International Journal of Nutrology
(Official Journal of the ABRAN - Brazilian Association of Nutrology)

ORIGINAL ARTICLE

DOI: 10.54448/ijn26114

Epigenetic modifications in adipose tissue following calorie-restricted diets in adults with obesity: a randomized controlled experimental trial

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DOI: https://doi.org/10.54448/ijn26114
Received: 12-15-2025; Revised: 02-20-2026; Accepted: 02-28-2026; Published: 03-04-2026; IJN-id: 26114

Editor: Dr. Idiberto José Zotarelli-Filho, MSc, Ph.D., Post-Doctoral.

Abstract

Obesity is a complex disease that is characterized by an unhealthy proportion of body fat and metabolic diseases. It has also been recently shown that epigenetics (e.g., DNA methylation, histone changes, and non-coding RNAs) must be considered in treating obese clients because epigenetics can manipulate adipocytes and energy metabolism. Calorie-restriction (CR) methods have already been known to yield iweight-loss effects. Recent studies have established that epigenetic modification in adipose tissue are central to CR intervention can initiate a more preferable remodelling of epigenetics in adipose tissue, in a way that will enable a change in metabolic state. The article recounts the effects of CR intervention on the adipose tissue epigenetics in obese adults, and as case illustrations of a clinical nutrology perspective. The recent studies gave significant results, such as coordinated alterations in obesity-related locus CR-induced methylation, histone acetylation, and changes in microRNA expression that result in better insulin sensitivity, reduced inflammation, and lipid metabolism. It means that epigenetic markers can be considered as markers of dietary responsiveness that would allow individualized nutrition in the case of differences in responding to CR interventions, including potential confounders. These are just initiations to the incorporation of epigenetics into the nutrition sciences, and It consider CR not only as a calorie-limiting intervention but also as an intervention that can alter gene regulation. This will enable us to advance the nutrition practice in the future with precision nutrology, developing sustainable obesity management, and providing metabolic health in the long term.

Keywords: Obesity. Adipose Tissue. Calorie Restriction. Epigenetics. DNA Methylation. Histone Modification. MicroRNAs.

Introduction

Obesity is an important global health problem, with more than 650 million adults affected by it, and with it playing a major role in the growing metabolic disease burden (such as type 2 diabetes, cardiovascular disease, and non-alcoholic fatty liver disease) [1]. The problem of obesity was formerly treated as an energy intake/energy expenditure issue, but it is now attributed to a multifactorial interaction of genetic, lifestyle, and environmental exposures. Combined with the complex interaction of metabolism and weight, adipose tissue (and also a passive store of energy) is dynamic and endocrine: ie., regulates systemic metabolism by adipokines, cytokines, and lipid mediators [2].

More recently, advances in molecular biology have established that epigenetic mechanism play a large role

in regulating the function of adipose tissue and its metabolic outcomes. Epigenetic changes include: DNA methylation, histone acetylation, and methylation of non-coding RNA **[3]**. Epigenetic changes regulate gene expression even though the DNA sequence remains unchanged. These epigenetic changes are dynamic and modulated via dietary substrates or environmental exposures, suggesting a mechanism for nutrition to regulate longterm metabolic health **[4,5]**. In the future, identifying maladaptive epigenetic changes that occur in obesity associated with compromised adipogenesis, chronic inflammation, and impaired insulin signalling may aid in understanding energy homeostasis.

Calorie restriction (CR) is a dietary approach that limits daily energy intake within a malnutrition-free level. CR has consistent positive effects on weight loss, insulin sensitivity, and inflammation levels **[6,7]**. Moreover, obesity research is beginning to show that these positive effects may, in part, happen via epigenetic remodelling of adipose tissue. For example, a CR state may lead to alterations in DNA methylation at loci associated with lipid metabolism and glucose regulation, changes in histone acetylation patterns, and changes in microRNA profiles **[8,9]**.

Caloric restriction effects on the adipose epigenome are relevant to nutrology to assist in the identification of diet-responsive biomarkers and whether dietary strategies need to be personalized **[10,11]**. The objective of this paper was to provide a summary of the existing evidence-based and clinical inferences of the management of obesity.

Methods

Study Design

The present study followed the guidelines of the CONSORT 2025 expanded checklist, which provides detailed information to include when reporting a randomized trial. Available at: https://www.consortspirit.org/_files/ugd/b5740e_a6856e5e2cf94a1db5a8005853404160.pd f> Accessed on: December 10, 2025.

Ethical Approval

The study was approved by the institutional ethics committee in Kalinga University. Department of Pharmacy, Naya Raipur, Chhattisgarh, India, and adheres to the ethical principles outlined in the declaration of Helsinki, as revised in 2024.

Informed Consent

Informed consent was obtained from all participants involved in the study, with all procedures explained in detail before participation.

Participants, Sample Size and Calorie Restriction and Epigenetic Assessment

A total of 60 participants are recruited in the study that met the inclusion criteria of 25 to 55 years of age, and BMI of 30 kg/m^2 or above. To predetermine the sample size, a statistical power analysis was performed to determine that the sensitivity of the study was sufficient to detect meaningful differences in epigenetic markers and metabolic outcomes in calorie restriction. The calculations of power have been made under the assumption of an intermediate effect (Cohen d=0.5), a significance level (α) of 0.05, and desired statistical power of 0.80. According to these parameters, a sample of 54 participants was taken as the minimum; hence, the enrolment of 60 participants was possible in this case in case of any dropouts without compromising with the statistical power. Such a sample size was sufficient to identify meaningful results of calorie restriction levels and time-points with repeated-measures analyses, which confirms the validity of the research results.

Figure 1 shows the general methodological structure of the study, where the participants will be recruited and baseline data will be recorded, and, subsequently, they will be pursued by the means of a calorie-restricted diet intervention. The participants are monitored regularly during the period of intervention to monitor compliance and physiological changes. Adipose tissue biopsy is then used to collect biological samples which allow downstream molecular analysis. Epigenetic studies such as DNA methylation, histone modification profiling, are done using genomic DNA, whereas gene expression is done using parallel RNA extraction. These molecular datasets are then analyzed rigorously with respect to bringing out meaningful patterns and association. Lastly, findings of epigenetics, transcriptomics and clinical analyses are combined to offer an overall picture of the molecular and regulatory impact of calorie restriction to enable solid interpretation and biologically significant findings.

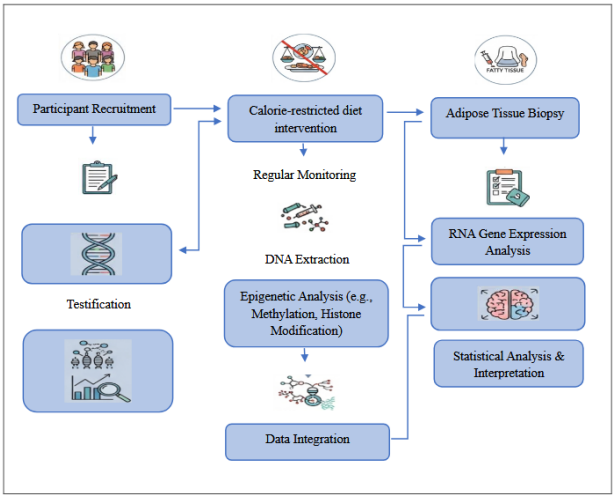

Figure 1. Schematic steps for the evaluation of epigenetic marks in adipose tissue. Source: Own authorship.

Calorie Restriction Procedures

The dietary study included a control energy reduction (−30-25%), energy deficit portioned by indirect calorimetry measurement, with consideration of physical activity levels. Macronutrient composition was balanced (50–55% energy - carbohydrates; 1-2), (25-30% energy - fat; 15-20% energy - protein) percentages of daily total energy intake. This process mix list outlined suitable food examples and included consideration for a micronutrient dietary pattern. Participants are generally adults, they are enlisted in a caloric restriction (12-to-16) trial with nutrition counselling, developing participant adherence, and minimizing drop out. Adherence to the dietary pathway and relevant intake behaviour (three-day dietary record), and urine nitrogen excretion measures within the urinary output period are assessed through the measurement of urinary nitrogen and balance rate within compliance checks.

Calorie Restriction–Epigenetic Remodelling–Metabolic Outcome Axis:

Epigenetic Response Dynamics in Equation 1,

$$\frac{dE}{dt} = k_{act} \cdot S(t) - k_{decay} \cdot E(t) \quad (1)$$

- *E(t)*: Epigenetic response scores (DNA methylation + histone + miRNA composite)
- *S(t)*: Calorie restriction signal (% deficit or kcal/day relative to baseline)
- k_{act}: activation constant
- k_{decay}: relaxation constant

Link to Metabolic Outcome in Equation 2,

$$M(t) = M_0 + \frac{\propto \cdot E(t)}{K_m + E(t)} \quad (2)$$

- *M(t):* Metabolic health outcome (insulin sensitivity index)
- M_0: baseline value
- α: maximum achievable improvement
- K_m: half-effect parameter

The first equation describes the dynamics of epigenetic response, where the rate of change over time of the epigenetic score, $E(t)$, is a function of the strength of the calorie restriction signal, $S(t)$, and a decay term. By using this model, it can describe how nutritional stimuli activate or facilitate the deactivation of DNA methylation, histone modifications, and microRNA by starting with the appropriate time scale and then capturing these processes over time.

The second equation connects the epigenetic score to a clinical metabolic outcome $M(t)$. In this equation, it gathered a saturating (Michaelis–Menten) solution to explain that anterior metabolic benefits continue to rise as epigenetic remodelling increases, but eventually taper off at higher levels. This demonstrates that it has both responsiveness vs eventual biological limits in obesity.

Adipose Tissue Sampling

Subcutaneous adipose tissue biopsies were taken at baseline and at the end of the CR intervention, employing a sterilized technique and localized anaesthetic for pain relief. The adipose tissue consisted of approximately 300 mg of total mass, which was obtained at the abdominal site, immediately transported and snap frozen in liquid nitrogen, and stored at -80°C until analyses.

Epigenetic Analyses

DNA was extracted with the double-phase phenol-chloroform method. Genome-wide DNA methylation profiling was conducted by means of Illumina Infinium Methylation EPIC Bead Chip arrays. Differential methylation at specific loci was validated by use of targeted bisulfite pyrosequencing. Histone marks, including acetylation (H3K9ac) and methylation (H3K4me3, H3K27me3), are profiled by chromatin immunoprecipitation and quantitative equilibrium PCR (ChIP-qPCR). MicroRNA expression profiling was performed by means of next-generation sequencing, and selected miRNAs were validated by qRT-PCR.

Statistical Analysis

Linear mixed-effect models were used to estimate the differential methylation and enrichment of histone marks with adjustments for age, sex, and baseline BMI. To control multiple testing, it applied the Benjamini-Hochberg false discovery rate (FDR). The correlations between the epigenetic changes and clinical outcome measures (weight loss, insulin sensitivity, adipokine concentrations) were established by the use of Pearson or Spearman correlation as a suitable method. The approach can be fully characterised using this methodological approach to determine how CR controls the adipose tissue epigenome, and to relate the molecular weight remodelling to metabolic phenotype.

Results and discussion

Table 1 describes important epigenetic processes that calorie restriction induces in obese individuals. It concentrates on three relevant epigenetic changes - DNA methylation, histone changes, and the expression of microRNAs - that regulate the remodelling of adipose tissue. Each epigenetic process involves specific molecular modifications, influence on adipose

tissue physiology, and associated clinical phenotype. The Table 1 method enables the reader to define the relationship between nutrient availability and molecular plasticity through calorie restriction, and this is further evidence that calorie restriction is a nutrology-based intervention in the management of obesity.

Table 1. Key Epigenetic Modifications Observed Under Calorie Restriction.

Epigenetic Mechanism	Molecular Change	Effect on Adipose Tissue	Clinical Impact
DNA Methylation	Hypomethylation at metabolic gene promoters	Increases lipid oxidation and mitochondrial activity	Improved insulin sensitivity
Histone Acetylation	SIRT1-mediated deacetylation of histones	Suppresses inflammatory gene expression	Reduced systemic inflammation
microRNAs	↓ miR-27a, ↓ miR-34a, ↑ miR-193b	Enhances lipid catabolism and adipocyte differentiation	Improved metabolic flexibility

Source: Own authorship.

Clinical and Nutritional Implications of Epigenetic Reprogramming

Reprogramming of adipose tissue by epigenetic mechanisms following calorie restriction (CR) may have important clinical and nutritional implications in the treatment of obesity. Of high importance is that both CR and diet can modulate expression of metabolic programming and epigenetic alteration, contrary to the paradigm a few decades ago, in which diet was the factor of energy homeostasis. This becomes particularly ironic to nutrology, which recognizes that food is not merely fuel; in fact, it does influence the health of cells and molecules.

Clinically, the truth that CR may result in the alteration of DNA methylation, histone modifications, and miRNA expression indicates that specific nutrients can alter the pathogenic epigenetic signatures resulting in obesity. It is also known that insulin sensitivity can be altered by epigenetics, chronic inflammation, and lipid metabolism, and they are among other risk factors to consider in the curative treatment of obesity, curative treatment of obesity, type 2 diabetes mellitus, etc **[12]**. Nevertheless, certain of the epigenetic effects of weight loss response raise the significant question as to whether CR can yield metabolic advantages over time, independent of weight loss.

Nutritionally, epigenetic markers present hope to the future of dietary responsiveness, in which variations in weight loss, which can be seen with the same CR, indicate that individuals could be divided into responders versus non-responders based on baseline epigenetic profile. This offers avenues towards precision nutrition whereby people are provided with avenues to undertake dietary intervention in terms of the molecular signature, as opposed to the usual means. Micronutrient sufficiency should also be taken into consideration in any calorie-restriction intervention. Numerous vitamins and bioactive compounds (folate, vitamin B12, polyphenols, etc.) are used as cofactors in one-carbon metabolism and histone modification signalling that regulates epigenetics **[13,14]**.

Nutrology paradigm also comes in handy in the introduction of early intervention and prevention. The malleability of adipose tissue was discussed, highlighting that, in terms of nutritional strategies, it appears not to be limited to the treatment of obesity-related complications. Practically, clinicians might have structured mechanisms at their disposal to consider caloric control and epigenetic control **[15,16]**.

To sum up all that, as it is incorporate epigenetic insights into our paradigm of inducing weight loss, it is also refocus on a new centre by making CR more than a caloric pathway in two respects: by focusing a dietary intervention as a form of molecular therapy that comprises not only nutritional research but also modern clinical practice, and by making us a prospective extension of nutrology as a frame of necessary future development of the obesity care continuum.

Molecular Pathways Connecting Calorie Restriction to Epigenetic Remodelling

DNA Methylation and One-Carbon Metabolism

CR influences DNA methylation dramatically, partially connected with the alterations in the supply of methyl groups, i.e., the availability of methyl donors such as folate and vitamin B12. CR, in turn, affects the contribution of the DNA methyltransferase (DNMT) activity. Humans consume less and are modifying adipogenesis-related genes that may imply asymmetrical demethylation, that is, loss of metabolic plasticity.

Histone Modifications and Sirtuin Activity

CR activates the sirtuin-1 (SIRT1) enzyme, which is a nicotinamide adenine dinucleotide (NAD^+) dependent deacetylase of histones. By increasing SIRT1 activation, CR increases relaxation of chromatin in *loci* responsible for lipid oxidation. This chromatin relaxation also improves the inhibitory regulation of inflammatory genes in adipose tissue, ensuring enhanced adipose tissue function.

MicroRNA Regulation

CR also alters microRNA expression by downregulating the negative effect of adipocyte hypertrophy (associated with insulin resistance) through the expression regulation of miR-27a and miR-34a. At the same time, CR also maintained miR-193b, enabling better regulation of the lipid catabolism in mitochondria.

Energy sensing pathways

Finally, CR interacts with various nutrient-sensing signals, such as AMPK and mTOR, that engage with epigenetic enzymes that link the energy status and gene expression, thereby allowing us to link and mechanistically explain how CR anticipates reshaping adipose tissue biology through epigenetic remodelling.

Epigenetic Remodelling in Adipose Tissue

Calorie restriction (CR) resulted in significant changes in the adipose tissue epigenome of adults with obesity. Genome-wide profiling of DNA methylation should identify global changes within *loci* related to metabolic regulation, including several genes related to lipid storage, insulin signalling, and inflammatory pathways. The differentially methylated CpG sites are significantly enriched near the promoters of obesity-related genes such as PPARG, LEP, and IRS1. Bisulfite sequencing analysis for validation confirmed significant demethylation of loci in adipogenesis genes, while pro-inflammatory genes should to increase methylation, indicating a functional change favouring metabolic health.

The temporal epigenetic response (E/10) to alternative degrees of calorie restriction (CR 10%, CR 20%, and CR 30%) at different time points is shown in Figure 2. The findings indicate that the dose dependency is evident, and more pronounced levels of calorie restriction always have stronger epigenetic effects, as time goes by. At the early time points, the changes in epigenetics are not significant in all groups, and there is little distinction between the levels of CR **[17,18]**. With the continuation of intervention, the intensity of response is also heightened, especially in the CR 20% and CR 30% groups, suggesting a gradual build-up of epigenetic changes. CR 30% condition shows the strongest and sustained response at the later time points, whereas the CR 10% group shows a relatively smaller and sloping response. Having said that, the figure underlines the fact that the duration and the intensity of calorie restriction have a significant role in regulating the epigenetic responses, and the stronger and longer-lasting the effect of the restriction is, the higher the restrictions are.

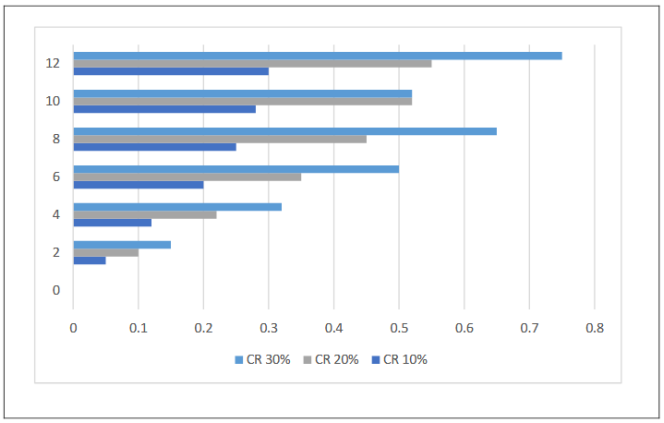

Figure 2. Epigenetic Response over Time (E, 0–1 scale). Source: Own authorship.

Additionally, the histone modifications observed are consistent with the epigenetic profile that is observed. CR is associated with increased levels of H3K9ac and increased levels of H3K4me3 in regulatory regions of genes involved in promoting lipid mobilization and mitochondrial function. Conversely, H3K27me3 levels that are used in the regulation of insulin responsiveness are reduced with CR. The total of these histone modification changes is a more favourable chromatin landscape for the activation of metabolically flexible-related genes.

The profile of microRNA revealed a shift in the expression of key regulators, such as the downregulation of miR-27A and miR-34A, regulators of hypertrophic adipocytes and insulin resistance, and upregulation of miR-193b, a lipid catabolism regulator. Comparing molecular and clinical outcomes revealed that the more intense epigenetic remodelling would be correlated with higher weight loss and insulin sensitivity. Notably, inter-individual variation was substantial; the respondents had higher DNA methylation and histone alterations compared to non-responders. Our results are in favour of the future application of epigenetic signatures as biomarkers of food responsiveness to control obesity **[19,20]**.

Mechanistic Insights and Nutrology Perspectives

All these results point towards calorie restriction as a driving force of the adipose tissue epigenome. The remodelling of the DNA methylation is as tall as the histone landscape is evidence that nutritional manipulations can reprogramme the transcriptional networks controlling adipocyte dynamics. A combination of these phenotypes of gene demethylation of adipogenesis and mitochondrion promoters of activity and silencing of pro-inflammatory loci is all indicative of a mechanism of CR to enhance insulin sensitivity and low-grade inflammation in

obesity. Molecular changes are consistent with previous accounts of DNA methyltransferase and histone deacetylase activity changes in response to CR, which provide evidence that CR directly contributes to transcriptional environment changes.

Changes in microRNA are another level of regulation. The down-regulation of insulin resistance-related miRNAs (e.g., miR-27a, miR-34a) and the up-regulation of lipolytic miRNAs emphasize the is tall-regulated role played by post-transcriptional regulation in the metabolic response to CR. The results are in line with the model that suggests that CR triggers the alteration of multiple epigenetic pathways simultaneously, and the pathways converge at the stage of recreating metabolic homeostasis **[21,22]**.

The epigenetic responses being flexible, especially in view of inter-individual disparities, as those individuals who show remodelling in greater amounts appear to be responders, gives support to the hypothesis that dietary outcomes are predetermined by the epigenetic state before CR. This assists in integrating other emerging ideas of precise nutrition, wherein epigenetic biomarkers can be utilized to foresee responsiveness in subjects as till as tailoring interventions. In addition, micronutrient presence in one-carbon metabolism, histone modification, and miRNA biogenesis is evidence that CR protocols should be balanced with nutrients so that they can maximize the beneficial effects of epigenetic change.

Table 2, which was built to describe the calorie restriction-epigenetic remodellingmetabolic outcome axis, has been summarised in Table 2. All the parameters are transformed into a biological parameter that facilitates the conversion to nutrology action for the quantitative modelling. In order to demonstrate the correlation between the theoretical constructs and the clinical realities, the table provides an excursion into fixed values such as the rate of activation, the decay constant, the maximum effect, and the half-effect value, and how these definitions interrelate with the behaviour of adipose tissue. This is translationally effective on the model and helps in assessing its predictive value. Limitations also need to be stated: biopsies are taken on subcutaneous fat, the duration of the study was insufficient, and follow-up was lacking. However, it is counted as a consequence of mechanistic data on the way CR can be other than a caloric therapy as a molecular therapy in which the adipose biology is restructured. As soon as the findings are implemented as clinical nutrology practices, the treatment of obesity may subsequently begin to make a more personalized and molecularly focused approach to treatment.

Table 2. Model Parameters and Biological Interpretation.

Parameter	Symbol	Meaning	Biological Interpretation
Activation rate	k_{act}	Speed of epigenetic activation under CR	Reflects responsiveness to calorie restriction
Decay constant	k_{decay}	Rate of loss of epigenetic signal without CR	Indicates persistence of remodelling effects
Maximum effect	α	Upper limit of metabolic improvement	Represents the therapeutic potential of CR-induced remodelling
Half-effect constant	K_m	Epigenetic level at which 50% of the effect occurs	Indicates sensitivity of outcomes to epigenetic change

Source: Own authorship.

Epigenetic Modifications and Precision Nutrition in the Context of Obesity Management

Epigenetic Biomarkers for Dietary Responsiveness

The increased potential of the epigenetic alterations in adipose tissue following an energy restriction (and more so, the energy restriction) creates opportunities for unexplored scales in the future of obesity management. To explain, it shows that calorie restriction has consequences at the molecular level and alters the responsiveness of tissues in the aftermath of body weight loss **[17]**. It now has a duty to think of the future of obesity treatment practice that employs evidence using new technology in the field of precision nutrition, adopts a personcentred contemporary approach, and promotes its prevention.

Figure 3 depicts the correlation between the normalized metabolic outcome and epigenetic response, which is the percentual change in insulin sensitivity. The value shows that there is a clear positive relationship with the increase in the metabolic improvements as the epigenetic response values rise. When the levels of epigenetic response are low, the degrees of metabolic gains are also low, meaning that there are no significant physiological effects. An increase in epigenetic response is associated with a significant increase in insulin sensitivity, with significant improvements at mid and higher response levels. The trend is then leveled off at the maximum values of the epigenetic response values, and it is possible that there is a saturation effect, as extra epigenetic changes will give smaller returns in terms of metabolic effects. Altogether, the number demonstrates the practical value of epigenetic regulation, and it is possible to agree that more significant epigenetic changes triggered by dietary intervention are directly correlated with significant changes in the metabolic status.

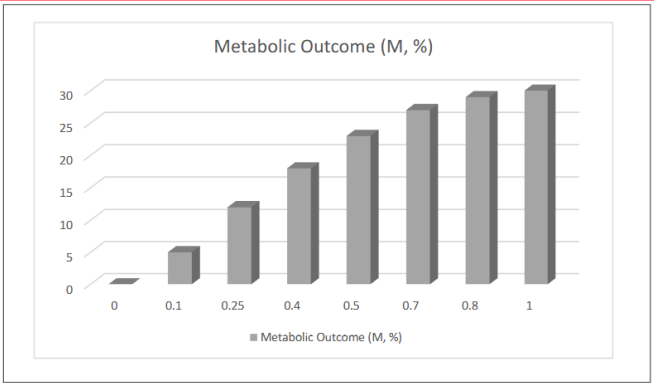

Figure 3. Epigenetic Response vs Metabolic Outcome (M, % improvement in insulin sensitivity). Source: Own authorship.

Integration of Multi-Omics Approaches

One avenue to explore is to identify epigenetic biomarkers that can predict an individual's response to dietary interventions. At the moment, in clinical practice, body mass index and biochemistry are the accepted anthropometric and biochemical measures used to measure patient homework (i.e., degree of weight loss) on the path to improved health and well-being. However, using anthropometric and biochemical measures to predict brain-body interactions, does not account for the intra- and inter-individual variability it sees in the outcomes from calorie restriction. If clinicians are able to predict, quantify, and utilize pre-specified DNA-methylation signatures or histone modification or small nucleic-acid signatures such as microRNA expression at baseline, then they could stratify patients into groups, such as "likely responders" or "low responders". Segmentation of patients in this manner would support clinicians by identifying ineffective interventions and signalling which moderation to employ within the dietary prescription, thus ameliorating loss of composure and fatigue amongst the patient.

Digital Health and Precision Nutrition Tools

Finally, multi-omics information should be incorporated into the nutrology and practice, which is a rational choice, and should be presented for the future of obesity management. Epigenomics and transcriptomics, proteomics, and/or metabolomics could be combined to provide more credible and legitimate means of altering adipose tissue biology in the context of calorie restriction. A multi-omic approach could help the researchers, clinicians, and nutritionists to discover more of these regulatory processes and then identify the targets of treatment.

Long-Term and Transgenerational Effects of CR

Digital health and machine learning could also assist in developing the field of precision nutrition, where continuous monitoring is possible, and wearable devices that may be applied to measure energy expenditures, diets, metabolic alterations, etc., in real-time could be used **[23,24]**. Combining artificial intelligence algorithms with the epigenetic profile of the person, it is possible to construct a personal eating schedule that, in addition to not spending unnecessary calories, will help achieve the most effective epigenetic changes. These potential developments would represent a giant leap in the discipline of the older, more classic interventions that focus on weight loss, when it permits one to take an individualized, accurate approach to managing obesity via reactive and passive methods of managing the obesity via proactive molecular adjustment.

Nutrient–Epigenome Interactions in CR Regimens

Moreover, the necessity to talk about the stability and transgenerational effect of CR induced epigenetic changes is still widespread. There are reports of short-term remodelling, but it is not clear whether dietary changes are sustained with weight regain. There is also emerging evidence of inter-generational epigenetic processes of offspring's metabolic health because epigenetic modification appears hereditary. Of interest will be the possibility of CR in adults being able to permanently modify the epigenetic programming of their children, since there are important implications for public health.

Towards Personalized Nutrology-Based Interventions

The future intervention would be to have a conceptual nutrology pathway, which would be used in such a way that there would be a realization that caloric restriction would be used to supplement the need for micronutrients. One-carbon metabolic cofactors and histone modifiers are vitamins such as folate, B12, and, to a slightly lesser degree, B6, bioactive substances such as polyphenols. The development of CR regimens, which would include such nutrients, might further strengthen the positive epigenetic remodelling and negate the potentially adverse effect of nutrient deficiency.

The treatment of obesity in the future will be determined by the aftermath of epigenetics that will be integrated into the nutrology practice. As per what ought to be protective sources of more-targeted approaches to the nutritional practices of precision nutrition, health practitioners can potentially control CR dietary plans through the predictive identification of multi-omics biomarkers/nutrients; use digital aids to

contribute to more effective and lasting remedies to the obesity disease process, and treat the obesity disease process.

Limitations

Although more longitudinal multi-tissues are needed, there is a possibility that the area indeed can be a breakthrough, and with infinitely greater impact when the epigenetic measurement is put in practice and studied. Finally, it should consider epigenetic remodelling not only as the flag bearer and mediator of CR response, but also to compel us to make nutrology-based interventions more refined and metabolic health more effective and sustainable.

Conclusion

Not only is caloric restriction an efficient method of weight loss in obese individuals, caloric restriction is also an efficient modulator of adipose tissue's epigenetics. It is have shown that caloric restriction will modify the DNA methylation and histone modification and microRNA expression and will cause lipid metabolism, insulin sensitivity, and inflammatory gene networks, among others. All these molecular modifications contribute to metabolic plasticity and offer a protective reaction to the obesity associated complications. The fact that it presents this contribution lends some form of credibility to the belief that nutrology is a field of study that develops the nexus in nutrition and molecular Biology. To begin with, dietary changes in the allegedly fixed epigenomic landscapes will be a prerequisite to caloric restriction as an intervention to reprogram cellular activity and repair the body. The fact that the responders and the non-respondents are different will justify the argument that the epigenetic signatures may serve as pre-emptive biomarkers of dietary response. It is perhaps the case in this event that the potential of precision nutrition can be unmatched when the interventions aimed at nutritional change are planned in terms of individual differences, which is operationalized as molecular properties.

CRediT

Author contributions: **Conceptualization -** Khalmurad Akhmedov, Muhammadjon Osbayov, Ravshan Sultanov, Khulkar Kasimova, Ahmad Hussyn, Hemlata Dewangan; **Data curation**: Khalmurad Akhmedov, Muhammadjon Osbayov, Ravshan Sultanov, Khulkar Kasimova; **Formal Analysis**: Khalmurad Akhmedov, Ahmad Hussyn; **Investigation**: All authors; **Methodology**: Khalmurad Akhmedov, Muhammadjon Osbayov, Hemlata Dewangan; **Project Administration**: Khalmurad Akhmedov; **Supervision**: Khalmurad Akhmedov, Ravshan Sultanov; **Writing - Original Draft**: Khalmurad Akhmedov; **Writing - Review & Editing**: All authors.

Acknowledgment

The authors wish to express their gratitude to all individuals and institutions that provided support during the course of this study. Special thanks are extended to those who contributed to the study design, data collection, and analysis.

Ethical Approval

The study was approved by the institutional ethics committee in Kalinga University. Department of Pharmacy, Naya Raipur, Chhattisgarh, India, and adheres to the ethical principles outlined in the declaration of Helsinki, as revised in 2024.

Informed Consent

Informed consent was obtained from all participants involved in the study, with all procedures explained in detail before participation.

Funding

No funding was received for this study.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request, and all data is stored following privacy and ethical guidelines.

Conflict of Interest

The authors declare no conflicts of interest regarding the publication of this article.

Similarity Check

It was applied by Ithenticate@.

Application of Artificial Intelligence (AI)

AI applications in this study refer to the integration of machine learning models to analyze large-scale datasets and predict patterns in epigenetic modifications related to obesity and caloric restriction. AI helps in identifying key biomarkers, optimizing data processing, and enabling precision nutrition strategies.

Peer Review Process

It was performed.

References

1. Suárez R, Chapela SP, Álvarez-Córdova L, Bautista-Valarezo E, Sarmiento-Andrade Y, Verde L, Frias-Toral E, Sarno G. Epigenetics in obesity and diabetes mellitus: new insights. Nutrients. 2023 Feb 4;15(4):811. https://doi.org/10.3390/nu15040811
2. Shamsad A, Gautam T, Singh R, Banerjee M. Genetic and epigenetic alterations associated with gestational diabetes mellitus and adverse neonatal outcomes. World Journal of Clinical Pediatrics. 2025 Mar 9;14(1):99231. https://doi.org/10.5409/wjcp.v14.i1.99231
3. Lee S. Development of Explainable AI Models for Healthcare Applications. International Academic Journal of Science and Engineering. 2024;11(4):16-21. https://doi.org/10.71086/IAJSE/V11I4/IAJSE1165
4. Saeed S, la Cour Poulsen L, Visnovska T, Hoffmann A, Ghosh A, Wolfrum C, Rønningen T, Dahl MB, Wang J, Cayir A, Mala T. Chromatin landscape in paired human visceral and subcutaneous adipose tissue and its impact on clinical variables in obesity. Ebiomedicine. 2025 Apr 1;114.
5. Hameed AZ, Balamurugan R, Rizwan A, Shahzad MA. Analyzing and prioritizing healthcare service performance in hospitals using SERVQUAL model. Archives for Technical Sciences. 2025;1(32):165-175. https://doi.org/10.70102/afts.2025.1732.165
6. Dusa FC, Vellai T, Sipos M. Nutrition and DNA methylation: how dietary methyl donors affect reproduction and aging. Dietetics. 2025 Jul 14;4(3):30. https://doi.org/10.3390/dietetics4030030
7. Hartigan P. Diabetic diet essentials for preventing and managing chronic diseases. Clinical Journal for Medicine, Health and Pharmacy. 2023 Oct 9;1(1):16-31.
8. Axsom JE, Schmidt HD, Matura LA, Libonati JR. The influence of epigenetic modifications on metabolic changes in white adipose tissue and liver and their potential impact in exercise. Frontiers in Physiology. 2021 Aug 26;12:686270. https://doi.org/10.3389/fphys.2021.686270
9. Kapoor R, Iyer S. Renewable Energy Integration in Sustainable Healthcare Systems. International Journal of SDG's Prospects and Breakthroughs. 2024 Dec 30:7-12.
10. Pribić T, Das JK, Đerek L, Belsky DW, Orenduff M, Huffman KM, Kraus WE, Deriš H, Šimunović J, Štambuk T, Frkatović-Hodžić A. A 2-year calorie restriction intervention may reduce glycomic biological age biomarkers–a pilot study. npj Aging. 2025 Aug 1;11(1):71.
11. Moein AR, Pourvaghar MJ, Kazeminasab F. High-Intensity Interval Training Reduces Adipocyte Size and enhances the Thermogenic Activity of White and Brown Adipose Tissue in Male Wistar Rats. International Journal of Preventive Medicine. 2025 Sep 1; 16:55.
12. Rapps K, Kisliouk T, Marco A, Weller A, Meiri N. Epigenetic regulation of miR-211 in the hypothalamic arcuate nucleus of female rats during diet-induced obesity and caloric restriction. Physiology & Behavior. 2025 Oct 15; 300:115026. https://doi.org/10.1016/j.physbeh.2025.115026
13. Chaudhary S, Chaudhary MR, Jena MK, Rath PK, Mishra BP, Paital B, Vyas A, Sahoo DK, Singh P, Mehdi MM. Calorie restriction mimetics against aging and inflammation. Biogerontology. 2025 Aug;26(4):126.
14. Jaisil P, Eid SA, Guo K, Savelieff MG, Jang DG, Kim B, Pacut C, Hayes JM, Rigan DM, Carter A, Teener SJ. Dietary and exercise interventions improve cognition and alter hippocampal transcriptomics in a mouse model of the metabolic syndrome. Experimental Neurology. 2025 Sep 28:115483. https://doi.org/10.1016/j.expneurol.2025.115483
15. Gao W, Liu JL, Lu X, Yang Q. Epigenetic regulation of energy metabolism in obesity. Journal of molecular cell biology. 2021 Jul 1;13(7):480-99. https://doi.org/10.1093/jmcb/mjab043
16. Xiao Y, Liu D, Cline MA, Gilbert ER. Chronic stress, epigenetics, and adipose tissue metabolism in the obese state. Nutrition & metabolism. 2020 Oct 19;17(1):88. https://doi.org/10.1186/s12986-020-00513-4
17. Zhai J, Pan Y, Hao C, Wang X, Sun J. Caloric restriction induced epigenetic effects on aging. Frontiers in cell and developmental biology. 2023 Jan 13; 10:1079920.https://doi.org/10.3389/fcell.2022.1079920
18. Zhang Z, Shu Y, Bi J, He D, Wu M. Associations of weight change and different obesity indices

with all-cause and cause-specific mortality: the mediating role of epigenetic aging. medRxiv. 2025 Nov 10:2025-11. https://doi.org/10.1101/2025.11.08.25339825

19. Ouni M, Schürmann A. Epigenetic contribution to obesity. Mammalian genome. 2020 Jun;31(5):134-45.https://doi.org/10.1007/s00335-020-09835-3
20. Asif S, Morrow NM, Mulvihill EE, Kim KH. Understanding dietary intervention-mediated epigenetic modifications in metabolic diseases. Frontiers in Genetics. 2020 Oct 15; 11:590369.https://doi.org/10.3389/fgene.2020.590369
21. Lan Q, Liufu S, Chen B, Wang K, Chen W, Xiao L, Liu X, Yi L, Liu J, Xu X, Liu C. Gut-resident Phascolarctobacterium succinatutens decreases fat accumulation via MYC-driven epigenetic regulation of arginine biosynthesis. npj Biofilms and Microbiomes. 2025 Aug 2;11(1):150. https://doi.org/10.1038/s41522-025-00792-w
22. Jiao P, Lu H, Hao L, Degen AA, Cheng J, Yin Z, Mao S, Xue Y. Nutrigenetic and epigenetic mechanisms of maternal nutrition–induced glucolipid metabolism changes in the offspring. Nutrition Reviews. 2025 Apr;83(4):728-48. https://doi.org/10.1093/nutrit/nuae048
23. Alkhatib AJ, Mutlaq LM. Molecular Basis of Diabetes and Obesity Interactions: A Mini-Review. Advancements in Biomedical and Physical Sciences. 2025 Aug 20;1(1):21-6.
24. Lagarde CB, Kavalakatt J, Benz MC, Hawes ML, Arbogast CA, Cullen NM, McConnell EC, Rinderle C, Hebert KL, Khosla M, Belgodere JA. Obesity-associated epigenetic alterations and the obesity-breast cancer axis. Oncogene. 2024 Mar 7;43(11):763-75.https://doi.org/10.1038/s41388-024-02954-0.

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