CHAPTER 11

ETIOLOGY AND PATHOPHYSIOLOGY OF METABOLIC DYSFUNCTION: FROM OBESITY TO SYSTEMIC METABOLIC DISORDERS

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INTRODUCTION

Contemporary metabolic disease is increasingly understood as a systemic regulatory problem rather than a set of unrelated diagnoses. Obesity, insulin resistance, type 2 diabetes mellitus, dyslipidemia, arterial hypertension, metabolic dysfunction-associated steatotic liver disease (MASLD), cardiovascular disease, and related conditions commonly cluster within the same patient and are connected by overlapping biological processes. This shared background makes metabolic dysfunction a major challenge for modern medicine.[1]

A simple energy-balance model explains only part of this complexity. Sustained caloric excess is clearly important in obesity, yet comparable body mass index values can be associated with very different cardiometabolic profiles, and substantial metabolic impairment may also occur without overt obesity. Attention has therefore shifted toward where and how energy is stored, the functional state of adipose tissue, ectopic lipid deposition, insulin sensitivity, inflammatory and redox control, inherited susceptibility, and communication between the host and its intestinal microbial ecosystem.

Adipose tissue has an active endocrine and metabolic role in this system. Visceral fat is especially relevant because its release of free fatty acids, adipokines, cytokines, and other mediators can influence hepatic metabolism, insulin action, vascular biology, and systemic inflammation. Consequently, the consequences of excess weight depend not only on adipose mass but also on its distribution and functional state. This helps explain why metabolic impairment may be pronounced in some normal-weight individuals, whereas some people

[1] Plakida A., Iushkovska O., Sierpińska L. E. Metabolically associated fatty liver disease: What hepatologists need to know about this systemic disease. World Journal of Hepatology. 2026. Vol. 18, No. 3. Art. 113284. DOI: 10.4254/wjh.v18.i3.113284; Lim S., Kim J. W., Targher G. Links between metabolic syndrome and metabolic dysfunction-associated fatty liver disease. Trends in Endocrinology & Metabolism. 2021. Vol. 32, No. 7. P. 500–514. DOI: 10.1016/j.tem.2021.04.008.

with obesity retain a comparatively favorable metabolic profile for considerable periods.[2]

With prolonged nutrient surplus, the ability of adipose tissue and other metabolic organs to accommodate and process substrates may become insufficient. The resulting rise in lipolysis and ectopic lipid storage is accompanied by mitochondrial strain, oxidative imbalance, and inflammatory activation, progressively disrupting glucose and lipid regulation. Insulin resistance is central to this process, but it is better viewed as both a product and a driver of adipose dysfunction, lipotoxicity, oxidative stress, and low-grade inflammation. These reciprocal effects allow metabolic disturbances to perpetuate and amplify one another.

The intestinal microbiota adds another regulatory layer to this model. Microbial communities contribute to nutrient transformation, generation of bioactive metabolites, epithelial barrier maintenance, and mucosal and systemic immune regulation. Diet and the metabolic state of the host can alter microbial structure and function; conversely, microbial metabolites and microbial-associated signals can modify permeability, inflammatory responses, insulin action, and metabolism outside the intestine. The relevant unit of interpretation is therefore an interacting host–microbiome system rather than a series of isolated organs.

The purpose of this chapter is to summarize the principal etiological factors and interconnected pathophysiological mechanisms underlying metabolic dysfunction, with particular emphasis on obesity, visceral adiposity, insulin resistance, lipid overload, oxidative stress, chronic low-grade inflammation, and gut–host interactions. These mechanisms provide the conceptual framework for interpreting the experimental effects of mineral water administration on microbial and host metabolic responses presented in the subsequent section.

1. Etiological basis of metabolic dysfunction

1.1. Obesity, diet, and visceral adiposity

Excess adiposity is a major driver of metabolic dysfunction, although body mass by itself is an incomplete predictor of its biological consequences. The phenotype that develops reflects cumulative energy excess together with dietary composition, adipose-tissue distribution and function, physical activity, age, genetic background, and environmental influences.

[2] Bou Matar D., Zhra M., Nassar W. K. et al. Adipose tissue dysfunction disrupts metabolic homeostasis: mechanisms linking fat dysregulation to disease. Frontiers in Endocrinology. 2025. Vol. 16. Art. 1592683. DOI: 10.3389/fendo.2025.1592683.

During early positive energy balance, adipocyte triglyceride storage serves an adaptive purpose by limiting lipid exposure of non-adipose tissues. Problems arise when subcutaneous storage capacity becomes inadequate or dysfunctional: adipocytes enlarge, tissue oxygenation and extracellular-matrix organization deteriorate, inflammatory-cell recruitment increases, and insulin becomes less effective at restraining lipolysis. Greater free-fatty-acid flux then favors lipid deposition in the liver, skeletal muscle, pancreas, and other sites not designed for sustained energy storage.

Where fat is stored is therefore clinically and biologically important. Compared with subcutaneous depots, visceral adipose tissue has a more adverse metabolic and inflammatory profile and is closely linked to insulin resistance. Progressive visceral adiposity is associated with altered adipokine signaling, including increased pro-inflammatory mediators such as TNF-α and IL-6 and reduced metabolically protective adiponectin. Liver-focused studies further associate visceral fat with steatosis, inflammatory activity, and fibrosis.[3]

Diet modifies metabolic regulation through both the amount and the nature of supplied substrates. High intake of saturated fat, refined carbohydrate, and simple sugars favors excess substrate delivery and hepatic de novo lipogenesis. Large fructose loads are particularly relevant because hepatic fructose metabolism can facilitate lipogenesis, triglyceride accumulation, and cellular metabolic stress. In contrast, fiber-rich, minimally processed plant foods affect satiety and energy density while also changing substrates available to intestinal microorganisms and their metabolite production.[4]

Accordingly, obesity becomes metabolically hazardous when safe storage and utilization of surplus energy can no longer be maintained. Visceral fat expansion, impaired adipocyte function, increased fatty-acid flux, disturbed adipokine signaling, and ectopic lipid deposition form a set of transitional events linking prolonged nutritional excess to systemic metabolic disease.

1.2. Genetic and epigenetic susceptibility

The development and severity of metabolic disorders vary considerably among individuals exposed to similar nutritional and environmental conditions, indicating an important role for inherited susceptibility. Genetic factors can influence adipose tissue distribution, insulin signaling, lipid metabolism, energy

[3] van der Poorten D., Milner K. L., Hui J. et al. Visceral fat: a key mediator of steatohepatitis in metabolic liver disease. Hepatology. 2008. Vol. 48, No. 2. P. 449–457. DOI: 10.1002/hep.22350.

[4] Yki-Järvinen H., Luukkonen P. K., Hodson L., Moore J. B. Dietary carbohydrates and fats in nonalcoholic fatty liver disease. Nature Reviews Gastroenterology & Hepatology. 2021. Vol. 18. P. 770–786. DOI: 10.1038/s41575-021-00472-y.

expenditure, hepatic lipid handling, inflammatory responses, and the propensity to develop organ-specific complications.

Evidence from steatotic liver disease provides a well-characterized example of this genetic contribution. Variants in **PNPLA3**, particularly rs738409, influence hepatic triglyceride remodeling and are strongly associated with hepatic steatosis and disease progression. Other variants, including **TM6SF2** rs58542926 and **MBOAT7** rs641738, affect very-low-density lipoprotein handling and phospholipid remodeling, respectively. These observations illustrate a broader principle: metabolic dysfunction arises from the interaction between environmental exposure and biological susceptibility rather than from either component alone.[5]

Genetic predisposition is further modified by epigenetic regulation. DNA methylation, histone modifications, and non-coding RNAs can alter gene expression without changing the nucleotide sequence and provide a biological interface through which nutrition, physical activity, metabolic status, aging, and environmental exposures may influence long-term phenotype. Alterations in microRNA expression, including miR-122 and miR-223, have been described in metabolically associated liver injury and illustrate how epigenetic regulation may accompany disease progression.

Importantly, genetic and epigenetic mechanisms should not be interpreted deterministically. Most common metabolic diseases are polygenic and strongly modified by lifestyle and environmental exposure. Genetic variants influence susceptibility and the threshold at which metabolic compensation fails, whereas epigenetic mechanisms may contribute to adaptation – or maladaptation – to persistent nutritional and metabolic stress.

1.3. Environmental and lifestyle factors

The rapid global increase in metabolic disorders cannot be explained by genetic changes occurring over such a short period. Environmental and behavioral factors therefore represent major determinants of disease expression in genetically susceptible populations.

Reduced physical activity is particularly important. Skeletal muscle constitutes a major site of insulin-mediated glucose disposal, and regular muscular activity improves insulin sensitivity, mitochondrial function, fatty acid oxidation, and energy expenditure. Sedentary behavior therefore contributes not merely to reduced caloric expenditure but to deterioration of metabolic flexibility and insulin responsiveness.

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[5] Plakida A., Iushkovska O., Sierpińska L. E. Metabolically associated fatty liver disease: What hepatologists need to know about this systemic disease. World Journal of Hepatology. 2026. Vol. 18, No. 3. Art. 113284. DOI: 10.4254/wjh.v18.i3.113284.

Sleep disturbance, chronic psychosocial stress, smoking, alcohol exposure, medications, and disruption of circadian rhythms can further modify metabolic regulation. These influences interact with endocrine and autonomic mechanisms, dietary behavior, inflammatory activity, and glucose and lipid metabolism. Environmental factors may also modify the intestinal microbiota, adding another level through which lifestyle becomes biologically embedded.[6]

Accordingly, the etiology of metabolic dysfunction is best described as **multifactorial and interactive**. Nutritional excess and obesity remain major drivers, but their consequences are shaped by adipose tissue distribution, inherited susceptibility, epigenetic regulation, physical activity, environmental exposures, and the capacity of multiple physiological systems to adapt to prolonged metabolic challenge.

2. Major pathophysiological networks

2.1. Insulin resistance and metabolic inflexibility

Insulin resistance denotes an inadequate biological response of insulin-sensitive tissues to prevailing insulin concentrations and disrupts both glucose and lipid handling in adipose tissue, skeletal muscle, and liver. Within metabolic disease it is not simply a downstream effect of obesity. Instead, it participates in reciprocal interactions through which several metabolic abnormalities sustain and intensify one another.

Loss of insulin-mediated restraint of adipose lipolysis increases circulating free fatty acids and their delivery to liver and muscle, where intracellular lipid excess can further weaken insulin signaling. Hepatic insulin resistance also reduces insulin's ability to suppress glucose output, even while de novo lipogenesis remains active or becomes enhanced. Thus, excessive hepatic glucose production can coexist with continued lipid synthesis. Our MASLD review discusses this paradox within the broader reciprocal relationship linking insulin resistance, hepatic lipid accumulation, oxidative stress, and inflammation.[7]

Skeletal muscle insulin resistance reduces glucose uptake and glycogen synthesis, thereby increasing the metabolic burden placed on pancreatic β-cells. Compensatory hyperinsulinemia may initially preserve near-normal glucose

[6] Breuninger T. A., Wawro N., Breuninger J. et al. Associations between habitual diet, metabolic disease, and the gut microbiota using latent Dirichlet allocation. Microbiome. 2021. Vol. 9. Art. 61. DOI: 10.1186/s40168-020-00969-9.

[7] Armandi A., Rosso C., Caviglia G. P., Bugianesi E. Insulin resistance across the spectrum of nonalcoholic fatty liver disease. Metabolites. 2021. Vol. 11, No. 3. Art. 155. DOI: 10.3390/metabo11030155.

concentrations, but prolonged metabolic stress can ultimately contribute to impaired glucose tolerance and type 2 diabetes.

Metabolic inflexibility describes a related failure to adjust fuel selection appropriately to fasting, feeding, and changing energy requirements. Healthy metabolism shifts toward lipid oxidation during fasting and toward glucose use and storage after feeding. Obesity and insulin resistance blunt this transition, while persistent substrate availability, mitochondrial stress, ectopic lipid accumulation, and defective insulin signaling progressively narrow the capacity to adapt fuel utilization.

Insulin resistance consequently functions as both an indicator and a propagator of systemic metabolic disturbance. By linking adipose tissue, skeletal muscle, liver, and pancreatic responses, it helps convert initially compensatory adaptations to nutrient excess into persistent pathological regulation.

2.2. Lipid overload and lipotoxicity

A second major disturbance emerges when lipid supply exceeds the capacity of adipose tissue to buffer surplus energy. Free-fatty-acid concentrations rise and lipid begins to accumulate in tissues whose primary function is not long-term energy storage.

The presence of intracellular triglyceride should not itself be equated with toxicity, because esterification into triglyceride can initially sequester fatty acids in a relatively safer form. Injury is more closely related to free cholesterol and bioactive lipid intermediates that can provoke endoplasmic-reticulum stress, mitochondrial dysfunction, oxidative damage, inflammatory signaling, and apoptosis. In the liver, fatty acids derived from adipose lipolysis and diet combine with de novo synthesis to increase lipid burden and activate inflammatory and fibrogenic pathways.[8]

Lipotoxicity is not confined to hepatic tissue. Ectopic lipid deposition in skeletal muscle interferes with insulin signaling and substrate oxidation, while lipid accumulation in and around the pancreas may contribute to β-cell dysfunction. Similar mechanisms affect the cardiovascular system and kidneys. Lipid overload should therefore be viewed as a systemic redistribution problem arising when normal energy-storage capacity becomes insufficient.

Lipotoxicity and insulin resistance can therefore reinforce each other. Reduced insulin control of adipose tissue increases fatty-acid release; greater lipid delivery promotes ectopic accumulation; lipid intermediates interfere with

[8] Yki-Järvinen H., Luukkonen P. K., Hodson L., Moore J. B. Dietary carbohydrates and fats in nonalcoholic fatty liver disease. Nature Reviews Gastroenterology & Hepatology. 2021. Vol. 18. P. 770–786. DOI: 10.1038/s41575-021-00472-y.

insulin signaling; and the resulting deterioration of insulin sensitivity further accelerates lipolysis. This reciprocal cycle links dysfunctional adipose storage to metabolic injury across multiple organs.

2.3. Oxidative stress and chronic low-grade inflammation

Oxidative stress reflects a loss of balance between oxidant generation and the antioxidant systems that normally preserve redox control. Reactive oxygen species are not intrinsically pathological and have physiological signaling functions; damage develops when their formation is excessive or antioxidant capacity is no longer sufficient to contain it.

Chronic substrate excess places sustained pressure on mitochondrial metabolism, favoring incomplete fatty-acid oxidation, electron leakage, and increased formation of reactive oxygen species. Lipid oxidation generates reactive products such as malondialdehyde and 4-hydroxynonenal, while oxidative injury can also affect proteins and nucleic acids. The cumulative result includes impaired mitochondrial performance, membrane damage, disturbed signaling, and less efficient cellular energy production.[9]

Redox and inflammatory disturbances are tightly coupled. Oxidant excess can trigger stress-responsive inflammatory pathways, whereas cytokines and activated immune cells can increase oxidant generation in return. Within expanding adipose tissue, adipocyte hypertrophy, relative hypoxia, cellular stress, and immune-cell recruitment favor a pro-inflammatory shift with increased production of mediators including TNF-α, IL-6, and IL-1β.

The inflammatory state associated with obesity differs from the intense short-lived response to acute infection or tissue injury. It is lower in magnitude but persistent and integrated with metabolism. Over time, inflammatory mediators impair insulin signaling, alter adipocyte and hepatic function, affect vascular endothelium, and contribute to the spread of insulin resistance across the organism.[10]

Inflammatory regulation also involves the intestinal ecosystem. Greater translocation or exposure to microbial-associated signals, including lipopolysaccharide, can engage pattern-recognition receptors and maintain innate immune activation. As emphasized in our microbiota work, these responses are

[9] Masenga S. K., Kabwe L. S., Chakulya M., Kirabo A. Mechanisms of oxidative stress in metabolic syndrome. International Journal of Molecular Sciences. 2023. Vol. 24, No. 9. Art. 7898. DOI: 10.3390/ijms24097898.

[10] Schwärzler J. et al. The pathophysiology of MASLD: an immunometabolic perspective. Expert Review of Clinical Immunology. 2024. Vol. 20, No. 4. P. 375–386. DOI: 10.1080/1744666X.2023.2294046.

better interpreted as part of disturbed host–microbiome communication than as isolated immune abnormalities, because their consequences can extend from the intestine to metabolically active peripheral tissues.

Consequently, oxidative stress and chronic inflammation form a mutually reinforcing axis connecting nutritional excess, mitochondrial dysfunction, insulin resistance, intestinal disturbances, and organ injury.

2.4. Gut microbiota and intestinal barrier

The gut microbiota is a changing ecological community with functions that include nutrient transformation, synthesis of bioactive products, immune maturation, support of epithelial integrity, and participation in host energy regulation. Its metabolic influence consequently reaches well beyond the intestinal lumen.[11]

Barrier function depends on several coordinated components rather than the epithelium alone. Mucus, epithelial cells and their tight junctions, mucosal immune defenses, antimicrobial peptides, immunoglobulin A, and the gut-vascular barrier collectively permit controlled nutrient absorption while limiting inappropriate passage of microorganisms and microbial products.[12]

Obesity and unfavorable dietary patterns can restructure microbial communities and alter their function, but such changes cannot be captured reliably by labeling individual organisms as universally 'beneficial' or 'harmful.' The effect of a taxon depends on its ecological setting, available substrates, interactions with neighboring microorganisms, metabolic activity, and host conditions. Functional reorganization of the microbial ecosystem is therefore a more useful framework for metabolic disease than a simple good-versus-bad classification.

Microbial functional changes may alter short-chain-fatty-acid generation, bile-acid conversion, choline pathways, tryptophan-derived signaling, and numerous other bioactive products. At the same time, loss of barrier integrity increases host contact with microbial components. Lipopolysaccharide and related molecular patterns may then reach epithelial, vascular, and systemic compartments and stimulate innate immune pathways that contribute to metabolic inflammation.

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[11] Vallianou N. G., Kounatidis D., Psallida S. et al. NAFLD/MASLD and the gut-liver axis: from pathogenesis to treatment options. Metabolites. 2024. Vol. 14, No. 7. Art. 366. DOI: 10.3390/metabo14070366.

[12] Benedé-Ubieto R., Cubero F. J., Nevzorova Y. A. Breaking the barriers: the role of gut homeostasis in metabolic-associated steatotic liver disease (MASLD). Gut Microbes. 2024. Vol. 16, No. 1. Art. 2331460. DOI: 10.1080/19490976.2024.2331460; Mouries J., Brescia P., Silvestri A. et al. Microbiota-driven gut vascular barrier disruption is a prerequisite for non-alcoholic steatohepatitis development. Journal of Hepatology. 2019. Vol. 71, No. 6. P. 1216–1228. DOI: 10.1016/j.jhep.2019.08.005.

The direction of influence is not exclusively from microbiota to host. Hyperglycemia, dietary exposure, changes in bile-acid composition, inflammatory activity, medications, and other features of the host metabolic state can reshape the intestinal environment in return. Gut microorganisms are therefore participants in a bidirectional regulatory system, not an isolated upstream cause of metabolic disease.

2.5. Gut–liver and systemic metabolic communication

Communication between intestine and liver is especially direct because portal venous flow delivers absorbed nutrients and a wide range of gut-derived metabolites and microbial products to the liver. Bile-acid derivatives and immune signals add further layers to this interaction. The gut–liver axis is consequently an anatomical connection as well as a metabolic, immunological, and endocrine one.[13]

An intact intestinal barrier limits hepatic and systemic exposure to potentially inflammatory microbial material. Once barrier function deteriorates, portal delivery of microbial products may increase and activate hepatic innate immunity, while altered microbial metabolites can influence lipid and glucose handling, inflammatory tone, and cellular stress pathways.

These interactions are not confined to the liver. Adipose tissue, skeletal muscle, pancreas, vascular endothelium, and intestine continuously exchange substrates, hormones, inflammatory mediators, and metabolites. Dysfunction in one compartment changes the signals received by the others. Consistent with this view, our microbiota review frames obesity-associated metabolic dysfunction as a coordinated multiorgan process rather than an isolated hepatic disorder.

A network model also requires caution when assigning causal direction. Insulin resistance can increase lipid overflow and hepatic steatosis, while a metabolically dysfunctional liver can further impair systemic insulin action. Adipose inflammation promotes hepatic injury, yet liver-derived mediators can modify peripheral metabolism. Likewise, microbial restructuring may contribute to metabolic and inflammatory disturbance while the altered host environment simultaneously selects for further microbial change.

Taken together, these reciprocal interactions are better represented as a self-reinforcing network than as a single linear sequence. Nutritional excess, visceral

[13] Ohtani N., Kamiya T., Kawada N. Recent updates on the role of the gut-liver axis in the pathogenesis of NAFLD/NASH, hepatocellular carcinoma, and beyond. Hepatology Communications. 2023. Vol. 7. Art. e0241. DOI: 10.1097/HC9.0000000000000241; Vallianou N. G., Kounatidis D., Psallida S. et al. NAFLD/MASLD and the gut-liver axis: from pathogenesis to treatment options. Metabolites. 2024. Vol. 14, No. 7. Art. 366. DOI: 10.3390/metabo14070366.

adipose dysfunction, insulin resistance, lipotoxicity, redox imbalance, chronic low-grade inflammation, barrier impairment, and microbial reorientation converge across organs. The clinical and experimental phenotype that emerges depends on the strength of the continuing metabolic challenge relative to the adaptive capacity of host regulatory systems.

This integrated framework is particularly relevant for interpreting interventions that do not act on a single molecular target. Natural therapeutic factors, including mineral waters, contain multiple biologically active components and may influence several interconnected regulatory domains simultaneously. The experimental data presented in the following section therefore provide an opportunity to examine whether modification of the intestinal microbial phenotype during mineral water administration occurs together with coordinated changes in systemic metabolic, redox, and hepatic functional indices.

3. Experimental evidence: mineral water modulation of microbial and host metabolic responses

3.1. Experimental model and rationale

The multifactorial nature of metabolic dysfunction raises an important question regarding the possibility of modifying several interconnected regulatory domains simultaneously rather than targeting an isolated metabolic abnormality. This issue is particularly relevant to balneology, where natural mineral waters represent complex therapeutic factors whose biological effects may involve gastrointestinal, metabolic, neurohumoral, and systemic regulatory mechanisms.[14]

To investigate these relationships, an experimental study was conducted in 18 twelve-month-old female outbred Wistar rats divided into three groups (n = 6 each): intact animals, animals with experimentally induced metabolic syndrome (MetS), and animals with MetS receiving mineral water (MW). Metabolic disturbances were induced over 72 days by combining the standard diet with daily administration of 30 g of white bread per animal and unrestricted access to a 10% fructose solution. This nutritional challenge was maintained unchanged throughout the experiment, including the period of MW administration.

During the final 12 days, animals in the treatment group received low-mineralized alkaline bicarbonate-sodium cold groundwater from well No. 2,

[14] Gozhenko A. et al. The role of macronutrients in the implementation of the corrective effect of low-mineralized water in experimental metabolic syndrome. Roczniki Państwowego Zakładu Higieny. 2020. Vol. 71, No. 4. P. 423–430. DOI: 10.32394/rpzh.2020.0136.

Stara Huta, Ivano-Frankivsk region, Ukraine. Total mineralization of the water was 0.7787 g/L. MW was administered once daily by intragastric gavage at a volume corresponding to 1% of body weight; untreated MetS animals received an equivalent volume of water.

This design is methodologically important for interpretation of the findings. MW was introduced after metabolic and microbial alterations had already developed, while the metabolic challenge itself continued. Consequently, the observed responses cannot be attributed to withdrawal of the dietary stimulus. Rather, they reflect biological changes occurring during continued exposure to the same adverse metabolic conditions.

The experimental assessment integrated two complementary domains. The intestinal microbial component was evaluated by culture-based analysis of fecal samples, while host responses were characterized using biochemical indices reflecting carbohydrate and lipid metabolism, purine metabolism, redox status, membrane-associated ATPase activity, and hepatic functional state. This multidomain approach allowed microbial and host responses to MW administration to be considered within a common experimental framework.

3.2. MetS-Associated restructuring of the culturable intestinal microbiota

Sustained nutritional challenge was accompanied by progressive restructuring of the culturable fecal microbial phenotype. Importantly, the observed changes did not consist of a uniform increase or decrease across microorganisms. Different taxa demonstrated distinct trajectories, indicating ecological reorganization rather than a single-direction microbial response.

By day 60, MetS animals demonstrated marked depletion of Bifidobacterium bifidum and lactose-positive Escherichia coli, whereas Lactobacillus acidophilus increased. At the same time, increased representation of Enterococcus faecalis, Enterobacter cloacae, and Candida albicans was observed, together with detectable Actinomyces spp. These changes indicate that prolonged metabolic challenge affected several microbial groups simultaneously, but in different directions.

This pattern is relevant to the interpretation of obesity- and MetS-associated microbial alterations. Individual microorganisms should not be classified rigidly as intrinsically “beneficial” or “harmful.” Their functional significance depends on abundance, ecological context, interactions with other community members, available substrates, and the physiological state of the host. The simultaneous depletion, expansion, persistence, or emergence of different culturable taxa therefore more appropriately reflects restructuring of the microbial ecosystem than a simple transition from a “normal” to an “abnormal” microbiota.

The culture-based approach used in this experiment necessarily characterizes only the cultivable component of the intestinal microbial community. Nevertheless, its longitudinal application allowed the direction of changes in selected microbial groups to be followed under standardized experimental conditions. The results demonstrated that sustained metabolic challenge was associated with a progressively altered culturable microbial phenotype rather than a stable microbial state.

3.3. Taxon-specific microbial reorientation during mineral water administration

Administration of MW during the final phase of continued metabolic challenge was followed by additional changes in the culturable fecal microbiota. These changes were neither uniform nor equivalent to restoration of the microbial profile observed in intact animals.

Instead, individual taxa demonstrated different response trajectories. Some MetS-associated changes shifted toward the values or detection patterns characteristic of intact animals, whereas others persisted or followed distinct directions. Thus, MW exposure was associated with taxon-specific microbial reorientation rather than a generalized reversal of the MetS-associated microbial phenotype.

This distinction is important. The term restoration would imply re-establishment of a previous microbial state, while normalization would require a defined reference configuration toward which the microbial community consistently returned. Neither interpretation adequately reflects the observed data. The microbial response was heterogeneous and context-dependent, occurring while the nutritional challenge responsible for metabolic disturbance remained active.

The findings therefore suggest that MW acted within an already altered intestinal environment and modified the trajectory of selected culturable microbial populations without erasing the microbial consequences of sustained metabolic stress. From an ecological perspective, such a response may be more biologically plausible than a rapid return to the initial microbial configuration.

The present observations also emphasize the importance of considering microbial dynamics rather than isolated endpoint comparisons. A microorganism that increases during metabolic challenge and subsequently decreases during intervention does not necessarily represent a “pathogenic” taxon that has been eliminated, just as an organism that increases during MW administration cannot automatically be interpreted as beneficial. The relevant phenomenon is the reorganization of relationships within the culturable microbial phenotype under changing host and environmental conditions.

3.4. Multidomain host metabolic response

Microbial reorientation during MW administration occurred together with broad changes in host biochemical indices. In untreated MetS animals, prolonged nutritional challenge was associated with disturbances in carbohydrate, lipid, and purine metabolism, together with altered redox balance and membrane-associated enzymatic activity.

MW administration was accompanied by substantial shifts in several metabolic parameters toward values observed in intact animals. Fasting glucose decreased from 8.20 to 6.17 mmol/L, total cholesterol from 2.22 to 1.61 mmol/L, triglycerides from 2.85 to 1.07 mmol/L, and uric acid from 199.36 to 139.59 μmol/L. The magnitude and direction of these changes indicate a broad metabolic response rather than modification of a single biochemical pathway.

At the same time, indices characterizing redox homeostasis changed in a concordant direction. Malondialdehyde, reflecting lipid peroxidation activity, decreased from 4.25 to 3.08 nmol/(min·mg), whereas catalase activity increased from 0.25 to 0.38%. These findings are consistent with attenuation of the redox imbalance associated with prolonged metabolic challenge.

Changes were also observed in membrane-associated ATPase activities. Mg^{2+}/Ca^{2+}-dependent ATPase increased from 2.65 to 3.84 mg P/g tissue, while $Mg^{2+}/Na^{+}/K^{+}$-dependent ATPase increased from 3.12 to 4.71 mg P/g tissue. Taken together with the metabolic and redox indices, these findings suggest that MW administration was associated with responses involving several levels of host metabolic regulation.

Importantly, movement toward intact-group values should not automatically be described as complete normalization. Glucose and uric acid, in particular, retained evidence of residual metabolic disturbance. The overall host response is therefore better characterized as multidomain metabolic reorientation with partial attenuation of MetS-associated abnormalities.

This interpretation is also consistent with the experimental design. Because the adverse nutritional challenge continued throughout MW administration, improvement in several host indices occurred without removal of the primary metabolic stressor. The findings therefore suggest modulation of the host response to sustained metabolic challenge rather than simple recovery following cessation of the experimental exposure.

3.5. Potential Links Between Microbial and Host Responses

The simultaneous observation of taxon-specific microbial changes and multidomain host metabolic responses raises the possibility that these processes were biologically interconnected. However, interpretation of this relationship requires particular caution.

The intestinal microbiota participates in several mechanisms capable of influencing host metabolism, including production of microbial metabolites, regulation of intestinal barrier function, modulation of immune signaling, and transformation of dietary and endogenous substrates. Conversely, glucose and lipid metabolism, redox state, intestinal substrate availability, host secretions, and other physiological factors can modify the microbial environment. The relationship between microbial and host responses is therefore inherently bidirectional.[15]

Within the present experiment, MW-associated microbial reorientation occurred in parallel with reductions in glucose, cholesterol, triglycerides, uric acid, and malondialdehyde and with increases in catalase and membrane-associated ATPase activities. This directional concordance is compatible with coordinated microbial and host responses to the intervention.

It does not, however, demonstrate that microbial changes mediated the metabolic effects of MW. The experiment did not directly assess short-chain fatty acids, intestinal permeability, circulating endotoxin, inflammatory mediators, or other potential intermediates that would be required to establish specific mechanistic pathways. Nor does the experimental design establish a temporal sequence sufficient to determine whether microbial changes preceded, followed, or developed simultaneously with host metabolic responses.

An equally plausible interpretation is that MW influenced the host and intestinal environment through several parallel mechanisms and that the microbial changes constituted one component of this broader physiological response. Alterations in gastrointestinal conditions, mineral exposure, substrate availability, host metabolism, or other factors could modify microbial ecology while simultaneously affecting systemic metabolic regulation.

Accordingly, the present results are compatible with several established mechanisms of host–microbiome interaction but do not identify a single causal pathway. Distinguishing among these possibilities will require studies integrating longitudinal microbiome assessment with measurements of microbial metabolites, intestinal barrier function, inflammatory signaling, and other intermediate biological variables.

This distinction is important not only methodologically but also conceptually. Complex natural therapeutic factors such as mineral waters may not act through a single molecular target. Their biological effects may instead emerge from simultaneous modification of several interconnected regulatory systems. The parallel microbial, metabolic, redox, and functional responses observed in this experiment are consistent with such a multidomain mode of action.

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[15] Benedé-Ubieto R., Cubero F. J., Nevzorova Y. A. Breaking the barriers: the role of gut homeostasis in metabolic-associated steatotic liver disease (MASLD). Gut Microbes. 2024. Vol. 16, No. 1. Art. 2331460. DOI: 10.1080/19490976.2024.2331460.

Integrative Interpretation

Taken together, the experimental findings indicate that sustained metabolic challenge produced a coordinated but heterogeneous pattern of intestinal microbial and host metabolic alterations. Subsequent MW administration did not simply reverse these changes. Instead, it redirected their trajectories: selected microbial populations underwent taxon-specific reorientation while multiple host biochemical indices shifted toward a more favorable metabolic and redox profile.

This observation is particularly relevant when viewed against the pathophysiological framework described in the preceding sections. Metabolic dysfunction develops through interactions among nutrient overload, insulin resistance, lipid metabolism, oxidative stress, inflammatory regulation, and intestinal microbial ecology. An intervention associated with simultaneous changes across several of these domains may therefore be more appropriately understood at the level of the integrated regulatory network than through an isolated endpoint.

At the same time, the findings should not be interpreted as evidence that MW "restored" metabolic homeostasis or normalized the intestinal microbiota. The metabolic challenge remained active, several abnormalities persisted, and microbial responses were heterogeneous. The experimental evidence instead supports a more restrained conclusion: under conditions of continuing metabolic stress, MW administration was associated with a coordinated reorientation of selected microbial and host metabolic responses.

This interpretation provides an experimental extension of the systems-based concept of metabolic dysfunction outlined in this chapter and supports further investigation of natural mineral waters as complex modifiers of host–microbiome–metabolic interactions.

CONCLUSIONS

Metabolic dysfunction is a systemic process that develops through the interaction of nutritional, genetic, epigenetic, environmental, microbial, and host-related factors rather than through a single pathogenic mechanism. Obesity represents one of its major determinants; however, metabolic risk depends not only on the amount of adipose tissue but also on its distribution, functional state, and capacity to safely accommodate excess energy. Visceral adiposity, adipocyte dysfunction, increased free-fatty-acid flux, and ectopic lipid deposition create conditions in which initially adaptive metabolic responses progressively become maladaptive.

Insulin resistance occupies a central position within this process and interacts bidirectionally with lipid overload, mitochondrial dysfunction, oxidative stress,

and chronic low-grade inflammation. These mechanisms form interconnected and self-reinforcing networks affecting the liver, adipose tissue, skeletal muscle, pancreas, vascular system, and other metabolically active organs. The intestinal microbiota and intestinal barrier constitute an additional regulatory domain within this network. Microbial restructuring, altered microbial metabolism, barrier dysfunction, and increased exposure to microbial-derived signals may influence host metabolic and immune regulation, while metabolic changes in the host simultaneously modify the intestinal microbial environment. Accordingly, host–microbiome interactions should be viewed as dynamic and bidirectional rather than as a simple linear causal pathway.

The experimental findings presented in this chapter extend this systems-based concept to the effects of natural mineral water. Under conditions of continuing metabolic challenge, mineral water administration was associated with taxon-specific reorientation of the culturable intestinal microbiota together with coordinated changes in carbohydrate and lipid metabolism, purine metabolism, redox balance, and membrane-associated enzymatic activity. These responses did not represent complete restoration of the initial microbial or metabolic state but rather a redirection of selected microbial and host trajectories despite persistence of the adverse nutritional exposure.

The parallel nature of these changes is compatible with coordinated host–microbiome responses but does not establish a specific causal mechanism linking microbial reorientation to systemic metabolic effects. Further studies integrating microbial profiling with assessment of microbial metabolites, intestinal barrier function, inflammatory signaling, and host metabolic responses are required to distinguish among potential pathways. Nevertheless, the observed multidomain response supports further investigation of natural mineral waters as complex biological modifiers within integrated strategies aimed at influencing metabolic regulation.

SUMMARY

Metabolic dysfunction represents a systemic condition arising from complex interactions among nutritional excess, obesity, genetic and epigenetic susceptibility, environmental factors, and impaired physiological adaptation. Visceral adipose tissue dysfunction, insulin resistance, ectopic lipid accumulation, lipotoxicity, oxidative stress, and chronic low-grade inflammation form interconnected pathogenic networks that progressively disturb metabolic homeostasis across multiple organs. The intestinal microbiota and intestinal barrier constitute an additional regulatory component through which dietary, microbial, immune, and metabolic signals interact with the host. Rather than representing a unidirectional cause of metabolic

disease, the intestinal microbial ecosystem participates in bidirectional host–microbiome communication and undergoes restructuring in response to changes in the metabolic environment. Experimental metabolic syndrome in rats was accompanied by progressive reorganization of the culturable fecal microbial phenotype together with disturbances in metabolic, redox, and functional biochemical indices. Administration of low-mineralized alkaline bicarbonate-sodium mineral water during continued metabolic challenge resulted in taxon-specific microbial reorientation and simultaneous shifts in several host metabolic parameters. These changes were characterized by attenuation of abnormalities in carbohydrate, lipid, and purine metabolism, improvement of redox balance, and changes in membrane-associated ATPase activities. The parallel microbial and host responses are compatible with several established mechanisms of host–microbiome interaction but do not establish a direct causal relationship between individual microbial changes and systemic metabolic effects. The findings support a systems-based interpretation of metabolic dysfunction and provide an experimental rationale for further investigation of natural mineral waters as multidomain modifiers of host–microbiome–metabolic regulation.

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