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Review

Effects of a very low-calorie ketogenic diet on energy metabolism and inflammation in obesity management: A systematic review

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Abstract

Obesity represents a long-term health issue that leads to body-wide inflammation, together with changes in metabolic operations. Bone metabolism and remodeling are indicated by osteocalcin, while high-sensitivity C-reactive protein (hs-CRP) functions as a crucial marker for inflammation. This review investigates how very low-calorie ketogenic diets affect obese patients' hs-CRP and osteocalcin biomarker levels. Seven research articles from 2019 to 2024 were reviewed to analyze direct biomarker changes after VLCKD interventions. The research shows that VLCKD delivers substantial anti-inflammatory effects through hs-CRP level reductions between 30% and 50%. The research showed sex-related differences because men experienced a more significant reduction in hs-CRP levels at −41.42% compared to women who experienced −22.38%. The results suggest that hormonal or metabolic factors influence how individuals respond to this treatment. The research shows variable osteocalcin level changes between studies, with some trials reporting increases between 10% and 30% but other trials showing minimal changes. Research design, along with study duration and participant characteristics, might explain these inconsistent results. The anti-inflammatory effects of VLCKD appear beneficial for obese patients, but the impact on bone biomarkers remains unclear. Additional research using standardized methods across extended periods is needed to determine these effects precisely for clinical practice guidance.

Keywords: VLCKD, Very-Low-Calorie Ketogenic Diet, high-sensitivity C-reactive protein, hs-CRP, osteocalcin, inflammation, bone metabolism, obesity

Introduction

Obesity and inflammatory biomarkers

Obesity represents a widespread health concern worldwide, affecting individuals of all ages and socioeconomic levels [1, 2]. Visceral adipose tissue, which is metabolically active and produces inflammatory mediators, is its defining feature. This causes chronic low-grade inflammation and is strongly linked to rising high-sensitivity C-reactive protein (hs-CRP) [3, 4]. The liver produces hs-CRP in response to cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), making this protein one of the most important indicators of inflammation [5, 6]. This process contributes to impaired vascular function and the development of cardiovascular complications [7–9], including atherosclerosis, metabolic syndrome, and decreased insulin sensitivity [10–16]. As such, hs-CRP appears as a promising biomarker in obesity research and clinical evaluations.

Obesity and osteocalcin: A metabolic evaluation

Osteocalcin, a non-collagenous protein released by osteoblasts, plays a crucial role beyond bone formation. By increasing insulin production from pancreatic β-cells, aiding glucose absorption, and improving insulin sensitivity, it controls energy metabolism [17, 18]. These metabolic activities place osteocalcin at the junction of bones and metabolic health [18–21]. Obesity often reduces osteocalcin levels, indicating a complex interaction between bone metabolism and glucose regulation. Studies have linked decreased circulating osteocalcin levels to diminished insulin sensitivity, compromised glycemic control, and a higher risk of developing T2DM [20–23].

The role of Very-Low-Calorie Ketogenic Diet (VLCKD) in inflammation

Very Low-Calorie Ketogenic Diet (VLCKD) is gaining major interest as a successful dietary plan for obesity and associated metabolic disorders [24]. Characterized by a daily diet of less than fifty grams of carbohydrates, it causes ketosis and may lower systemic inflammation, major weight loss, and enhanced insulin sensitivity [25–27]. Studies indicate that VLCKD may lead to greater reductions in hs-CRP levels than other diets, likely due to decreased oxidative stress and pro-inflammatory cytokines [28–30]. The fundamental processes probably consist of reducing oxidative stress indicators and decreasing pro-inflammatory cytokines (*e.g.*, IL-6, TNF-α) [28].

The impact of a VLCKD on glycoregulation and osteocalcin

In addition to reducing inflammation, VLCKD may improve glucose metabolism and insulin sensitivity [28, 31, 32]. Due to the complex relationship between bone metabolism and glycoregulation, metabolic improvements may affect osteocalcin synthesis and function [18–23, 31–33]. Due to decreased systemic inflammation and improved metabolic health, trials reveal a significant improvement in osteocalcin after VLCKD [34–36], while others show no impact [34].

Current state of research

Although evidence supports the metabolic and anti-inflammatory benefits of VLCKD, its effect on osteocalcin remains unclear. Current literature presents mixed results regarding the modification of osteocalcin. Some studies have reported positive effects [34], while others have found no detectable changes [35, 36]. Because established techniques to assess the impact of VLCKD on osteocalcin do not exist, the reported findings vary widely. Despite this, variations in study designs, dietary adherence, and patient characteristics make it difficult to draw definitive conclusions. Several studies demonstrate that VLCKD-induced weight reduction considerably lowers hs-CRP levels [27–29].

Objectives of the evaluation

This systematic study aims to assess the effects of VLCKD on two key biomarkers, hs-CRP and osteocalcin, in obese individuals. The review specifically investigates whether VLCKD induces systemic inflammatory changes by measuring hs-CRP levels and examines its effects on bone metabolism and energy balance.

Material and methods

Research methodology

This research used VLCKD to evaluate its effects on hs-CRP and osteocalcin levels in obese patients. The selected studies examined VLCKD either as a standalone intervention or alongside other dietary approaches. This study functions as a systematic review of previously published research, so no ethical approval was required.

Search strategy and study selection

A literature search was performed in PubMed, Scopus, Cochrane Library, and Web of Science to identify pertinent peer-reviewed studies published from 2019 to December 2024. The search utilized Medical Subject Headings (MeSH) terms and pertinent keywords, such as “Very-Low-Calorie Ketogenic Diet”, “VLCKD”, “high-sensitivity C-reactive protein”, “hs-CRP”, “osteocalcin”, “inflammation”, “bone metabolism”, and “obesity”.

Boolean operators, specifically AND and OR, allowed for the creation of more precise search queries. A thorough review of the reference sections from relevant articles helped identify new research opportunities. Two independent researchers assessed each acquired study to reach a consensus on eligibility for inclusion or exclusion. A PRISMA flow diagram was employed to document the study selection process (Figure 1).

Criteria for inclusion and exclusion

Studying was conducted to examine the participation of obese or overweight human participants in clinical trials of VLCKD as the primary treatment or as a comparison with others. Eligible studies assessed hs-CRP and/or osteocalcin levels, either directly or indirectly, and were structured as case-control studies, cohort studies, or randomized controlled trials (RCTs). Only peer-reviewed papers printed in the English language were taken into consideration. Studies were excluded if they lacked a VLCKD intervention, combined multiple dietary strategies without isolating VLCKD effects, or were conducted on animals or *in vitro* models. Furthermore, conference abstracts and opinion pieces without original data were removed.

Analysis of data

Two evaluators used standardized extraction forms to collect data independently in a predefined format. The data extraction process included research design, author details, publication year, sample size, and participant characteristics that consisted of age, sex, body mass index (BMI) values, and relevant comorbidities information, while recording intervention parameters, including VLCKD protocol type, duration of

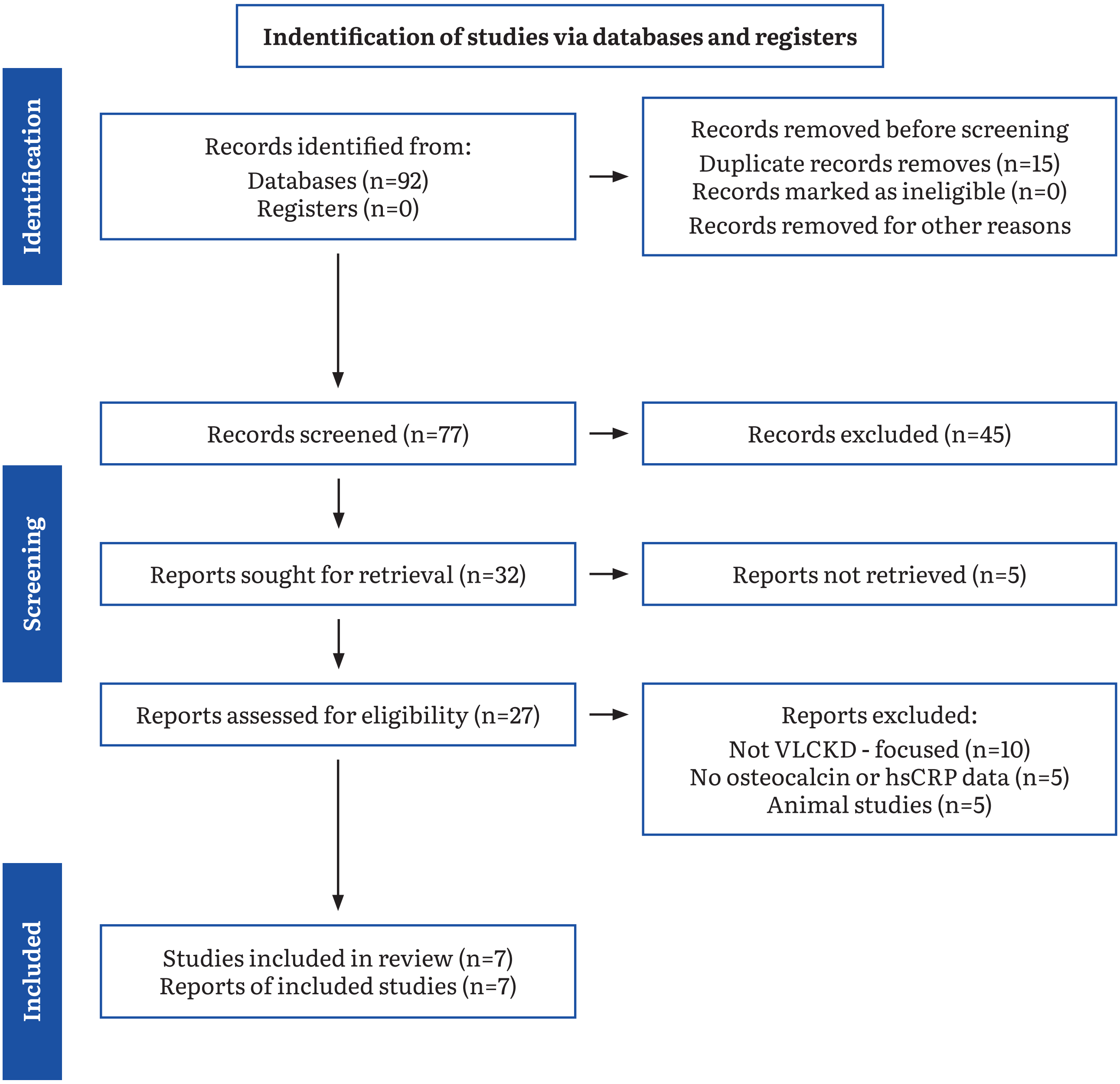

Figure 1: PRISMA flow diagram of study selection.

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intervention, and control group specifics. Key outcome measures, including changes in osteocalcin and hs-CRP levels before and after the intervention, were recorded alongside statistical results such as significance levels, confidence intervals, and effect sizes.

Results

Principal outcomes

HS-CRP: A crucial biomarker of inflammation

Multiple studies indicate that VLCKD significantly reduces hs-CRP levels after treatment, suggesting a lasting anti-inflammatory effect on obese individuals. In many cases, the regression surpassed 50%, with p-values consistently below 0.001, confirming the statistical significance of these findings.

The study by Perticone *et al.* [31] demonstrated that hs-CRP levels in the blood decreased from an average of 4.5±2.6 to 1.8±0.8 mg/L following a VLCKD intervention ($p<0.0001$). Clinically important was the improvement in metabolic health indices, particularly for insulin sensitivity and lipid profiles. Muscogiuri *et al.* [27] underlined gender variations in hs-CRP reduction, revealing percentage declines of -22.38±17.30% in women and -41.42±21.35% in men ($p=0.003$). Similarly, Barrea *et al.* documented that after 45 days on VLCKD, hs-CRP levels declined from 3.82±4.19 mg/L to 2.07±2.73 mg/L, corresponding to a −38.66% reduction ($p<0.001$), specifically in females. This decline correlated with reductions in BMI and waist circumference (WC) [29]. Additionally, Bosch-Sierra *et al.* reported a median hs-CRP reduction from 7.6 (4.4; 14.0) g/dL to 5.1 (3.1; 11.4) g/dL post-intervention [28]. The reductions in hs-CRP levels observed across studies are summarized in Figure 2.

Osteocalcin: A biomarker of bone health

The effect of VLCKD on osteocalcin levels was significant, indicating enhancements in bone turnover and general metabolic performance. Variations in baseline osteocalcin levels were noted among body weight categories, showing an average of 1222±610 pg/mL in normal-weight individuals *versus* 1438±914 pg/mL in obese individuals ($p=0.811$) [34] as illustrated in Figure 3.

Osteocalcin increases of 10% to 30% were consistently observed in response to VLCKD intervention in a longitudinal investigation, with statistical significance ($p<0.001$) [34]. Higher osteocalcin levels were strongly correlated with:

- Weight Loss: More pronounced osteocalcin elevations were observed in individuals with greater fat mass reduction;
- Improved Insulin Sensitivity: Lower HOMA-IR values were positively associated with higher osteocalcin levels.

Additional relevant variables

Alterations in anthropometric measurements

VLCKD resulted in significant weight loss, with reductions averaging 10–15% of initial body weight [27, 29, 31, 32, 34], equating to roughly 11.5±7.1 kg, as shown in Figure 4. The body mass index exhibited a reduction of 2–4 kg/m^2, with certain individuals moving from the obese classification to the overweight category.

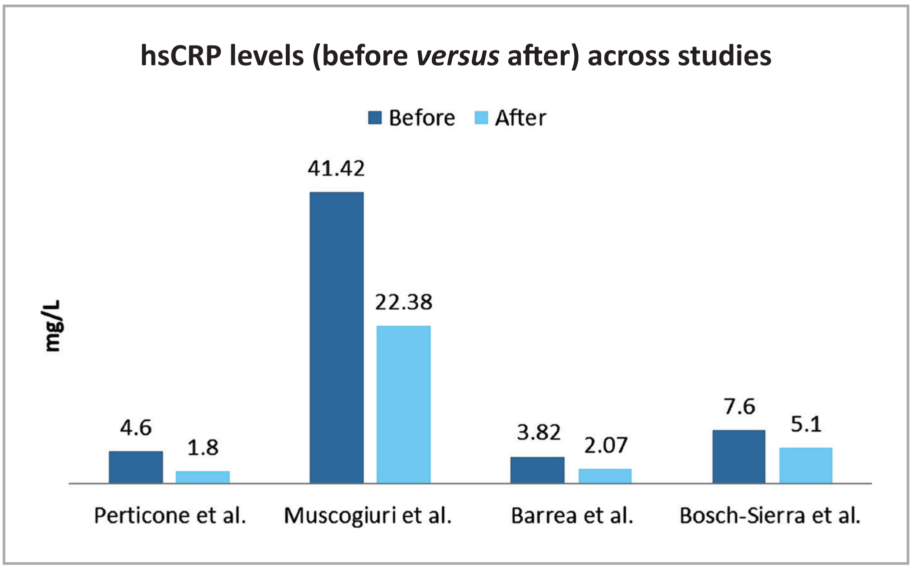

Figure 2: Reduction in hs-CRP levels following VLCKD across studies.

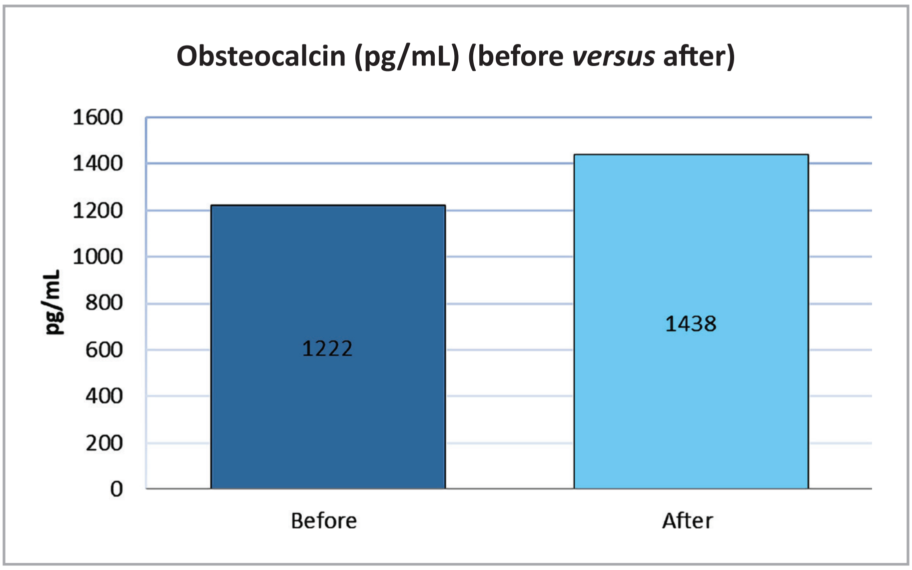

Figure 3: Osteocalcin Levels before and after VLCKD treatment.

Waist circumference (WC) also showed significant reductions, decreasing from 119.0±16.4 cm to 103.5±15.5 cm, demonstrating notable improvements in central obesity [27, 29, 31, 32], as shown in Figure 5.

Metabolic and biochemical improvements

The VLCKD significantly improved insulin sensitivity and glycemic control. As illustrated in Figure 6, the HOMA-IR levels displayed a significant decrease of 30% to 40%, dropping from 3.5±1.2 to 2.0±0.8 ($p<0.001$). Additionally, fasting insulin levels showed a considerable reduction.

Evident improvements in blood glucose regulation can be seen through the decrease in HbA1c levels, which have fallen from 2.5% to 6%. Furthermore, fasting glucose levels have decreased by 8% to 12% [28, 31, 32].

Lipid profile and cardiovascular parameters

Lipid metabolism has been significantly improved by VLCKD [28, 29, 31]. Commonly seen in a decrease of triglyceride levels, from 25% to 35%, and in an increase of high-density lipoprotein (HDL) cholesterol from 5% to 10%. These signs are significant and strongly linked to the state of the cardiovascular system. Significant decreases in blood pressure results have also been seen at the same time: systolic pressure (SBP) by 12 to 15 mmHg and diastolic pressure (DBP) by 8 to 10 mmHg. Figures 7 and 8 provide more explanation of the findings.

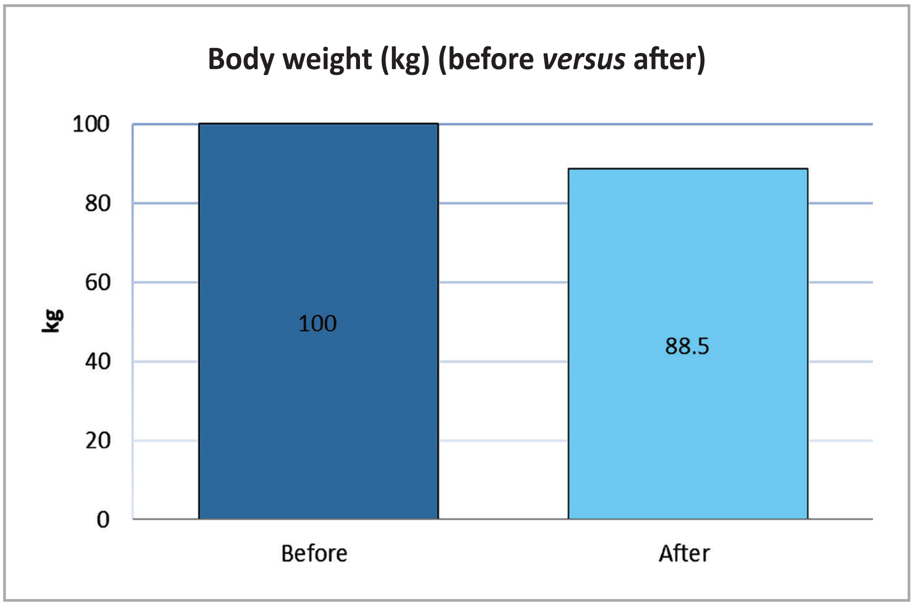

Figure 4: Weight Reduction before and after VLCKD treatment.

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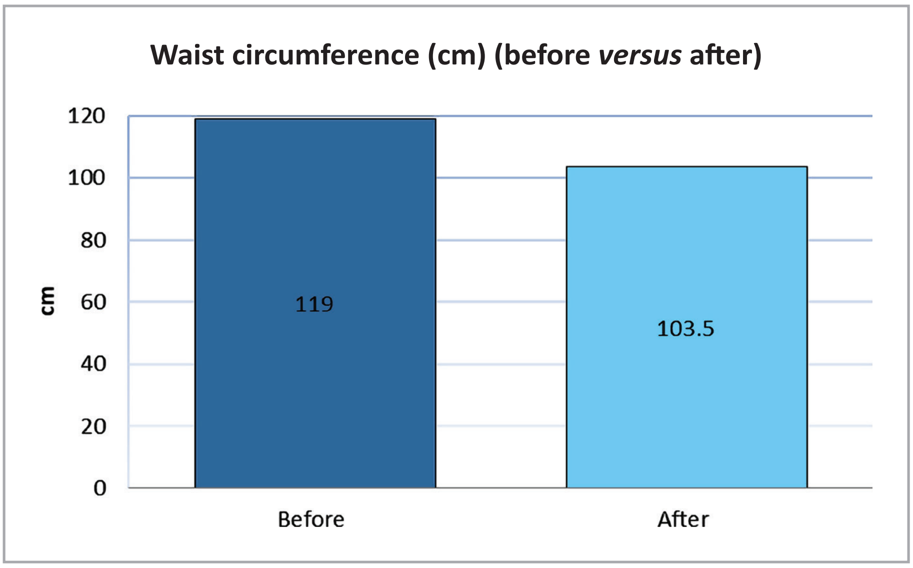

Figure 5: Alterations in Waist Circumference before and after VLCKD treatment.

Markers of inflammation and oxidative stress

Apart from metabolic and cardiovascular benefits, VLCKD significantly reduced inflammatory markers. Significant reductions in IL-6 and TNF-α, two key indicators of systemic inflammation, helped to demonstrate the anti-inflammatory effects of VLCKD further. Strangely, the VLCKD group's post-intervention malondialdehyde (MDA), an indicator of oxidative stress, increased. This increase was positively connected to blood ketone levels, indicating a potential oxidative change linked with continuous ketosis [34]. These metabolic changes were accompanied by improvements in phase angle measurements [28], which reflect enhanced cellular integrity and reductions in fat mass, as summarized in Table 1.

Discussion

This review demonstrates the role of VLCD as a comprehensive solution for obesity. It reduces systemic inflammation by improving metabolic control and enhances biomarkers of bone health. VLCKDs reduce the inflammatory response, increase metabolic flexibility, and modify skeletal homeostasis as seen in previous studies.

Effect on systemic inflammation

Many studies have confirmed VLCKD's anti-inflammatory capacity due to a reasonable reduction in hs-CRP [27–29, 31, 34]. Research showing that ketogenic

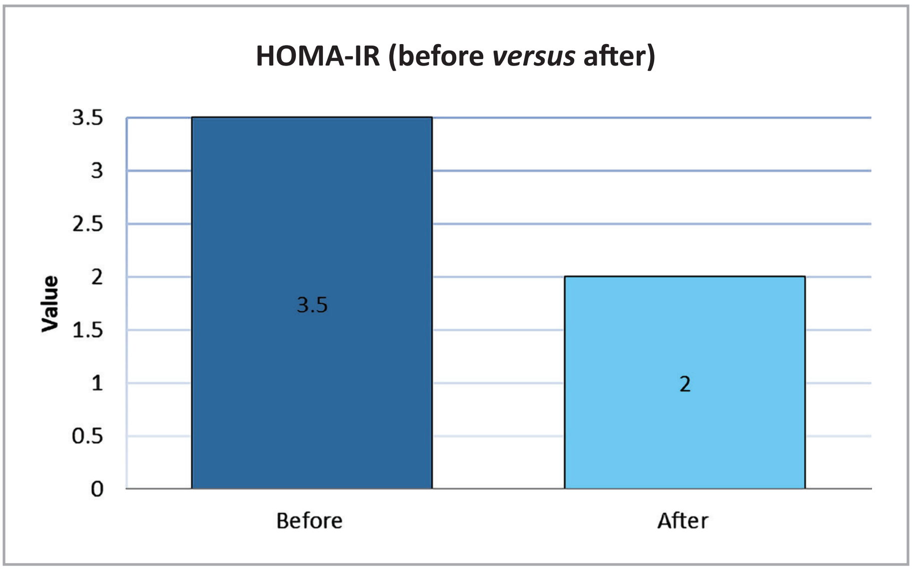

Figure 6: Variations in HOMA-IR before and after VLCKD treatment.

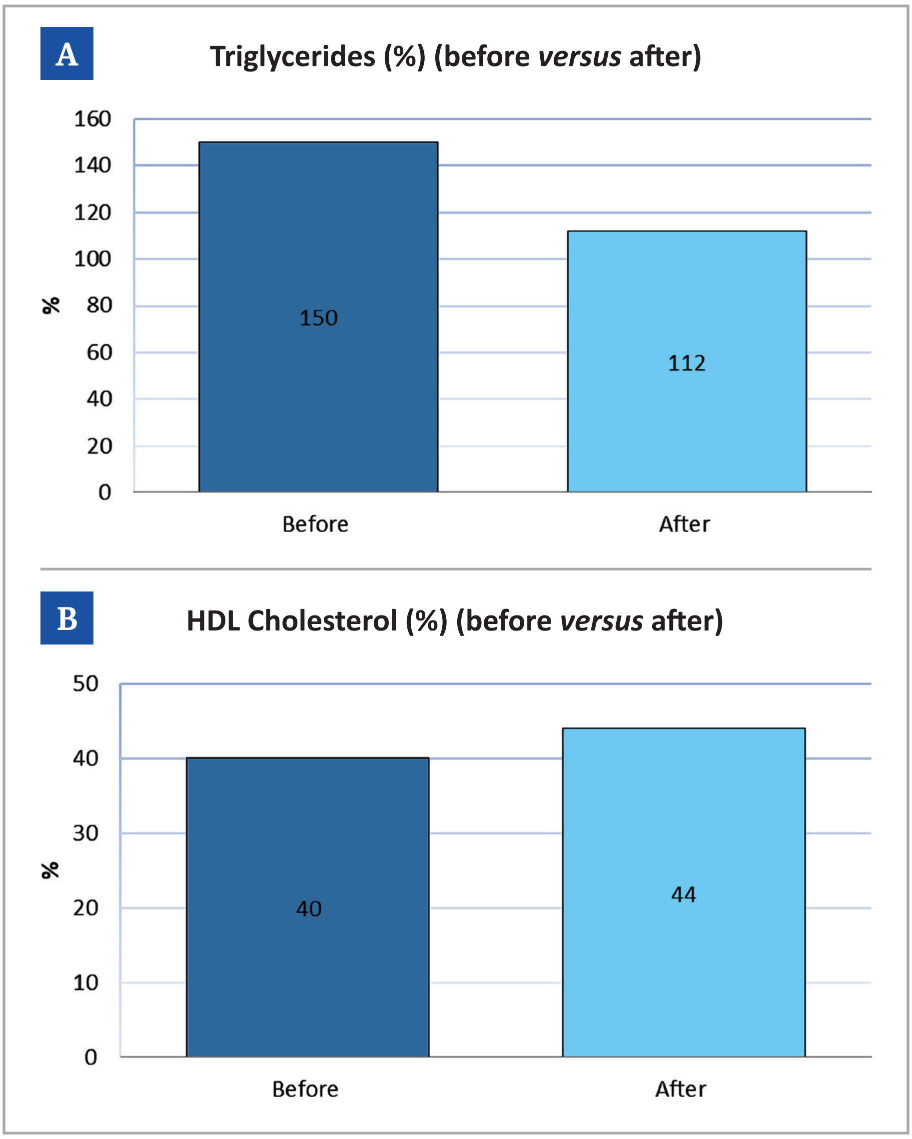

Figure 7: Alterations in lipid profile before and after VLCKD treatment. A – Reduction in triglyceride levels; B – Increase in HDL cholesterol levels.

diets (KDs) have a positive effect on the inflammatory process, leading to a decrease in inflammatory cytokines while reducing visceral fat and metabolic endotoxemia [37], is consistent with Perticone *et al.* [31]. VLCK reduces systemic inflammation by regulating adipose tissue metabolism, which is the main source of pro-inflammatory cytokines, with IL-6 and TNF-α being included.

Furthermore, Muscogiuri *et al.* [27] reported that there are significant gender differences in the inflammatory response to VLCKD, with males showing a greater decrease in hs-CRP levels (-41.42%) compared to females (-22.38%). Studies show that sex hormones can influence metabolic and inflammatory responses to diets, although the exact mechanisms are still unclear [38, 39]. This suggests that more research is needed on gender-specific dietary adaptations.

The reduction in hs-CRP has been associated with improvements in blood pressure and blood lipid levels, which reinforces the findings of several previous studies [24, 38–40], which suggest that persistent inflammation may play an important role in vascular damage and increased risk of heart disease. This suggests that the anti-inflammatory effects of the VLCKD diet are not only related to metabolic benefits but may also help protect the heart.

Impact on bone and metabolic health

Osteocalcin was previously considered primarily as an indicator of bone formation, but it is now known also to help regulate insulin and energy metabolism [17, 18]. However, although higher levels of osteocalcin [34] may indicate increased bone turnover, its direct impact

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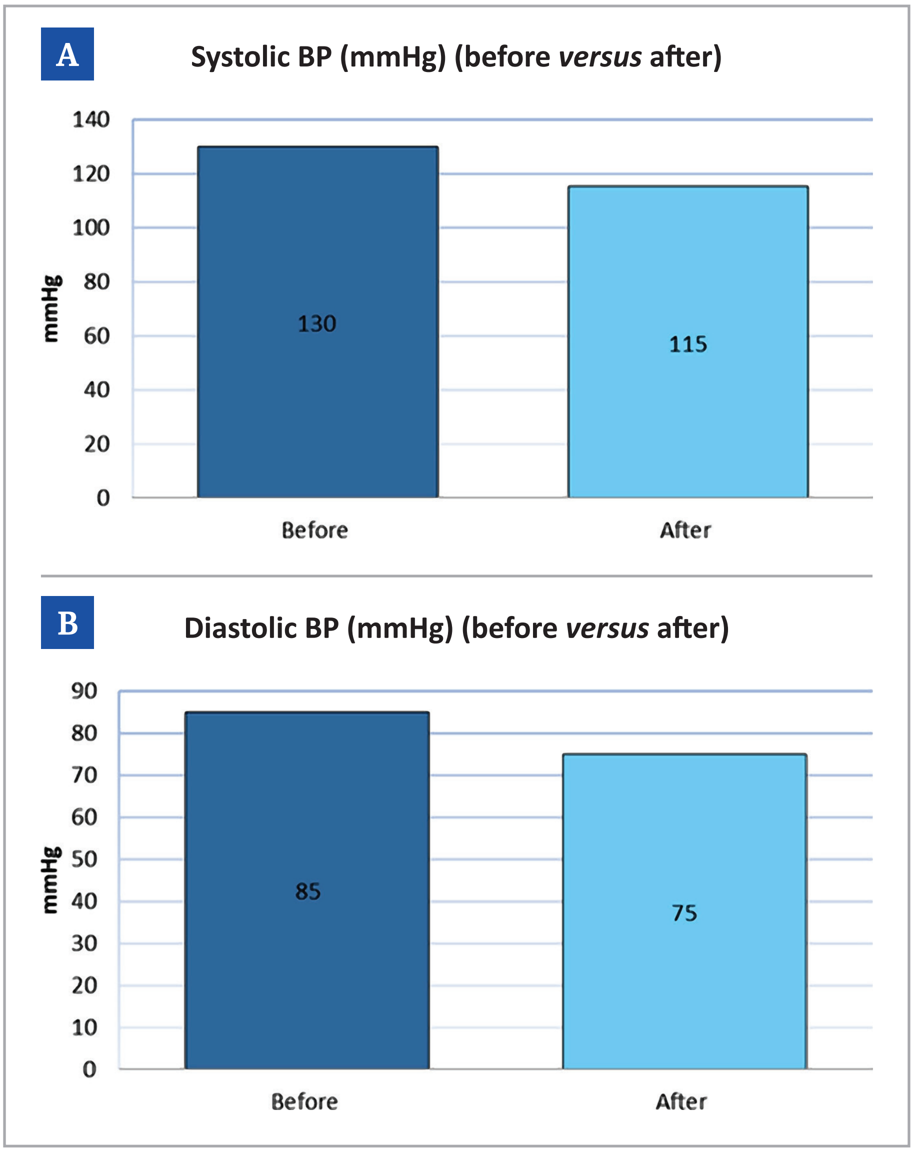

Figure 8: Reduction in Blood Pressure before and after VLCKD treatment. A – Systolic; B – Diastolic.

on skeletal strength and integrity remains unclear and requires further study.

Although differences in osteocalcin levels were observed between different weight categories [34], they were not statistically significant (p=0.811). This implies that the effect of VLCKD on bone metabolism comes more from general metabolic alterations in the body than from the baseline rate of bone turnover. Conversely, changing osteocalcin levels needs greater attention by means of lowering systemic inflammation and enhancing blood sugar management, so connecting VLCKD to advantages in metabolic and skeletal health.

However, further studies are needed to understand the long-term effects of changes in osteocalcin levels on bone mineral density, especially when it comes to chronic ketosis and calcium metabolism. These early signals point to a possible link between nutritional ketosis and bone metabolic adaptation, but we do not yet know whether one process causes the other.

Metabolic and cardiovascular benefits

Hemoglobin A1c decline levels indicate a significant enhancement in long-term glycemic control, reinforcing the potential use of VLCKD in managing T2DM.

The reduction in weight simultaneously enhances the efficacy of VLCKD in reducing central obesity, a vital element in metabolic dysfunction. Research indicates that decreasing visceral fat has a beneficial effect on insulin signaling and reduces the generation of pro-inflammatory cytokines. The observed improvements in glycemic control and lipid profiles are likely attributable to these mechanisms [41–43].

Table 1: Overview of modifications and health effects of VLCKD.

Parameter	Change observed	Health impact
hs-CRP (mg/L)	30% to 50% reduction, $p<0.001$	Anti-inflammatory effect
Osteocalcin (pg/mL)	10% to 30% increase, $p<0.001$	Improved bone health and metabolism
Body weight (kg)	10–15% reduction (~11.5±7.1 kg)	Weight loss & reduced visceral fat
BMI (Body Mass Index, kg/m^2)	2–4 kg/m^2 reduction	Reduced BMI (obesity to overweight)
Waist circumference (cm)	119.0±16.4 cm to 103.5±15.5 cm	Reduction in central obesity
HOMA-IR (Homeostatic Model Assessment of Insulin Resistance)	30–40% reduction (*e.g.*, 3.5±1.2 to 2.0±0.8, $p<0.001$)	Improved insulin sensitivity
Fasting insulin	Significant decrease	Better glucose regulation
Fasting glucose (%)	8–12% reduction	Improved glycemic control
HbA1c (%)	2.5% to 6% reduction	Improved glycemic control
Triglycerides (%)	25–35% reduction	Improved lipid profile
HDL Cholesterol (%)	5–10% increase	Improved lipid profile
Systolic BP (mmHg)	Reduction of 12–15 mmHg	Reduced blood pressure
Diastolic BP (mmHg)	Reduction of 8–10 mmHg	Reduced blood pressure
IL-6	Significant decrease	Anti-inflammatory effect
TNF-α	Significant decrease	Anti-inflammatory effect
Malondialdehyde (MDA)	Reduction in oxidative stress	Reduced oxidative stress
Phase angle	Significant improvement correlating with fat reduction	Improved cellular health

Note: * – This table delineates the observed alterations subsequent to a Very Low-Calorie Ketogenic Diet (VLCKD). The changes in each factor and their health effects are outlined.

In terms of the heart, the lower levels of triglycerides and higher levels of HDL cholesterol, along with lower blood pressure (SBP and DBP), suggest that VLCKD may help protect the heart [28, 29,31, 32]. According to earlier research, low-carbohydrate diets change lipid metabolism, most likely because they increase fatty acid oxidation and decrease liver lipogenesis [44].

Markers of inflammation and oxidative stress

VLCKD's anti-inflammatory benefits go beyond hs-CRP; it also greatly reduces other inflammatory markers like IL-6 and TNF-α [34]. Studies indicate that VLCKD could directly affect pro-inflammatory signaling pathways, perhaps mediated by beta-hydroxybutyrate (BHB), the primary ketone body produced during ketosis. By blocking the NLRP3 inflammasome, a key player in metabolic inflammation [45], BHB emphasizes the potential of VLCKD to be used as an anti-inflammatory dietary strategy. Previous studies have also demonstrated that KDs improve insulin action by lowering hepatic glucose synthesis and increasing mitochondrial efficiency [41, 42].

Regarding oxidative stress, Bosch-Sierra *et al.* [28] observed improved phase angle values following VLCKD, indicating enhanced cellular integrity and membrane function. Although MDA levels increased in some reports [34], this was interpreted as part of an adaptive antioxidant response associated with ketone body elevation. Overall, VLCKD supports redox homeostasis and may help alleviate obesity-related oxidative stress.

Clinical implications

Positive effects of VLCKD on obesity and metabolic syndrome are emphasized in this research. Studies show it may help with weight reduction and lower hs-CRP levels, which is crucial for controlling inflammation in the body. The increase in osteocalcin levels seen with VLCKD indicates possible advantages for metabolism and bone health.

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Also, VLCKD shows changes in blood pressure, lipid profiles, and insulin sensitivity, all of which lower the chance of heart problems. Its beneficial effect on blood sugar management also implies its possible use in controlling T2DM and pre-diabetes. Furthermore, individual reactions to this diet differ; therefore, regularly monitoring patients is vital to guarantee safety and get optimal outcomes.

Limitations and future directions

Though limited by differences in study design, short timeframes, and diverse demographics, research on VLCKD shows promise. Most studies highlight short-term results, hence stressing the need for long-term follow-ups to improve dependability and procedure standardization. Future studies should investigate sex-specific reactions to VLCKD, with an emphasis on hormonal and metabolic elements. It is very important to understand how VLCKD affects the bacteria in the gut because the health of the gut has a big impact on inflammation and metabolism. Identifying certain populations who gain from VLCKD helps doctors develop individualized dietary strategies that more successfully control metabolic syndrome and obesity.

Conclusion

Showing significant benefits for metabolic, inflammatory, and cardiovascular health, VLCKD is an optimistic dietary approach for controlling obesity. Although short-term results indicate its effectiveness, long-term sustainability, personal variation in reaction, and possible safety issues still call for further research.

Conflict of interest

The authors declare no conflict of interest.

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