and metabolic disease, with obesity-associated chronic inflammation increasingly recognised as a key driver in the development of HFpEF. HFpEF is characterised by myocardial steatosis, diffuse fibrosis, vascular endothelial dysfunction, and impaired ventricular relaxation rather than isolated haemodynamic dysfunction alone. As obesity therapeutics expand into cardiovascular indications, the ability to characterise early myocardial remodelling and tissue-level therapeutic response is becoming increasingly important for clinical development and mechanistic differentiation.

The shift has accelerated following the success of incretin-based therapies in cardiovascular outcomes studies. In the SUMMIT trial, tirzepatide reduced the risk of cardiovascular death or worsening heart failure events, including heart failure events by 38% in patients with obesity-associated HFpEF33, reinforcing the concept that metabolic therapies can directly modify cardiac disease biology beyond weight reduction.

Multiparametric cardiac MRI can quantify the inflammatory pathology underlying HFpEF, through integrated evaluation of myocardial tissue composition, cardiac structure, and ectopic fat deposition. T1 and T2 mapping allow sensitive detection of inflammatory tissue injury and diffuse fibrosis, while MRI-based assessments of epicardial adipose tissue and myocardial steatosis provide insight into metabolically active fat depots implicated in cardiac dysfunction. Elevated T1 and T2 values have been associated with adverse cardiovascular outcomes in inflammatory cardiomyopathies, supporting their role as markers of myocardial inflammatory burden.34



Functional assessment further links tissue pathology to prognosis. Structural remodelling, including left ventricular hypertrophy, is a common feature of HFpEF and independently contributes to disease progression and mortality risk.

Importantly, these imaging biomarkers may detect biologically meaningful therapeutic effects before overt structural failure or clinical deterioration occurs. This creates opportunities for earlier pharmacodynamic assessment and more sensitive evaluation of therapies targeting inflammatory and metabolic cardiac pathways. As obesity drug development increasingly expands towards HFpEF and broader cardiovascular protection, quantitative cardiac imaging is likely to become increasingly important for demonstrating organ-level therapeutic benefit and differentiation across competing therapeutic classes.

3.4 Renal:
Multiparametric MRI Biomarkers

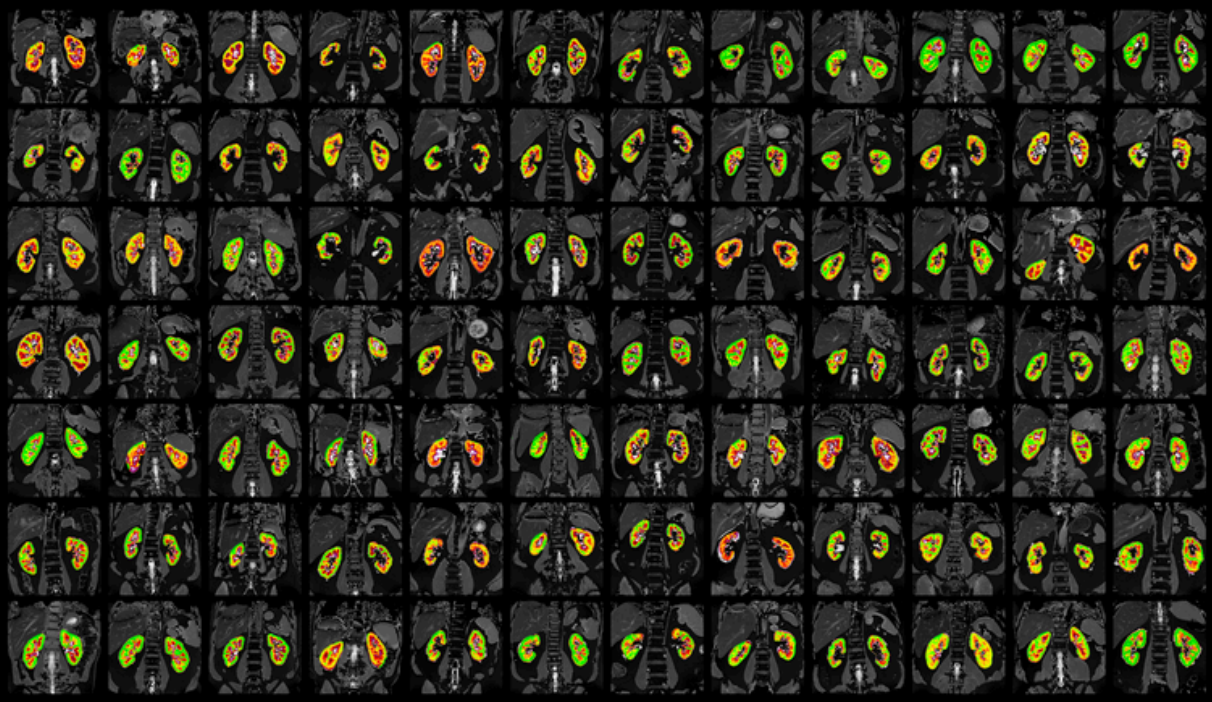
Chronic kidney disease (CKD) is a rapidly growing component of the obesity and cardiometabolic therapeutic landscape, driven by the close interrelationship between obesity, T2D, hypertension, vascular dysfunction and chronic inflammatory injury.

In obesity-related CKD, metabolic inflammation contributes to progressive fibrotic and inflammatory remodelling, altered haemodynamics, hypoxia, and ectopic fat accumulation long before substantial decline in renal function becomes clinically apparent.

The importance of renal protection in obesity therapeutics has increased substantially following the emergence of positive renal outcomes data with incretin-based therapies and SGLT2 inhibitors. In the FLOW trial, semaglutide significantly reduced major kidney outcomes in people with T2D and CKD37

Multiparametric renal MRI enables non-invasive quantification of renal tissue composition, inflammation, fibrosis, oxygenation, haemodynamic changes, and renal sinus fat accumulation within a single scan. These biomarkers provide mechanistic insight into tissue remodelling that is often not captured by conventional clinical measures such as eGFR or albuminurea alone, particularly during earlier stages of disease progression.

The value of this approach is illustrated by the REMODEL trial which used renal MRI alongside kidney biopsies to characterise tissue-level renal effects associated with semaglutide treatment in diabetic kidney disease. 38



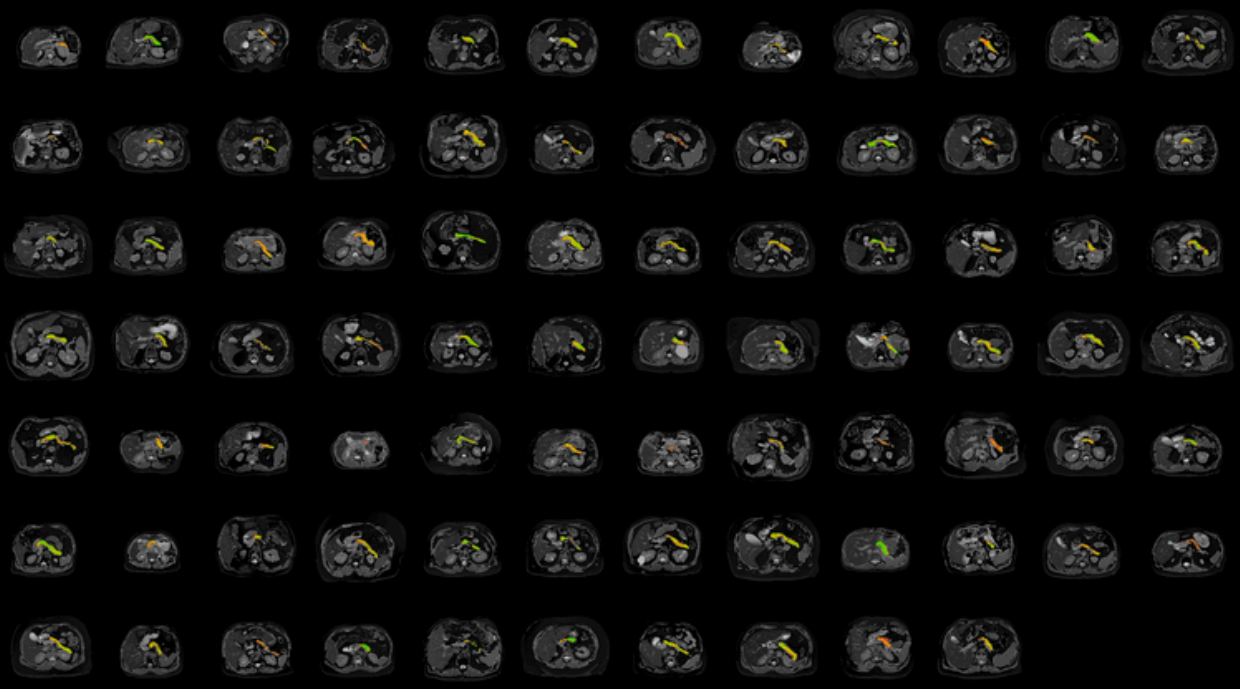
MRI detected changes in renal fat, vascular resistance, and cortical fibrosis that were independent of weight loss or glycaemic improvement, supporting a more detailed understanding of renal therapeutic response and mechanism of action.

Further recent evidence has also exemplified that renal sinus fat, a pro-inflammatory ectopic fat depot, is associated with impaired renal haemodynamics and poor renal outcomes,39,40 and hence may be a particularly relevant imaging biomarker in obesity-related CKD and cardiometabolic disease.

3.5 Pancreas:
Quantitative MRI of Inflammation

Pancreatic inflammation and structural remodelling remain relatively under-characterised in obesity and T2D despite their potential importance in beta-cell dysfunction, glycaemic control, and long-term metabolic disease progression.

Multiparametric MRI enables quantitative assessment of pancreatic tissue composition and inflammatory change through biomarkers such as scanner-referenced pancreatic T1 (srT1), fat quantification, and volumetric analysis. Increased pancreatic srT1 and pancreatic fat have been associated with T2D and impaired glycaemic control, suggesting that subclinical inflammatory tissue injury may accompany progressive metabolic dysfunction.7,42

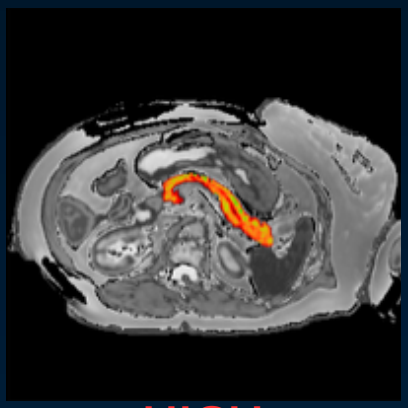


Automated segmentation of the pancreas into head, body, and tail allows regional quantification of srT1 and pancreatic fat, enabling detection of spatial heterogeneity in inflammation and fat deposition, supporting sensitive longitudinal monitoring in clinical trials. Additionally, emerging evidence also suggests that pancreatic inflammation may be associated with increased risks of pancreatic cancer,43 further highlighting the broader biological relevance of pancreatic tissue remodelling in metabolic disease.

By integrating pancreatic tissue characterisation within a broader multi-organ imaging framework, MRI may provide earlier insight into therapeutic effects on organ function in metabolic disease that are not detectable through conventional endpoints alone.

4. Applications of Multi-Organ Imaging

PANCREAS



HIGH

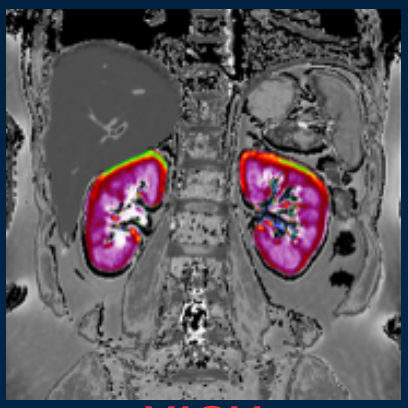
Pancreas srT1

888 ms

Normal Reference:

<836ms

KIDNEYS



HIGH

Cortical T1

L: 1555 ms

R: 1685ms

Normal Reference:

L: 1288 - 1527ms

R: 1278 - 1516ms

CASE 1

Discordance Between Adiposity and Fibro-Inflammation

This case illustrates how metabolic inflammation can be present independently of steatosis and excess adiposity. A 47-year-old woman with T2D and a BMI of 27 kg/m² showed normal HbA1c, eGFR, pancreas fat, and kidney fat, yet multiparametric MRI revealed elevated pancreatic srT1 and renal cortical T1, suggesting inflammatory activity in both organs.

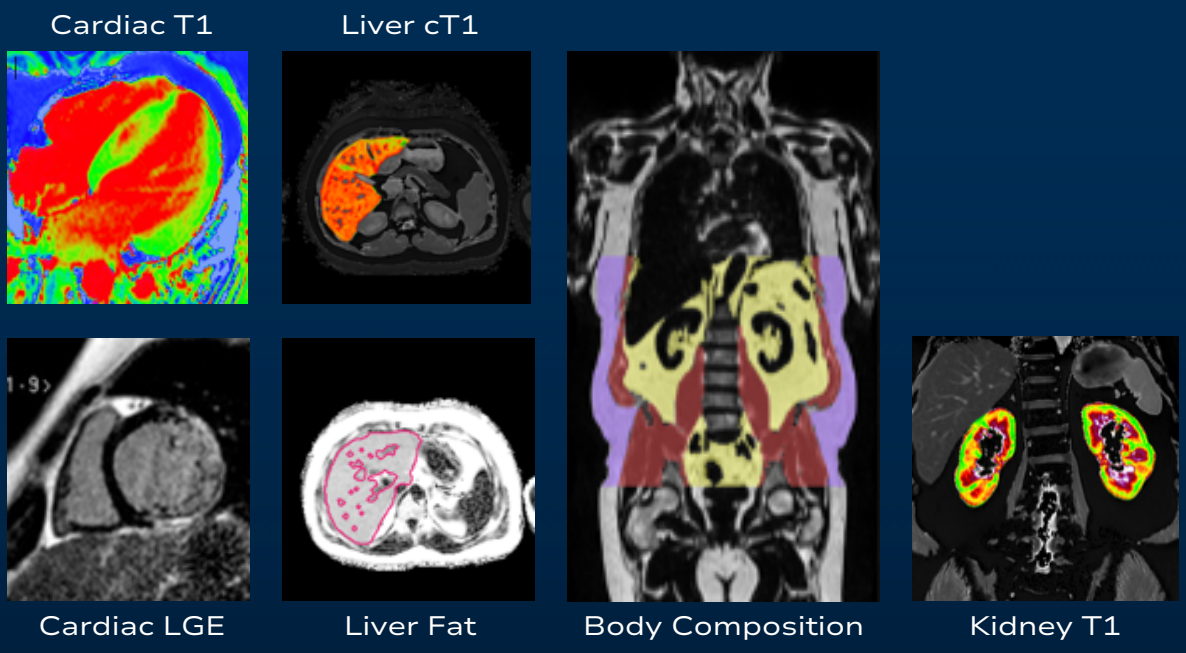
This highlights the value of multiparametric MRI in distinguishing inflammation from fat through the use of a single, comprehensive scan.

This has the potential for direct implications on clinical trial design and regulatory strategy, through the enablement of earlier therapeutic response detection, improved stratification of high-risk patients, and clearer differentiation of treatment effects on organ-level inflammation.

CASE 2

Multi-Organ Inflammation in a Single Scan

In under 45 minutes, multiparametric MRI can provide a comprehensive, multi-organ assessment of tissue health and inflammation within a single scan. Liver cT1 quantifies hepatic fibro-inflammation associated with MASH severity and progression, while liver proton density fat fraction (PDFF) measures hepatic steatosis. Cardiac T1 mapping evaluates diffuse myocardial inflammation and fibrosis associated with HFpEF in obesity, with optional late gadolinium enhancement identifying focal scar tissue. Renal cortical T1 reflects fibro-inflammatory injury linked to CKD progression. Integrated body composition MRI quantifies adipose tissue and muscle volume/quality, important determinants of metabolic inflammation. These quantitative metrics have been standardised across major scanners and field strengths, and show high repeatability and reproducibility, enabling reliable longitudinal monitoring and robust use as endpoints in clinical trials. **This integrated MRI-based approach uniquely enables early detection of organ-level therapeutic effects, supporting clinical trial efficiency, regulatory positioning, and differentiation of therapies beyond weight loss alone.**



5. Perspectum Operations

Perspectum's operational framework is specifically designed to translate advanced imaging biomarkers into scalable, regulatory-grade clinical trial endpoints.

Clinical Trial Operations & Project Management

- End-to-end support for multi-centre, global clinical trials, extending beyond imaging into site and project management
- Standardised, trial-specific imaging acquisition manuals provided prior to site activation, covering subject positioning, anatomical coverage, and scanner parameters

Standardisation & Quality Assurance

- Phantom scanning to verify scanner calibration across participating sites
- Centralised image verification, preprocessing, and quantification pipelines to ensure technical accuracy and reproducibility
- Central reads by in-house MRI analysts, to minimise variability and ensure high-quality datasets

Data Management & Compliance

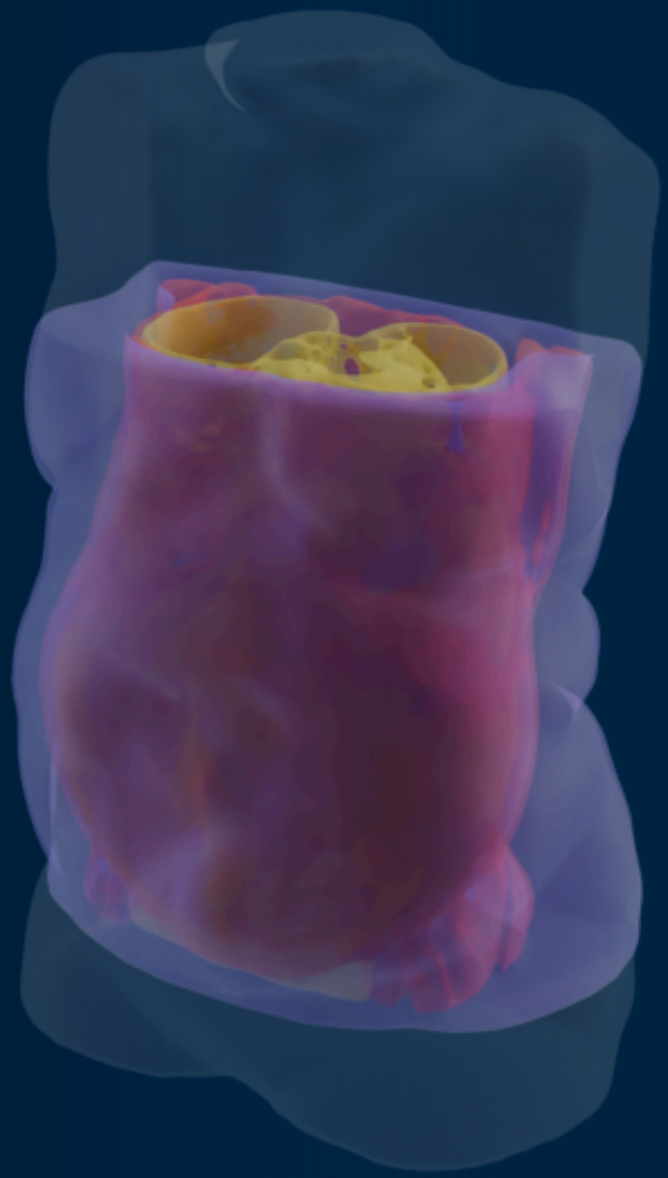
- ISO 27001-certified trial management system compliant with 21 CFR Part 11, GDPR, and HIPAA
- Secure, cloud-based Perspectum Portal for data upload, patient tracking, and imaging data management
- Customisable user permissions and automated notifications for sites and sponsors

Scalability & CRO Integration

- Seamless integration with large, full-service CROs, improving trial workflows, endpoint reliability, and data reproducibility
- Global network of 950+ imaging centres, enabling rapid study start-up and scalability for large Phase 3 programmes
- SaaS-based infrastructure supporting multiple modalities without additional scanner hardware upgrades

Conclusion

Obesity is increasingly recognized as a heterogeneous, systemic inflammatory disease characterized by dysfunction across multiple organs, rather than a disease of excess body weight alone. As drug development shifts beyond weight reduction toward disease modification in indications including MASH, HFpEF, CKD, and broader cardiometabolic indications, traditional endpoints are no longer sufficient to characterise the biological complexity of disease progression or therapeutic response. This creates a need for clinical trial strategies that demonstrate coordinated multi-organ improvement to fully capture therapeutic benefit, support regulatory differentiation, and maximise cardiometabolic portfolio value.



Another important consideration is that therapies with similar effects on adiposity may produce substantially different effects on inflammatory activity, tissue remodelling, and organ protection. Conversely, meaningful improvements in tissue health may occur without major changes in body weight.

As a result, the ability to assess organ-level disease biology is becoming increasingly important for pharmacodynamic evaluation, mechanistic differentiation, and demonstration of disease modification across a broader cardiometabolic development programme.

This shift creates growing demand for biomarkers capable of quantifying inflammatory activity, alongside adiposity, ectopic fat depots, fibrosis, and structural remodelling in a single, scalable examination.

Multiparametric, multi-organ MRI is uniquely well positioned to provide an approach to assessing these changes longitudinally within clinical trials, supporting greater sensitivity to treatment effects, improved patient stratification, and efficient development strategies across cardiometabolic indications. As a result, as obesity therapeutics increasingly compete on the basis of organ protection and long-term cardiometabolic benefit, multi-organ MRI is likely to become increasingly important for generating the mechanistic and regulatory evidence required for therapeutic differentiation and lifecycle expansion.

By combining quantitative body composition analysis with organ-specific inflammatory and structural biomarker, Perspectum supports the generation of robust, reproducible evidence packages aligned with the evolving needs of obesity and cardiometabolic drug development.

Perspectum's **standardised** multi-organ imaging platform enables **scalable assessment of organ health** across the liver, heart, kidneys, pancreas, skeletal muscle, and adipose tissue within a **unified framework designed specifically for clinical development**

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