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Metabolic remodeling and multi-system health management in middle-aged and older adults: Pathophysiology and clinical evidence

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Abstract
Against the backdrop of global population ageing, the metabolic transition occurring after age 45 represents a critical biological window shifting the human body from homeostasis to multi-system decompensation. This systemic remodeling is driven by basal metabolic shifts, skeletal muscle anabolic resistance, endocrine axis alterations, mitochondrial attrition, gut microbiota dysbiosis, and inflammaging. These factors sequentially induce insulin resistance, glucolipid disturbances, hyperuricemia, metabolic dysfunction-associated steatotic liver disease (MASLD), chronic kidney disease (CKD), and sarcopenic obesity, amplifying risks of disability and mortality. While traditional models assumed a linear decline in basal metabolism, recent doubly labeled water studies reveal that total energy expenditure remains stable between ages 20 and 60, with significant decline initiating only post-60 at roughly 0.7% annually. Nonetheless, latent pathological changes—including ectopic visceral fat accumulation and subclinical inflammation—accumulate during middle age, erupting later in life. Synthesizing landmark trials (e.g., DPP, IMPROVE-IT, DAPA-CKD, CANTOS, CALERIE) alongside high-quality cohorts and meta-analyses, this review examines the underlying mechanisms, screening thresholds, and risk-stratified interventions across six core axes: glucose, lipids, uric acid, thyroid, liver, and kidney. We further dissect skeletal muscle–bone coupling, mitochondrial ageing, SASP, and inflammaging cross-tissue networks. Based on these findings, we establish an integrated management framework centered on "stratified assessment, precision intervention, and dynamic monitoring," prioritizing lifestyle foundations, risk stratification, and the preservation of functional independence. An expert commentary outlines real-world clinical dilemmas, Asian population localization challenges, and overdiagnosis risks. Finally, we discuss translational prospects for anti-ageing therapeutics, senolytics, and microbiota interventions, delivering high-level evidence to support clinical practice in geriatrics, endocrinology, and public health policy.

Keywords: Metabolic transition, basal metabolic rate, insulin resistance, inflammaging, sarcopenia, multi-system metabolic comorbidity

Introduction

Global life expectancy continues to rise, yet the gap between healthy life expectancy and total life expectancy continues to widen. A large number of middle-aged and older adults over 45 years of age suffer from multiple chronic metabolic diseases over the long term, with impaired physical self-care capacity and continuously increasing pressure on family and social medical care. The World Health Organization defines 45–59 years as early middle age and 60–74 years as late middle age; 45 years is regarded as the critical threshold for the onset of the metabolic transition, marking a substantive decline in the body's metabolic reserve and damage repair capacity. Metabolic decline at this stage is characterised by multiple levels, accumulation, and insidious onset: at the cellular level, cumulative mitochondrial DNA mutations, elevated oxidative stress, and gradual accumulation of senescent cells; at the tissue and organ level, ectopic hepatic fat deposition, physiological decline in glomerular filtration rate, and the emergence of skeletal muscle anabolic resistance; at the systemic level, visceral fat drives chronic low-grade sterile inflammation, with multiple endocrine axes becoming dysregulated simultaneously. Injuries at different levels amplify one another, progressively advancing from a subclinical state to overt metabolic disease.

Pontzer *et al*. (2021) [27], publishing in Science, conducted a large-sample multinational study of energy expenditure using doubly labelled water, correcting decades of traditional understanding: after adjustment for body composition, total energy expenditure in humans remains relatively stable between the ages of 20 and 60, with a clear, measurable decline in energy expenditure appearing only after the age of 60, and the rate of decline further accelerating after the age of 80. This finding carries profound clinical implications: during middle age, metabolic indicators on laboratory reports may appear to lie within reference ranges, yet profound remodelling of body composition has already occurred—gradual loss of skeletal muscle mass, progressive accumulation of visceral fat, and conversion of lean body mass to adipose tissue, reshaping the systemic metabolic landscape, while the absolute value of total energy expenditure has not yet significantly decreased. This 'apparent homeostasis, internal remodelling' is precisely the core feature of the metabolic transition in middle-aged and older adults that is most readily overlooked by clinicians. After entering the sixth decade, decades of accumulated visceral fat burden, subclinical inflammation, and muscle anabolic resistance are superimposed upon a genuine decline in basal metabolic rate, and the incidence risks of type 2 diabetes, atherosclerotic cardiovascular disease, MASLD, chronic kidney disease, sarcopenia, and the falls–disability chain exhibit a steeply rising curve. Metabolic syndrome is a collective phenotype of multi-

system metabolic disturbance, comprising central obesity, dysglycaemia, dyslipidaemia, and hypertension, with prevalence rising rapidly in populations over 45 years of age. Cohort studies have confirmed that each additional abnormal component of metabolic syndrome increases the risk of disability in activities of daily living in middle-aged and older adults by 23%, suggesting that metabolic management in this population cannot be confined to the attainment of biochemical targets, and that physical functional outcomes must be incorporated as core clinical evaluation endpoints. At present, fragmented diagnosis and treatment are common in domestic clinical practice: endocrinology focuses on blood glucose and lipid control, nephrology on renal function protection, and orthopaedics solely on changes in bone mineral density, with a lack of cross-organ integrated metabolic assessment based on the biology of ageing. Metabolic diseases in middle-aged and older adults are, in essence, multi-system interactive diseases: insulin resistance simultaneously damages the liver, skeletal muscle, vascular endothelium, and kidneys; chronic low-grade inflammation is both a product of metabolic disturbance and, in turn, aggravates glucolipid abnormalities, bone loss, and muscle wasting; subclinical hypothyroidism further amplifies dyslipidaemia and hepatic fat accumulation; hyperuricaemia simultaneously mediates renal injury and vascular endothelial pathology. Isolated intervention on a single laboratory indicator often fails to improve patients' long-term functional prognosis.

Physiological Basis of the Metabolic Transition

1. Patterns of Change in Basal Metabolic Rate and Predictive Assessment Formulae

Basal metabolic rate (BMR) is defined as the energy expenditure required to maintain basic vital functions under conditions of wakefulness, rest, fasting, and a thermoneutral environment, accounting for 60%–70% of daily total energy expenditure, and is the core variable in energy balance management for middle-aged and older adults. BMR is highly dependent on lean body mass; skeletal muscle is the largest energy-consuming tissue in the human body, and age-related changes in body composition are the most important driver of changes in BMR. The Mifflin-St Jeor equation is currently the BMR prediction tool with the best applicability for middle-aged and older adults, incorporating four variables—height, weight, sex, and age—with age as a negative parameter, reflecting the metabolic down-regulation effect of ageing. The Harris-Benedict equation, in use for a century, remains usable in general adults, but multiple systematic reviews have confirmed that it systematically overestimates BMR in middle-aged and older adults, and it is therefore not recommended as the preferred tool for energy assessment in this population.

The decline in BMR during middle and older age is jointly driven by three core mechanisms. Firstly, progressive loss of skeletal muscle mass: after the age of 45, skeletal muscle is lost naturally at a rate of 1%–2% per year; the metabolic activity of adipose tissue is far lower than that of skeletal muscle, and although visceral fat possesses high inflammatory activity, its energy expenditure per unit mass is significantly lower than that of muscle; when 'muscle–fat body composition conversion' occurs, BMR declines insidiously even if body weight remains unchanged. Secondly, decline of anabolic endocrine axes: the activity of the growth hormone–IGF-1 axis declines with age; levels of sex hormones such as oestradiol and testosterone decrease; thyroid hormones regulate the metabolic rate of cells throughout the body, and the high incidence of subclinical hypothyroidism in middle-aged and older adults further lowers tissue metabolic levels. Thirdly, mitochondrial functional decline: ageing is accompanied by a decrease in mitochondrial number, impaired oxidative phosphorylation efficiency of the electron transport chain, and a large overflow of reactive oxygen species, with oxidative stress in turn further aggravating cellular damage, forming a vicious cycle of 'metabolic decline–oxidative damage–further metabolic decline'. Clinically, it is necessary to distinguish between 'body composition remodelling at constant body weight' and 'absolute decline in total energy expenditure'. A large number of middle-aged individuals maintain or even slightly gain weight, yet the proportion of muscle decreases and visceral fat increases; at this time, laboratory-measured total energy expenditure shows little change, but insulin sensitivity and lipid turnover are already significantly impaired. This phenotype is very common in Chinese middle-aged populations and represents a high-risk phenotype highly susceptible to missed diagnosis in the early stage of the metabolic transition.

2. Metabolic Adaptation to Caloric Restriction

CALERIE was the world's first randomised controlled trial of long-term caloric restriction in non-obese healthy adults. The study enrolled 218 participants aged 21–50 years, with the experimental group undergoing a 25% total caloric restriction intervention for 2 years. It was found that the caloric restriction group exhibited adaptive down-regulation of metabolic rate, together with a significant decrease in systemic oxidative stress biomarkers. This adaptive down-regulation of metabolism is not equivalent to pathological age-related metabolic decline: the metabolic down-regulation brought about by caloric restriction represents a protective adaptation involving cellular reprogramming, enhanced energy utilisation efficiency, and reduced oxidative damage; age-related pathological metabolic decline is accompanied by substantial muscle loss, hormonal dysregulation, and aggravated mitochondrial damage. The biological essences of the two are entirely different, and clinical intervention must strictly distinguish between them. For middle-aged and older adults, based on CALERIE and subsequent extension studies, a safe caloric restriction range has been proposed: moderate caloric restriction with a 10%–15% reduction in total energy, with extreme fasting strictly prohibited; at the same time, adequate protein intake of 1.0–1.2 g/kg ideal body weight must be ensured. If caloric restriction is implemented without adequate protein supply, anabolic resistance will be amplified, accelerating skeletal muscle loss and inducing sarcopenia, bone loss, and frailty syndrome, raising the risks of falls, infection, and death. This is the core safety red line in weight-loss intervention for obesity in older adults. Intermittent fasting has attracted much attention in recent years, but high-quality RCT evidence for populations over 65 years of age who are frail or have multiple comorbidities remains insufficient. For frail, low-body-weight, or high-risk sarcopenic middle-aged and older adults, long-term fasting regimens are not recommended; continuous moderate caloric restriction combined with adequate high-quality protein is preferred. Intermittent fasting should serve only as an alternative dietary regimen for middle-aged and

older adults with stable metabolic status and good physical function, with close monitoring of body composition, muscle strength, nutritional indicators, and hypoglycaemia risk during implementation.

3. Subclinical Biomarkers and Early Warning Signals

The early stage of the metabolic transition has no specific clinical symptoms, but a set of subclinical biological signals exists that can be used for early screening of high-risk populations. Body composition indicators: increased waist circumference, elevated visceral fat area, decreased appendicular skeletal muscle mass index; biochemical indicators: glycated haemoglobin 5.4%–5.6% (the grey zone of prediabetes), mildly elevated hs-CRP, decreased serum leucine levels, borderline elevated uric acid, slowly declining eGFR; functional indicators: decreased handgrip strength, slowed gait speed. Combining the above indicators allows identification of individuals who have not yet been diagnosed with chronic disease but are at high risk of future metabolic disease and disability, advancing the intervention window to middle age. The menopause is an important node in early middle age for women, and the rapid decline in oestrogen further amplifies the metabolic transition process. Oestrogen possesses multiple functions: promoting muscle protein synthesis, inhibiting visceral fat accumulation, maintaining vascular endothelium, and regulating bone remodelling. After menopause, with oestrogen withdrawal, visceral fat accumulates rapidly, anabolic resistance worsens, the risk of insulin resistance rises, and bone loss is simultaneously accelerated, with a significant increase in the risk of sarcopenia–osteoporosis comorbidity. In men, testosterone levels decline slowly during middle and older age, similarly contributing to lean body mass loss, visceral fat increase, and dyslipidaemia.

Core Disease Mechanisms of the Metabolic Transition

1. Insulin Resistance and Type 2 Diabetes

Type 2 diabetes is a disease that progresses slowly over 5–10 years, with insulin signalling pathway impairment as its core pathological basis. Under physiological conditions, insulin binds to cell membrane receptors, activating the IRS-1/PI3K signalling axis, prompting GLUT-4 glucose transporter translocation to the cell membrane, and completing glucose uptake in skeletal muscle, liver, and adipose tissue. During middle and older age, with visceral fat expansion, adipose tissue macrophages polarise towards the M1 pro-inflammatory phenotype, releasing large amounts of pro-inflammatory cytokines such as TNF-α and IL-6, interfering with IRS-1 tyrosine phosphorylation, inhibiting PI3K pathway activation, and inducing insulin resistance. Insulin resistance first occurs in the three major target organs—skeletal muscle, liver, and adipose tissue—and subsequently involves other tissues and organs such as blood vessels and kidneys. The diagnostic criteria for prediabetes are met if any one of the following is present: fasting plasma glucose 100–125 mg/dL; glycated haemoglobin 5.7%–6.4%; 2-hour plasma glucose on oral glucose tolerance test 140–199 mg/dL. Prediabetes is the only golden reversible intervention window for type 2 diabetes; once it progresses to overt diabetes, irreversible depletion of pancreatic β-cells occurs, and the disease becomes a chronic persistent course.

The DPP (Diabetes Prevention Program) is a landmark clinical trial in diabetes prevention. A total of 3,234 participants with prediabetes were randomised to an intensive lifestyle intervention group, a metformin intervention group, or a placebo control group. Over a mean follow-up of 2.8 years, the risk of developing diabetes decreased by 58% in the intensive lifestyle group and by 31% in the metformin group. The 22-year long-term DPPOS follow-up confirmed that early lifestyle intervention delayed the onset of diabetes by an average of 3.5 years and significantly reduced the risk of microvascular complications; in the subgroup aged over 60, lifestyle intervention still conferred a clear protective effect; for older populations, the weight-loss target was relaxed to a 5% reduction in body weight, avoiding the risk of muscle wasting associated with rapid weight loss. Clinically, attention must be paid to individualised targets for older adults with prediabetes: for older individuals already with sarcopenia, frailty, or multiple comorbidities, rapid and substantial weight loss should not be pursued; the focus of intervention should be on maintaining muscle mass, increasing physical activity, and optimising dietary structure, rather than using weight loss alone as the evaluation criterion. Insulin resistance is not only the source of abnormal glucose metabolism but also links dyslipidaemia, MASLD, and hyperuricaemia, and is the core hub connecting the six major metabolic axes. In Asian populations with prediabetes, elevated visceral fat is more prominent, and significant insulin resistance can occur even at a non-elevated BMI; this is an important clinical characteristic of Chinese middle-aged and older adults.

2. Lipid Metabolism Abnormalities and Atherosclerosis

Dyslipidaemia directly determines the risk of acute cardiovascular events in middle-aged and older adults. Clinical classifications include hypercholesterolaemia, hypertriglyceridaemia, and mixed dyslipidaemia; in middle-aged and older populations in Taiwan and mainland China, mixed dyslipidaemia accounts for more than half of cases and is the most common subtype. Modern lipid management abandons uniform fixed targets and sets LDL-C treatment goals based on overall cardiovascular risk stratification: low risk LDL-C <160 mg/dL; moderate risk <130 mg/dL; high risk (with diabetes or metabolic syndrome) <100 mg/dL; very high risk (previous myocardial infarction, ischaemic stroke, or confirmed atherosclerosis) <70 mg/dL. The IMPROVE-IT clinical trial enrolled 18,144 patients with acute coronary syndrome, comparing simvastatin monotherapy with simvastatin plus ezetimibe combination therapy. In the combination therapy group, LDL-C decreased to 53.2 mg/dL, significantly lower than the 69.9 mg/dL in the monotherapy group; the relative risk of the primary composite cardiovascular endpoint decreased by 6.4%. This large RCT confirmed that in very high-risk populations, LDL-C reduction below 70 mg/dL continues to yield cardiovascular benefit, supporting an intensive lipid-lowering strategy for very high-risk patients.

The atherosclerotic disease course is divided into four stages: LDL oxidative modification, vascular endothelial inflammatory injury, atheromatous plaque formation, and unstable plaque rupture. The vascular self-repair capacity of middle-aged and older adults is significantly reduced; at equivalent lipid levels, plaques are more prone to

conversion to an unstable phenotype, and the risk of acute thrombotic events is higher than in younger populations. It must be emphasised that lipid management in middle-aged and older adults requires balancing sarcopenia, nutrition, and frailty status; for frail older patients, lipid-lowering drugs require a full benefit–risk trade-off, and the targets for young high-risk populations must not be mechanically applied. Beyond LDL-C, the clinical value of residual cholesterol, lipoprotein(a), and high triglycerides in middle-aged and older adults with mixed dyslipidaemia is increasingly prominent. Visceral fat accumulation is accompanied by high triglycerides, driving hepatic synthesis of remnant lipoproteins; remnant cholesterol is a cardiovascular risk factor independent of LDL-C, and is particularly elevated in individuals with metabolic syndrome and prediabetes. At the lifestyle intervention level, moderate weight loss, omega-3 fatty acid supplementation, and strict restriction of refined carbohydrates and fructose can improve high triglyceride-mediated residual lipid risk.

3. Uric Acid Metabolism and Hyperuricaemia

Hyperuricaemia is not merely a precursor to gout but is also an independent risk factor for metabolic syndrome, chronic kidney disease, and cardiovascular disease. Hyperuricaemia in middle-aged and older adults has age-specific pathogenic mechanisms: accelerated cell turnover increases endogenous purine production; physiological ageing of the kidney leads to decline in glomerular filtration and renal tubular uric acid transport function; the kidney undertakes approximately 70% of uric acid excretion, and excretion efficiency decreases with age; ageing of the intestinal flora reduces the capacity of the intestinal pathway responsible for approximately 30% of uric acid decomposition and excretion, ultimately forming a dual imbalance of 'increased production and decreased excretion'. Clinical decision-making for asymptomatic hyperuricaemia must adhere to risk stratification, opposing both extremes of 'treating everyone with drugs' and 'completely ignoring the condition'. When patients have comorbid chronic kidney disease, hypertension, diabetes, or cardiovascular disease, active uric acid control can achieve target organ protection; for individuals without comorbidities and with only mildly elevated uric acid, first-line intervention prioritises lifestyle modification: restriction of high-purine animal foods, abstinence from alcohol, avoidance of high-fructose beverages, moderate weight management, and adequate water intake. An important clinical misconception is that uric acid should be lowered as much as possible; uric acid possesses important physiological antioxidant functions in the human body, and excessive uric acid reduction may carry potential risks such as impaired antioxidant defence in the nervous system. The therapeutic goal is therefore to maintain an appropriate concentration range, rather than to pursue unlimited reduction of uric acid. During acute gout attacks, anti-inflammatory analgesia is prioritised, and urate-lowering drugs are initiated in the non-acute phase, with drug dosage adjusted according to renal function.

4. Thyroid Function

T3 and T4 thyroid hormones are known as the master switches of systemic metabolic regulation. Subclinical hypothyroidism (SCH) is the most common endocrine abnormality in middle-aged and older adults, with a population prevalence of 10%–15%; its laboratory features are elevated TSH with free T3 and free T4 within the reference range. The TSH reference range in middle-aged and older adults is physiologically up-regulated with age; directly applying the reference standards for young people leads to a large number of overdiagnoses and over-replacement therapy, which is a prominent real-world problem in geriatric endocrinology. SCH interferes with metabolic homeostasis in middle-aged and older adults in three ways. Firstly, Lipid metabolism: insufficient thyroid hormone inhibits fat decomposition and cholesterol clearance, elevates LDL-C, accumulates visceral fat, and aggravates mixed dyslipidaemia; Secondly, Cognitive brain ageing: long-term untreated SCH can cause forgetfulness and decreased attention, accelerating cognitive decline; Finally, Bone remodelling: thyroid hormones participate in the balance between osteoblasts and osteoclasts, and abnormal function accelerates bone loss. Meta-analyses have confirmed that severe SCH with TSH ≥10 mIU/L is associated with a significantly increased risk of coronary heart disease events. In the subgroup with mild SCH and TSH between 4.5 and 10 mIU/L, if TPOAb thyroid autoantibodies are positive, this suggests the presence of autoimmune inflammatory damage, and close follow-up assessment should be conducted; for older adults with mildly elevated TSH and negative antibodies, the initiation of levothyroxine replacement therapy requires a weighing of benefits and risks, and universal administration is not recommended. Clinically, attention must also be paid to subclinical hyperthyroidism, which is likewise highly prevalent in older populations and can induce atrial fibrillation and rapid bone loss; screening cannot focus solely on elevated TSH. Thyroid function and MASLD and insulin resistance exhibit bidirectional interactions: thyroid abnormalities aggravate fatty liver, and metabolic inflammation in turn interferes with the feedback regulation of the pituitary–thyroid axis.

5. Metabolic Dysfunction-Associated Steatotic Liver Disease

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the terminal target organ injury where multiple metabolic abnormalities converge. The prevalence in middle-aged and older adults in Taiwan is as high as 40%–50%; more than 80% of patients with metabolic syndrome have comorbid MASLD. The complete disease spectrum is: simple steatosis → metabolic-associated steatohepatitis (MASH) → liver fibrosis → cirrhosis → hepatocellular carcinoma; the overall disease course can last 10–20 years. The simple steatosis stage has no hepatocellular inflammatory injury and is fully reversible; once MASH develops, oxidative stress and chronic inflammation are initiated, the fibrotic process begins, and the difficulty of reversal increases significantly. Lifestyle intervention is the fundamental means of MASLD/MASH management. A pooled analysis of the Pivens and FLINT trials showed that for every 1 kg of body weight lost, the odds of histological improvement in MASH increased by 7%, and the odds of improvement in liver fibrosis increased by 5%; in participants achieving ≥7% weight loss, the MASH inflammation resolution rate was 64%, and the fibrosis improvement rate reached 90%. The FLINT study confirmed that obeticholic acid can improve liver fibrosis, but the drug elevates LDL-C; in middle-aged and older

adults whose lipid metabolism is already declining, the cardiovascular risk must be carefully weighed, and it cannot be used as a first-line drug for general middle-aged and older adults with MASLD. The clinical characteristics of MASLD in older adults are often underestimated: many older individuals are not obese by BMI but have high visceral fat and comorbid sarcopenia, i.e., sarcopenic obesity, and still develop severe fatty liver. Even in middle-aged and older adults with normal BMI, MASLD should be included in metabolic screening programmes. The FIB-4 index, as a non-invasive screening tool for liver fibrosis, is suitable for large-scale health examination scenarios in middle-aged and older adults.

6. Chronic Kidney Disease (CKD)

Chronic kidney disease is staged G1–G5 using eGFR combined with the urine albumin-to-creatinine ratio. In healthy middle-aged and older adults, eGFR declines physiologically by approximately 1 mL/min/1.73 m² per year; when diabetes and hypertension are comorbid, the rate of eGFR decline accelerates to 2–4 units per year. Diabetes and hypertension together contribute to more than 60% of CKD aetiology; long-term accumulation of metabolic disturbances attacks the kidney; CKD in turn further interferes with glucose, lipid, uric acid, and calcium–phosphorus metabolism, forming a multi-system vicious cycle. DAPA-CKD is a landmark trial in renal protection, enrolling 4,304 participants with CKD with eGFR 25–75 mL/min/1.73 m² and proteinuria, randomised to dapagliflozin or placebo. Over a median follow-up of 2.4 years, the risk of the primary composite endpoint (≥50% decline in eGFR, end-stage renal disease, or renal or cardiovascular death) decreased by 39% in the dapagliflozin group (HR=0.61, 95% CI 0.51–0.72, P<0.001). The most critical breakthrough of this study is that the renal protective effect of SGLT-2 inhibitors is independent of glucose-lowering effects; non-diabetic CKD populations also obtain significant benefit. RAS blockers combined with SGLT-2 inhibitors have now become the standard treatment regimen for medium- to high-risk CKD. Core points in the management of CKD in middle-aged and older adults: distinguish physiological eGFR ageing from pathological renal injury; urine albumin reflects pathological injury better than eGFR alone; metabolic indicator control targets are dynamically adjusted according to the CKD stage, and uric acid, lipid, and glucose targets all need to be combined with CKD staging; avoid nephrotoxic drugs; nutritional intervention should not be rigidly low-protein; in CKD populations with comorbid sarcopenia, excessive restriction of protein intake aggravates muscle wasting, and protein intake must be individualised. At the same time, clinical attention should be paid to the potential impact of SGLT-2 inhibitors on body composition; some observational studies suggest that SGLT-2i may slightly reduce skeletal muscle mass, but handgrip strength and sarcopenia prevalence do not significantly worsen, and concomitant resistance exercise is recommended to offset potential risk.

Systemic-Level Metabolic Regulation

A single organ metabolic axis cannot fully explain the metabolic transition in middle-aged and older adults. Bone, skeletal muscle, mitochondria, the intestinal microbiome, and systemic chronic low-grade inflammation are interconnected, constituting a cross-tissue regulatory network that forms the underlying biological basis linking the six major metabolic axes.

1. Bone Metabolism and Calcium–Phosphorus Homeostasi

Age-related bone metabolic imbalance is essentially decreased osteoblast activity with relatively hyperactive osteoclast activity. Bone mineral density T-score criteria: T≥−1.0 normal bone mass; −1.0 to −2.5 osteopenia; ≤−2.5 osteoporosis. The population with osteopenia is enormous, yet clinical screening and intervention rates are low; this represents the most important intervention window before osteoporosis. The USPSTF systematic review included 11 RCTs with a total of 51,419 community-dwelling middle-aged and older adults. The results showed that additional calcium plus vitamin D supplementation in the general community population did not effectively prevent hip fracture (RR=1.09, 95% CI 0.85–1.39); however, in populations with severe serum 25-(OH)-D deficiency (<20 ng/mL), vitamin D supplementation significantly reduced the risk of falls. This evidence suggests that skeletal nutrition management has entered a precision era: test first, supplement later; dietary natural calcium intake is preferred over nutritional supplements; routine blind high-dose calcium supplementation is not recommended for all middle-aged and older adults. Bone is not a static supporting organ; osteocytes secrete osteocalcin and other bone-derived factors that participate in insulin sensitivity and systemic energy metabolism regulation, and bone possesses endocrine organ properties. Sarcopenia and osteoporosis are frequently comorbid, termed sarcopenia–osteoporosis comorbidity syndrome. Chronic low-grade inflammation, TNF-α and IL-6, both promote muscle protein breakdown and stimulate osteoclast activation; insulin resistance, hyperuricaemia, and CKD calcium–phosphorus metabolic disturbance further aggravate bone loss. Therefore, bone health management cannot focus solely on bone mineral density; muscle status, inflammation levels, and renal function must be assessed simultaneously.

2. Skeletal Muscle Metabolism, Anabolic Resistance, Sarcopenia, and Sarcopenic Obesity

Skeletal muscle is the largest metabolic organ in the human body, and muscle mass and function directly determine overall metabolic efficiency. The EWGSOP2 (2019) international consensus diagnostic criteria for sarcopenia: decreased muscle mass plus either decreased muscle strength (handgrip strength measurement) or decreased physical performance (gait speed measurement) confirms sarcopenia. The most core pathological feature of skeletal muscle in middle-aged and older adults is anabolic resistance: a significant decrease in the sensitivity of muscle cells to dietary protein-stimulated synthesis. In young people, 20 g of high-quality protein per meal is sufficient to achieve maximal muscle protein synthesis (MPS); middle-aged and older adults require 30–40 g per meal to overcome the anabolic resistance threshold. Leucine is the only essential amino acid that directly stimulates MPS, with a threshold of 2.5–3.0 g for maximal synthetic response. Key dietary strategy points: protein should be evenly distributed across three meals a day, with each meal reaching the required dose; protein supplementation within 2 hours after resistance exercise can further increase MPS by approximately 40%.

Sarcopenic obesity is a special phenotype with high incidence in late middle age: BMI normal or even overweight, with massive visceral fat accumulation and decreased appendicular skeletal muscle mass. This population cannot be identified by traditional BMI, and simultaneously bears high risks of insulin resistance, falls, and cardiovascular disease, with an extremely high clinical missed diagnosis rate. Health examinations for middle-aged and older adults should incorporate handgrip strength, gait speed, and appendicular skeletal muscle mass assessment. Sarcopenia and insulin resistance mutually aggravate each other: insufficient muscle mass reduces glucose disposal capacity, worsening insulin resistance; insulin resistance and chronic inflammation in turn inhibit muscle protein synthesis and promote muscle protein breakdown. Myokines, as signalling molecules secreted by skeletal muscle, mediate long-distance communication from muscle to liver, adipose tissue, bone, and blood vessels, and play an important role in the metabolic transition of middle-aged and older adults.

3. Mitochondrial Functional Decline

Mitochondrial ageing is the cellular root of metabolic decline in middle-aged and older adults, with four core features: accumulation of mtDNA mutations, reduced mitochondrial biogenesis, impaired mitophagy, and a shift in overall energy metabolic pathways. Mitochondrial dysfunction is a shared molecular mechanism of type 2 diabetes, cardiovascular disease, and neurodegenerative diseases. Exercise is the strongest non-pharmacological intervention for improving mitochondrial function. Robinson *et al*. (2017) [31], publishing in Cell Metabolism, enrolled 72 sedentary older adults aged 65–80 years, comparing HIIT interval aerobic training, resistance strength training, combined training, and a blank control group. After 12 weeks of intervention: the HIIT group showed a 69% increase in mitochondrial respiratory capacity, a 30% increase in insulin sensitivity, and a 17% increase in maximal oxygen uptake; resistance training significantly increased muscle mass and strength but had limited effect on improving mitochondrial respiratory function. This study established the principle of exercise prescription differentiation: increasing muscle mass and strength relies on resistance training; improving mitochondria and enhancing metabolic anti-ageing relies on interval aerobic training; the two functions are complementary and cannot replace each other. The exercise prescription for metabolic health in middle-aged and older adults must combine both types of exercise: resistance training 2–3 times per week, combined with aerobic (interval or moderate-intensity continuous aerobic) training; balance training should also be added to reduce fall risk. Simple walking is insufficient to reverse mitochondrial ageing; strength training alone yields limited improvement in mitochondrial oxidative metabolism. Mitochondria are simultaneously a source of oxidative stress and inflammatory signals; damaged mitochondria release DAMP damage-associated molecular patterns, activating the NLRP3 inflammasome and further amplifying systemic chronic low-grade inflammation, forming a vicious cycle of mitochondrial damage–inflammation–further mitochondrial damage.

4. Inflammaging, the SASP Phenotype of Senescent Cells

Franceschi *et al*. formally proposed the concept of inflammaging in 2000: a non-infectious, persistent, low-grade systemic sterile inflammatory state accompanying ageing, without the clinical manifestations of acute inflammation such as redness, swelling, heat, and pain, but continuously driving tissue damage and metabolic imbalance. Key markers include hs-CRP, IL-6, TNF-α, and IL-1β; IL-6 is the most important cytokine linking adipose tissue, liver, skeletal muscle, and blood vessels. Visceral fat secretes large amounts of IL-6, stimulating hepatic CRP synthesis while directly antagonising insulin signal transduction. Senescent cells stop the cell cycle but do not undergo apoptosis, continuously secreting the SASP senescence-associated secretory phenotype and releasing large amounts of pro-inflammatory cytokines and proteases, and are an important source of inflammaging. The CANTOS clinical trial was a landmark verification of the inflammation–atherosclerosis hypothesis. A total of 10,061 participants with previous myocardial infarction and hs-CRP ≥2 mg/L were randomised to canakinumab (an anti-IL-1β monoclonal antibody) or placebo. The canakinumab group showed a 15% reduction in the risk of the primary composite cardiovascular endpoint (HR=0.85, 95% CI 0.74–0.98, P =0.021), with no statistically significant difference in lipid levels between the two groups. The results confirmed that inflammation is a cardiovascular risk factor independent of blood lipids; anti-inflammatory intervention can reduce cardiovascular events without altering cholesterol levels; inflammation control should be incorporated into the metabolic management framework for middle-aged and older adults. Inflammation and metabolism form a closed vicious cycle: visceral fat expansion → release of pro-inflammatory cytokines → insulin resistance and mitochondrial damage; insulin resistance and mitochondrial damage further release DAMP molecules, activating inflammasomes, elevating pro-inflammatory cytokines, and continuously attacking muscle, bone, liver, blood vessels, and kidneys. Senolytics (senescent cell-clearing drugs) can selectively clear senescent cells and significantly improve metabolic phenotypes in animal experiments, but human clinical trial evidence is still insufficient, and they cannot yet enter routine clinical practice.

5. Intestinal Microbiome Disturbance

Ageing is accompanied by decreased intestinal microbial diversity, reduced abundance of beneficial bacteria, expansion of opportunistic pathogens, and increased intestinal barrier permeability (leaky gut); microbial products and endotoxins enter the circulation, driving systemic low-grade inflammation. Short-chain fatty acids (SCFAs) are products of dietary fibre fermentation by intestinal flora, and can improve insulin sensitivity and inhibit inflammatory signalling pathways; age-related changes in the flora of middle-aged and older adults result in reduced SCFA production. The intestinal flora also participates in uric acid decomposition and bile acid metabolism, and therefore directly participates in the regulation of glucose, lipid, and uric acid metabolism. At present, high-quality RCT evidence for probiotic and prebiotic intervention in middle-aged and older adults remains inconsistent. Animal and small-sample human

studies suggest that supplementation with specific probiotics can improve inflammatory indicators, but the results of large-sample RCTs are highly heterogeneous. At this stage, probiotics are not recommended as a routine treatment for metabolic diseases; at the dietary level, increasing diverse dietary fibre such as whole grains, vegetables, and legumes to maintain the intestinal microecology is the strategy with the highest level of evidence. Faecal microbiota transplantation in the field of geriatric metabolism is still at the basic research stage, and there is still a considerable distance before routine clinical application.

Integrated Management Framework for Metabolic Health

Based on the aforementioned pathophysiological mechanisms and clinical trial evidence, this article proposes a 'stratified assessment–precision intervention–dynamic monitoring' multi-system metabolic integrated management framework. Core principles: lifestyle intervention as the cornerstone; risk stratification guiding individualised targets; equal emphasis on biochemical indicators and physical function; preservation of independent living capacity as the ultimate clinical goal.

In addition to traditional blood glucose, blood lipids, liver and kidney function, uric acid, and thyroid function, metabolic assessment in middle-aged and older adults must supplement ageing–metabolic functional indicators.

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