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Nutrition, Physical Activity, and Age-Related Metabolic Syndrome

Lead Guest Editor: Farzad Amirabdollahian
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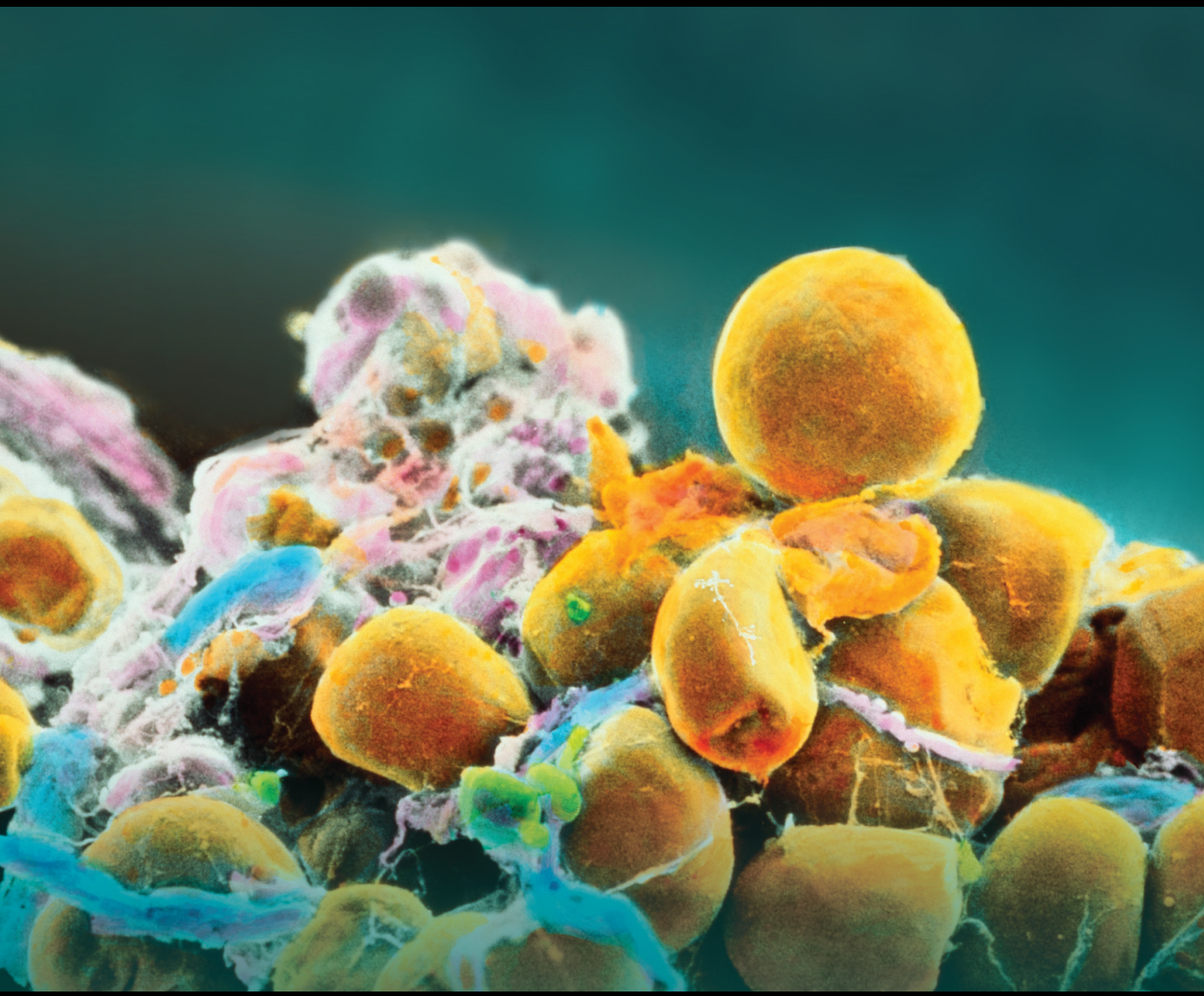

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Review Article

Possible Nonneurological Health Benefits of Ketogenic Diet: Review of Scientific Reports over the Past Decade

Katarzyna Daria Gołąbek and Bożena Regulska-Ilow

Wroclaw Medical University, Department of Dietetics, Wrocław, Poland

Correspondence should be addressed to Katarzyna Daria Gołąbek; katarzyna.golabek@umw.edu.pl

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The ketogenic diet (KD) has been used since the 1920s as a therapy for drug-resistant epilepsy. Due to the beneficial effects of this diet on the nervous system and the proposed multifaceted effects of ketones on health and disease, researchers have evaluated its use in other nonneurological conditions. The objective of this review was to analyze the most recent papers, which is why meta-analyses were used in which 75% of the studies were from 2012 to 2022. Authors also cited single studies from the last decade that lasted longer than 12 months to assess the long-term benefits of KD. Reports from the past decade have highlighted several significant areas regarding the impact of KD. One of these is the use of very low-calorie ketogenic diet (VLCKD) as an effective possibly safe and patient-motivating component of a long-term weight loss plan. Reports on the positive influence of KD on the health of obese individuals, and the possible resulting validity of its use, should be verified by patients' physical activity levels. A significant number of studies from the last decade evaluate the effect of KD on improving the health of individuals with type 2 diabetes as an effective tool in lowering glycated hemoglobin (Hb1Ac) and required doses of hypoglycemic drugs. The long-term studies indicate a possible beneficial effect of KD on cardiovascular function due to improvement lipid profile, changes in apolipoprotein (Apo) A1, adiponectin, and intercellular adhesion molecule-1 (ICAM-1).

1. Introduction

A ketogenic diet (KD) is a very low-carbohydrate diet. The reduced supply of carbohydrates decreases glucose availability in the body, which triggers a change in cellular energy utilization [1]. This promotes lipolysis and the utilization of free fatty acids rather than glucose for energy metabolism. In turn, limited glucose availability leads to the production of ketones (e.g., acetoacetate, β-hydroxybutyrate, and acetone) as alternative energy sources [2].

The KD has been used since the 1920s as a therapy for drug-resistant epilepsy [3]. In the last two decades, the popularity of this dietary strategy has grown. Between 2004 and 2019, the KD was the fifth diet that generated significant interest online [4].

Emerging evidence suggest that ketone bodies are not only energy substrates but exert pleiotropic effects on mitochondrial functioning, function of signaling mediators, and contribute to endogenous antioxidant defenses [5–7]. Due to the proposed multifaceted effects of ketone bodies, multiple studies have examined the possible benefits, efficacy, and safety of the KD on nervous system functioning and as a possible intervention across multiple diseases [8].

In KD, the proportion of energy obtained from carbohydrates oscillates between 14% and 20%, which is mostly less than 50 grams (g) of carbohydrates (CHO) per day (d) [9–13]. In the beginning of keto-adaptation, these values are frequently lowered to approximately 25 g/d [11, 12, 14, 15].

Over the course of two days to a week on average, very low carbohydrate intake causes an increase in serum levels of ketone bodies [14, 16]. In general, studies show that a concentration higher than 0.5 mM/L is indicative of stable ketosis, although others report a higher value (0.8–1 mM/L). In turn, this stabilization is linked to the resolution of initial adverse effects including nausea, malaise, dizziness, polyuria, low mood, and constipation, often termed as "keto flu"

[16–18]. Recent reports indicate that the level of ketone production and the body's response to ketosis may be genetically determined [19].

This narrative review focuses on research papers from the last decade evaluating the use of ketogenic diet in diseases unrelated to the nervous system. To analyze the most recent papers, meta-analyses were used in which 75% of the studies were from 2012 to 2022. Many studies indicate short-term beneficial effects of KD, but to complement them, the following article also cites single studies from the last decade that lasted longer than 12 months to assess the long-term benefits of KD.

2. The Use of the Ketogenic Diet in Individuals with Excessive Body Weight

For many years, low-carbohydrate diets such as the Atkins diet and the KD have been popular tools used for weight loss. In the last decade, many researchers have been evaluating the validity of the very low-calorie ketogenic diet (VLCKD) for weight loss by obese individuals. Assuming, in different variations depending on the authors' implementation, a 3-stage protocol in which stage 1 implements <600–800 kcal/d and about 30–50 g CHO, followed by the introduction of more calories and carbohydrates (about 800–1500 kcal/d of the so-called dietary re-education -stage 2), and then a diet of about 1500–2250 kcal/d.

A meta-analysis of 12 studies by Castellan et al. [20] evaluated the beneficial short- and long-term effects of VLCKD in overweight participants. Maintaining the ketosis stage for 4 weeks was associated with an average loss of 10 kg ($I^2 = 6\%$), and about 15.6 kg ($I^2 = 37\%$) between 4 and 12 weeks (6 studies). It was estimated that approximately (approx.) 66% of the weight lost was adipose tissue. The obtained anthropometric changes were stable in follow-ups of all studies, with the shortest lasting 3 weeks and the longest about 2 years. In this meta-analysis, both from the beginning of the study to 4 weeks and from 4 to 12 weeks, significant reductions in body mass index (BMI) values (−4.2; $I^2 = 77\%$; −6.2 kg/m2; $I^2 = 73\%$) and waist circumference (WC) values (−9.7; $I^2 = 67\%$; −15.6 cm; $I^2 = 76\%$) were reported along with the weight loss. Higher values were obtained with longer maintenance of ketosis. In addition, use of this dietary strategy was associated with reductions in glycated hemoglobin (HbA1c), total cholesterol (TC), triglycerides (TG), aspartate transaminase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), systolic blood pressure (SBP), and diastolic blood pressure (DBP). Changes in low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), serum creatinine, serum uric acid, and serum potassium were not observed.

Based on the cited meta-analysis, it is worth noting the 2 long-term (>12 m) studies used in it by Moreno et al. [21, 22]. The first, conducted in 2014 [21] on a group of 53 participants, compared the VLCKD protocol with a low-calorie diet (LCD) (about 90% total metabolic expenditure) containing 45–55% of carbohydrates. In the study, the ketosis stage lasted about 30–45 days. After 12 months of intervention, significantly higher weight loss (19.9 ± 12.3 vs 7.0 ± 5.6 kg; $p < 0.0001$) and thus BMI values were observed in VLCKD participants compared to LCD. Changes in lean body mass were not assessed in the VLCKD group. However, this method was also associated with a higher incidence of side effects like fatigue, headache, muscle weakness, constipation, hyperuricemia, and nausea compared to LCD. Most participants observed their resolution after a few weeks. However, after one year of intervention, 18.5% of participants still reported constipation, 7.45% hair loss, and 3.7% fatigue. During the study, changes in body weight and studied biochemical parameters were observed according to the stage of diet, carbohydrate content, and caloric value. In addition to anthropometric changes, significant reductions in HbA1c (5.50 vs 5.49%) and TC (207.2 vs 193.2 mg/dL) were observed in the VLCKD group at 12 month of the study.

A 2016 study by the same author [22] also compared the impact of the VLCKD protocol, which included a 2-month ketosis phase, with LCD over a 2-year period. The VLCKD group was evaluated to have significantly higher weight loss (12.5 vs 5.2 kg; $p < 0.001$), reduction in BMI (4.4 vs 1.9 kg/m^2; $p < 0.001$), and fat loss (8.8 vs 3.8 kg; $p < 0.001$) compared to the LCD group. Moreover, the VLCKD group lost significantly more visceral fat−666 vs 200 g ($p < 0.001$). After 2 years, significantly more (54%) of VLCKD group participants lost and maintained 10% weight loss compared to LCD (13%; $p < 0.001$).

The positive anthropometric changes described in previous papers were also confirmed in a meta-analysis of European studies [23] comparing the effect of VLCKD and other dietary strategies such as very low-calorie diet (VLCD), LCD, or Mediterranean diet with calorie restriction. Differently to the work of Moreno et al. [21, 22] and Castellana et al. [20] in which no changes in fat free mass (FFM) were noticed, in this meta-analysis [23] a decrease in FFM of −2.96 kg ($I^2 = 0\%$) was observed in the groups using VLCKD. However, this result was not significantly different from other assessed interventions. The use of VLCKD improved the biochemical profile of the participants; however, the reduction in the values of three parameters: homeostatic model assessment for insulin resistance (HOMA-IR) (−1,36; $I^2 = 98\%$), TC (−7,13 mg/dL; $I^2 = 51\%$), TG (~−29,90 mg/dL; $I^2 = 89\%$) was significantly higher in the VLCKD group compared to other dietary strategies.

In the last decade, researchers have been combining or contrasting the benefits gained from the ketogenic diet with the effects of the Mediterranean diet that has been recommended for years. The study by Petricone et al. [24] compared the use of VLCKD and a calorie-restricted Mediterranean diet (Total Daily Energy Expenditure (TDEE) reduced approx. 500 kcal; 55–60% CHO) in two 28-person groups over 12 months. Significant reductions were observed in WC (119.1 ± 22.9 vs 95.0 ± 17.4 cm), HbA1c (6.1 ± 1.4 vs 5.2 ± 0.15%), HOMA-IR values (7.3 ± 0.7 vs 2.6 ± 0.2), fasting insulin (28.0 ± 16.7 vs, 10.9 ± 4.9 μU/L), TG (151.3 ± 50.0 vs 72.3 ± 29.6 mg/dL), C-reactive protein (CRP) (4.5 ± 2.6 vs 1.8 ± 0.8 mg/dL) in the VLCKD group compared to the beginning of the study. It is worth noting that an

increase in 25 (OH)D status (18.4 ± 5.9 vs 29.3 ± 6.8 ng/mL) was observed in the blood of participants of this group. Participants following the Mediterranean diet showed no significant improvement in anthropometric and 25 (OH)D parameters, while significant biochemical changes were observed in fasting Glc, HbA1c, fasting insulin, HOMA, TG, and CRP.

In another study [25], a 20-day period of VLCKD (30 *g* CHO/d, 36% protein, 52% fat; approx. 976 ± 118 kcal) starting the study was combined with a 20-day low-carbohydrate nonketogenic diet (LCNKD) (25% CHO, 31% protein, 44% fat; approx. 1111 ± 65 kcal) and then a 4-month norm caloric Mediterranean diet (58% CHO, 15% protein, 27% fat; approx. 1800 ± 100 kcal). The entire cycle was then repeated extending the Mediterranean diet period to 6 months. In the study, both periods of VLCKD were associated with ketosis and contributed to significantly higher decreases in body weight (100.7 ± 16.54 vs 84.59 ± 9.71 kg) and body fat percentage (43.44 ± 6.34 vs 33.63 ± 7.6%) compared to the LCNKD or Mediterranean diet stages, during which no significant changes were assessed. Results were maintained until the end of the study, similarly to positive changes in TC, LDL-c, and fasting Glc, whose significant decrease was observed after 1 period of VLCKD and LCNKD.

Such trends were also observed in another population [26]. In addition, no significant changes in estimated glomerular filtration rate (eGFR), creatinine levels, or microalbuminuria were observed during the 12-month study with VLCKD. During the study, a subtle but significant improvement in uricemia was reported following the end of the ketogenic period. Changes in potassium, sodium, and magnesium status were not observed. Only calcium concentrations decreased slightly during the first 30 days of the study and then increased between days 30 and 90.

The protocols used in the above meta-analyses and studies that included VLCKD diet periods had a very high restriction of caloric supply. Therefore, it is difficult to conclude whether ketosis, caloric deficit, or their synergistic effects were the key to achieving the described benefits. Maintaining such a caloric regimen is a great challenge for participants, hence the assessed periods of ketogenic diet lasted 2 months at most. However, it is worth noting that after the restrictive periods, the caloric values from the VLCKD groups equaled other dietary strategies, remaining more effective long-term. Despite this, reports from this decade still do not provide a complete answer regarding the safety of long-term KD use. In most of them, carbohydrate content increases again over longer periods of time.

All the cited works support the effectiveness of introducing even short periods of KD as a tool for effective weight loss possible to be sustained long term. Even its short-term application is a viable achievement for patients that can increase motivation and traction to improve biochemical parameters of glycemia and lipid profile.

Apart from optimistic reports of using VLCKD, researchers also point to less calorically restrictive eating plans as positive tools for weight loss. For instance, in a long-term study involving six months of controlled dietary intervention and an 18-month follow-up, a nutrigenomic tailored and low glycemic index diet was found to be more effective in attaining and maintaining weight loss compared to the KD. Furthermore, it contributed to greater reductions in TC and fasting Glc and an increase in HDL-c compared to the results obtained in the KD [27].

3. The Ketogenic Diet Combined with Physical Activity for Weight Loss

Optimistic reports on the achieved effects of using VLCKD among overweight individuals without added physical activity are worth contrasting with the results of the meta-analysis by Asthary-Larky et al. [28] regarding the effects of less restrictive KDs combined with resistance training. Based on 13 studies (92.3% from the last decade) lasting maximum 3–4 months, the authors concluded that compared to diets providing 40–50% of carbohydrates and KD was associated with significantly greater reductions in body weight ($I^2 = 18$, 1%), fat mass ($I^2 = 62$, 4%), and percentage of body fat ($I^2 = 79$, 8%), as well as BMI ($I^2 = 68$, 9%). However, the same analysis (similarly to [23]) showed a negative effect of KD on FFM (WMD = −1.26 kg; 95% CI: −1.82, −0.70; $I^2 = 22$, 7%; $p < 0.001$). This may be because 10 of the 13 studies analyzed the outcomes of highly physically active individuals, both nonelite and elite athletes, in contrast to previously cited studies involving inactive obese individuals. Based on further subgroup analysis, it was found that KD had no significant effect on FFM in overweight participants.

Another meta-analysis [29] of 7 studies (the longest was 6 months) compared the benefits gained from KD (<50 CHO g/d) combined with physical activity (CrossFit, cycling, progressive resistance training, combination of aerobics, and resistance exercise) and among overweight participants with regular diets (contains approx. 40–55% CHO) who are increasing their physical activity. In the reviewed papers, the period of ketosis lasted an average of 9.2 weeks (min. 4; max. 24). The only significant favorable changes of anthropometric indices in the KD group were related to a decrease in WC (2 trials; $I^2 = 0\%$) compared to the control groups. A comparison of four studies showed no significant differences between groups for VO_2 max. However, in both studies the introduction of regular activity was associated with a significant increase in performance. Significantly higher decreases in TG (4 trials; $I^2 = 0\%$) were observed among KD users; however, more favorable changes were not observed in fasting Glc, LDL-c, and TC.

It appears that the participant's willingness to increase physical activity may prove to be a key element in selecting an appropriate dietary strategy for weight loss. The greater efficacy of KD in inactive individuals with excessive body weight is not as clearly confirmed in those who increase their level of physical activity. Diets that are easier to maintain, less restrictive in carbohydrate content, and caloric value, seem to be an equally valid choice, perhaps allowing for better maintenance of muscle mass. The selection of the appropriate type of physical activity predisposing to greater weight loss in combination with appropriate dietary strategies, including KD, seems to be an interesting research question.

4. The Use of the Ketogenic Diet in Patients with Type 2 Diabetes

Because of the limited intake of glucose sources and other simple sugars to regulate glycemia, low-carbohydrate diets are a common choice for patients with type 2 diabetes (T2D). Over the past decade, researchers have continued to evaluate the impact of KD use on required doses of hypoglycemic medications and observed additional lifestyle-related benefits of this dietary strategy.

A meta-analysis of 12 studies ranging from 1 to 52 weeks [30] involving overweight participants evaluated the effect of KD (max. 50 g CHO/d) on biochemical parameters associated with T2D. Compared to the beginning of the intervention, a reduction (95% CI) in Glc of 1.29 mmol/L (10 trials; $I^2 = 68\%$) and a significant reduction in HbA1c by −1.07% (8 trials; $I^2 = 71\%$) percentage points were observed, which is considered an ideal pharmacotherapeutic effect. Eight of these studies also evaluated TG reduction of 0.33 mmol/L ($I^2 = 67\%$), LDL-c of 0.05 ($I^2 = 71\%$), and HDL-c increase of 0.14 mmol/L ($I^2 = 78\%$). Similar to the studies with metabolically uncomplicated obese participants, this group also showed a significant decrease in body weight (8.66 kg; $I^2 = 92\%$), decrease in WC (−9.17 cm; $I^2 = 0\%$), and BMI values (3.13 kg/m$^{2;}$ $I^2 = 28\%$).

Another meta-analysis by Alarim et al. [31] observed more beneficial changes of using KD, mainly VLCKD (about 20–50 g CHO/d), compared to the work of Yuan et al. [30]. However, this meta-analysis included three times fewer more heterogeneous studies. The authors evaluated significantly higher weight loss ($I^2 = 81\%$), decreased BMI ($I^2 = 97\%$), decreased fasting Glc ($I^2 = 98\%$), HbA1c ($I^2 = 98\%$), TG ($I^2 = 95\%$), and TC ($I^2 = 98\%$) in the KD group compared to control groups following calorie-restricted and/or low glycemic index diets. However, despite increased fat intake, no increase in LDL-c was observed, and a significant increase in HDL-c ($I^2 = 97\%$) was additionally reported.

The results of meta-analyses are supported by long-term studies. One of them encompassed 16 participants [32] with excess body weight characterized by HbA1c >6% that used KD (20–50 g assimilable CHO/d) in combination with mindful eating and positive attitude techniques, improved sleep hygiene and physical activity to achieve ketosis (0.5–3 mmol/L), and improved health. This 12-month intervention reduced HbA1c from 6.6% to 6.1%, a mean loss of 7.9 kg, and a reduction in hypoglycemic medication doses. All the obtained results were significantly higher compared to the group following a low-fat diet (LFD) (45–50% CHO, TDEE reduced approx. 500 kcal). It is worth noting that the caloric content of both diets was not statistically different.

The effect of reducing the required doses of hypoglycemic drugs was also observed in the work of Tay et al. [33,34] at both 12- and 24-month periods. Although the effects of KD (approx. 70% of TDEE−1700 kcal, 14% CHO, 28% protein, and 58% fat) compared to a more isocaloric high-carbohydrate diet (approx. 70% of TDEE −1700 kcal, 53% CHO, 17% protein, and 30% fat) were not significantly different with respect to body weight (9% of body weight lost in both groups), decreases in blood pressure, body fat percentage, LDL-c, HbA1c, and fasting Glc. However, a low-carbohydrate diet was associated with more stable Glc levels throughout the day and less frequent hyperglycemic episodes after 52 weeks. The low-carbohydrate group also showed a greater reduction in TG after 52 weeks and 104 weeks. HDL-c was maintained after 104 weeks. In the carbohydrate-restricted group, a 20% reduction in the required doses of hypoglycemic medications was observed in a higher percentage of participants (52%; 67%) compared to the high-carbohydrate group (21%; 32%) after 52 weeks and 104 weeks. What is more, changes in non-HDL-c, TC, LDL-c, blood pressure, and CRP did not differ between groups. Endothelial function did not change in either group after 2 years.

Patients with diabetes often choose the macronutrient content and duration of low-carbohydrate diets by themselves. Webster et al. [35] in their study evaluated the effects of a low-carbohydrate high-fat (LCHF) diet in a group of participants following it for at least 6 months to a maximum of 6 years. Six months of LCHF use was the minimum period to be included in the study. During the 15-month study, participants consumed an average of 61 g of CHO/d. This intervention contributed to a decrease in median HbA1c from 7.5% to 5.9% and a reduction in hypoglycemic medication doses. Remission and discontinuation of medications as a result of the diet was achieved by 29% of participants (7 of 22). The majority of them reported reduced hunger, frequency of meals, snacking, and a desire to eat sweet foods while using KD.

Studies from the last decade suggest that in addition to improving glycemic parameters, KD may also improve other health components. The study executed by Vilar-Gomez et al. [36] observed its possible beneficial effect on hepatic steatosis, as 12 months of using KD resulted in reduced values of indices assessing hepatic steatosis and fibrosis risk. Such changes were not observed in diabetic patients receiving standard treatment. Improvements in diabetes-related parameters were associated with improvements in ALT levels in the KD group.

In addition, Moricione et al. [37] observed that a 3-month period of best adherence to KD decreased the incidence of emotional and uncontrolled eating in the T2D group, whereas incidents of uncontrolled eating increased in the comparison group using LCD. After 12 months, the VLCKD group showed improvement in physical and psychological quality of life, with participants showing higher levels of satisfaction with weight loss, well-being, and dietary management.

Additionally, other authors [38] reported improved overall sleep quality in patients with prediabetes and diabetes after 12 months of using KD as opposed to those receiving standard treatment. It is noteworthy that sleep quality significantly improved among poor sleepers during the intervention. Interestingly, increased ketone levels correlated with better sleep quality in the prediabetic group.

Both meta-analyses and long-term studies point to possible beneficial effects of KD in T2D other than weight loss and improved body composition. In particular, it concerns the lowering of HbA1c levels and decreasing the required doses of hypoglycemic drugs. It is worth emphasizing that this effect is also visible in comparison to isocaloric diets with other fat and carbohydrate contents.

5. The Use of the Ketogenic Diet in Individuals at Increased Risk for Cardiovascular Disease

Inflammation and oxidative stress are important pathogenic mechanisms implicated in cardiovascular disease (CVD) [39]. The KD, through lowered carbohydrate intake and better regulation of glycemic control, coupled with the possible anti-inflammatory effects of ketone bodies themselves might additively contribute to the prevention of CVD [5–7].

In addition to the observed beneficial changes in lipid profile resulting from the use of KD such as the observed reduction in TG [20, 21, 23, 24, 29–31, 34], TC [20, 22, 23, 25, 31], improvement in LDL-c [25, 30], and maintenance or increase in HDL-c [30, 31, 33, 34], researchers observe a possible long-term additional effect of KD on CVD.

In a nonrandomized study involving 226 patients with T2D, after 52 weeks of using KD, Bhanpuri et al. [40] reported a significant decrease in TG, TG/HDL-c ratio, and blood pressure, as well as an increase in apolipoprotein (Apo) A1, Apo B/Apo A1 ratio, LDL-c, and HDL-c compared to the beginning of the study.

In another group of participants not complicated by T2D and CVD, lowering CHO intake <40 g/d for 12 months did not alter proinflammatory interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF)-α levels. However, it induced a significant increase in adiponectin. After 12 months, no significant changes in resistin, leptin, and E-selectin concentrations were observed. The concentration of intercellular adhesion molecule –1 (ICAM-1), which promotes endothelial damage and atherosclerosis, did not increase in the KD group, in contrast to the LF diet group. The analyzed changes in adiponectin and ICAM-1 concentrations in 53.6% and 69.5% were not dependent on the level of weight loss [41].

The effect of KD on CVD requires more specific studies evaluating more factors that promote prevention or occurrence of CVD. The cited long-term studies from the last decade indicate a possible beneficial effect of KD on cardiovascular function due to changes in ApoA1, adiponectin, and ICAM-1. It is worth noting that KD also improves the lipid profile. These positive reports need to be verified by more specific, long-term studies, and meta-analyses, which are still scarce in the available current literature.

6. Limitations

Finally, it is worth emphasizing the limitations of this narrative review. The chosen papers indicate important current areas of research on the impact of KD, showing current trends and additions to data from previous decades. However, the work does not illustrate all available knowledge on the subject and does not represent a complete compendium on KD.

Another limitation is heterogeneity between studies used in meta-analyses. For most authors, the acceptable heterogeneity was determined by I^2 cut points <50% [20, 28–31], except for the study by Mascoguri G et al. [23] where a limit of <60% was set. Most of the obtained results, apart from the weight loss [20, 23, 28, 29], BMI [23, 28–30], and FFM [20, 23] were characterized as medium (I^2>50%–75%) or highly (I^2>75%) heterogeneous [42]. In this aspect, it is worth emphasizing the low heterogeneity (I^2 <25%) between studies in meta-analysis by Lee H et al. [29] (most results obtain $I^2 = 0$), in contrast to Alairm et al. [31] (most results exceed I^2>95%). It is important to carefully reach conclusions from cited meta-analyses also in the perspective of heterogeneity, not to overestimate positive results.

7. Conclusions

Reports from the past decade have highlighted several significant areas regarding the impact and following KD. One of these is the use of VLCKD as an effective and patient-motivating component of a long-term weight loss plan. In the cited studies, short periods of very low-calorie KD were effective and their effects were maintained even after increasing calories and equating them to comparable dietary strategies such as LF, reduced-calorie Mediterranean diet, VLCD, and LCD. Current evidence confirms that positive anthropometric changes (weight loss, reduction of body fat, including visceral fat), as well as the beneficial effects on lipid profile (TG, TC, and LDL-c reduction) obtained during VLCKD can be sustained in the long term (12–24 months).

Reports on the positive influence of KD on the health of obese individuals and the possible resulting validity of its use should be verified by patients' physical activity levels. Studies from the last decade do not present such a clear message in terms of the beneficial use of KD by physically active individuals as in trials that do not include increased activity. Doubts about the introduction of KD are particularly related to maintaining muscle mass.

A significant number of studies from the last decade evaluate the effect of KD on improving the health of individuals with T2D. Based on current reports, it can be concluded that using KD is more effective in lowering Hb1Ac as well as the required doses of hypoglycemic drugs compared to other dietary strategies. This beneficial effect was also observed when the period of adherence to 50 g CHO/d intake was short and lasted up to 6 months. Moreover, interesting new research topics have emerged, such as the effect of KD on the level of hepatic steatosis, appetite regulation, and sleep quality among T2D patients.

However, despite its beneficial influence, KD can be complicated by noticeable side effects that can last up to 12 months. Using KD requires constant health monitoring as well as selecting proper macronutrients and hydration, due to the possible occurrence of disorders such as kidney stones. Their prevalence in adults using KD is about 7.9% [43].

Current reports still do not provide complete data to determine whether the long-term regimen of carbohydrate

intake demonstrated over periods of 5, 10, and 15 years is safe. In most of the cited papers, the period of full ketosis and CHO restriction <50 g/d lasted less than 6 months.

There is still a lack of studies that comprehensively evaluate changes in health status in patients following KD. To prove its safety, several factors need to be explored, including the extent of weight loss, changes in lipid and glucose profiles/T2D, full blood counts, iron parameters, renal function, endocrine changes, gut microbiota, and micronutrient deficiencies.

Data Availability

All publications used in the work are available in PubMed and online.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

The Value of Serum Adiponectin in Osteoporotic Women: Does Weight Have an Effect?

Ali B. Roomi[1,2] **Wassan Nori**[3] **and Saad H. Al-Badry**[1,4]

[1]*Ministry of Education, Directorate of Education Thi-Qar, Nasiriyah, Thi-Qar 64001, Iraq*
[2]*Biochemistry and Biological Engineering Research Group, Scientific Research Center, Al-Ayen University, Nasiriyah, Thi-Qar 64001, Iraq*
[3]*Department of Obstetrics and Gynecology, College of Medicine, Mustansiriyah University, Baghdad 10052, Iraq*
[4]*College of Health and Medical Technology, Al-Ayen University, Nasiriyah, Thi-Qar 64001, Iraq*

Correspondence should be addressed to Ali B. Roomi; dr.ali_bader@alayen.edu.iq

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Osteoporosis (OP) has been observed to have a deleterious effect on postmenopausal women's life quality by increasing the risk of fragility fractures. The current research was adopted to verify the role of serum adiponectin, a cytokine released by adipose tissue, as a marker for OP across different body mass index groups, for a better understanding of fatty tissue role in OP. A case-control study recruited 210 eligible postmenopausal women and subgrouped into three groups based on their DEXA scan results: osteoporotic group, osteopenia group, and healthy controls; each includes 70 patients. Three datasets were collected: anthropometric, age, menopause duration, weight, height, body mass index (BMI), waist circumference, and fat percentage. Radiological examination estimated the bone mineral density (BMD) for the femoral neck and lumbar spines with their respective T-score. From blood, we measured alkaline phosphatase and calcium by a spectrophotometer and serum adiponectin, phosphate, CTX, and PICP by ELIZA. Total BMD, T-score, serum phosphate, and PICP were significantly higher among healthy controls. Serum adiponectin, CTX, and ALP scored higher levels among OP cases. A strong inverse relationship was proved between serum adiponectin and T-score in osteoporotic and osteopenia groups (−0.427, −0.301). A strong negative relationship was found between serum adiponectin and total BMD in healthy controls (−0.204). All correlations were statistically significant, P value <0.001. Serum adiponectin can be a valuable marker for reduced bone mineral density among the general populace, irrespective of the body mass index. Further research is warranted to explore therapeutic and preventive applications for this adipocytokine.

1. Introduction

Osteoporosis (OP) is a common metabolic age-related disease defined by skeleton remodeling and a reduced bone mineral density (BMD). It is expected to reach epidemic incidence in the coming century [1]. OP predisposes people, especially postmenopausal women (PMW), to fragility fractures with high morbidity and mortality; 24% of OP women have died because of their health consequences [2]. Osteoporosis is a silent multifactorial disease; some factors are unchangeable, such as age; elderly population has a 97% incidence rate, particularly those aged 75–84 years. In addition, OP has a particular predilection for PMW. Other nonmodifiable factors include multiparous women, early menopausal onset, and long menopause duration [1, 3]. One of the modifiable risk factors for OP is the body mass index (BMI); body weight claimed to be a key determinant factor in adulthood BMD and later on OP development risk [4]. Obesity increases the strain on the bones, increasing their density. Conversely, increased marrow adiposity impairs bone integrity, contributing to increased fracture risk. Considering the global obesity crisis and increasing life expectancy, osteoporotic fractures in obese older PMW and shorter recovery periods are expected [5, 6].

Adipocytes are cells found in the bone marrow besides the viscera and intestine. They have a pivotal role in skeletal integrity as they govern the development of stromal cells into osteoblasts, which create bones. In addition, they secrete

particular mediators known as "adipokines," such as adiponectin. Adipocytes rise in specific illnesses such as OP and obesity, and they have been related to bone strength deterioration, leading to higher fracture risk [7]. Estrogen is certainly a modulator of marrow adiposity; previous research stated that estrogen negatively influences adipocytes, and estrogen supplementation for two weeks reduces their number by 5%. As a result, there is a rising interest in bone marrow adipocytes as a targeted therapy for osteoporosis [8]. In addition, adiponectin receptors were described in osteoblasts, implying their role in bone formation by promoting proliferation and differentiation of osteoblast and inhibiting osteoclasts activity [9].

Studies linked adiponectin with an adverse effect on bone mass through intensive bone resorption, while others described a correlation between adiponectin plasma levels and BMD, highlighting its role as a predictor of osteoporotic changes [10]. The correlations between OP and BMI were investigated by earlier research; still, they gave inconsistent and sometimes contradicting results. Serum adiponectin levels were examined by other researchers, showing a negative correlation between visceral fat and BMI. Its levels were diverse among individuals with comparable BMIs, following age, sex, and hormonal influences [11]. The exact role of adiponectin in OP disease is not well understood [12].

Since OP is better prevented than treated, many researchers pursue serum biomarkers for earlier diagnoses to improve outcomes [3]. However, the relation of BMI, serum adiponectin to OP among the Iraqi populace, is scarce. This study primarily aimed to examine the levels of serum adiponectin in different BMI (as an anthropometric parameter) with BMD. The secondary aim was to verify serum adiponectin correlations between body mass index, BMD, and T-score for menopausal women with and without OP.

2. Patients and Methods

A descriptive case-control study taken from May 2020 to June 2021 recruited 210 postmenopausal women. All attended the geriatric clinic in our University Hospital and subdivided into 3 groups based on the DEXA scan results. The osteoporotic group (OP) included 70/210 osteoporotic postmenopausal females with OP changes, the osteopenic group (OPN) included 70/210 postmenopausal females, and the healthy controls group (CG) included 70/210 postmenopausal females. The study protocol was outlined to the participants, and written informed consent was sought after the Institute Ethical Committees approved it. Samples size was measured by the sample size equation. The number of samples required for the study was found.

$$n = \frac{Z^2 * P(1-P)}{d^2}, \tag{1}$$

where n represents the sample size, Z represents the Z statistic for a level of confidence, P represents the expected prevalence or proportion, and d represents the precision (in proportion of one; $d = 0.001$).

We enrolled women in menopause aged 50 years and up. Menopause was defined by the absence of menses for more than a year. With a detailed medical and gynaecological history, exclusion was made to women with renal, liver, endocrine, inflammation, whether acute or chronic, dietary, or physical activities disturbance in any of the participants, impairing the bone metabolism. Participants with disorders or risk factors for OP and those taking medications that impair the bone metabolism were omitted from the study. By the end of our assessment, we finally excluded cases who were underweight and morbidly obese (BMI (<18.5 and >34.9 kg/m^2)) to decrease the risk of bias.

Besides the participant's age and menopause duration, other anthropometric readings were done twice in a barefoot standing pose, and we used the sum of two measures, including weight, height, BMI, waist circumference, and fat percentage. Weight in kilograms was used to measure the body mass index. Kilograms were divided by height squared (in meters); BMI = weight (kg) divided by the square of height (m^2). Calculation of fat% score was done based on the following equation:

$$\begin{aligned}\text{Fat percentage} = [&1.20 \times \text{body mass index} - 0.23\,(\text{age}) \\ &- 10.8\,(0 \text{ for female}) - 5.4].\end{aligned} \tag{2}$$

After many natural breaths, the WC was estimated at a plane parallel to the ground, at the midaxillary line, midway between the tip of the iliac crest and the lower border of the last perceptible rib. Cutoff values for Asians were used to analyze the data (80 cm in women).

Radiological examination estimated lumbar spine and femoral neck BMD and their respective T-score

After one night fast, blood was aspirated, centrifuged, and sera divided into two; the first part was used to measure alkaline phosphatase and calcium by the spectrophotometer. The rest of the serum was stored frozen at −20°C for later estimation of serum adiponectin by enzyme-linked immunosorbent assay (ELISA), phosphate, CTX, serum human carboxyterminal propeptide of type I procollagen, a marker for bone degradation, and (PICP) serum procollagen I carboxyterminal propeptide, a marker for bone formation.

3. Statistics

The Shapiro–Wilk test defined the data normality, and analysis was made by SPSS software program version 22.0 (SPSS Inc., Chicago, IL, USA). Data expression was as mean ± standard deviation. The one-way ANOVA test compared the groups' quantitative variables. Pearson's correlation coefficient tested the correlation between serum adiponectin versus BMI, total BMD, and T-score. One-way ANOVA test compared the serum adiponectin in the three study subgroups. Significant was set at P value <0.001 for all tests.

4. Modeling Results

To 210 postmenopausal women, a descriptive case-control study was performed. Table 1 provides the essential criteria of the three groups under study. Age, menopause duration, fat%, waist circumference, BMI, and serum calcium failed to have statistical significance among the groups. Total BMD, including lumbar and femoral, T-score, including lumbar and femoral, serum phosphate, and PICP were significantly higher among CG. Serum adiponectin, CTX, and ALP scored higher levels among OP cases as $P < 0.001$.

In Table 2, serum adiponectin levels were compared to the BMI as an indicator of obesity. The main subgroup number was 69 samples instead of 70, where one sample was excluded because it was outside the study, subgroups, it had BMI (35.0–39.9 kg/m2). The subgroups were divided as follows:

BMI (18.5–24.9 kg/m^2): 7 samples
BMI (25.0–29.9 kg/m^2): 8 samples
BMI (30.0–34.9 kg/m^2): 8 samples

Serum adiponectin scored the highest levels in obese women (BMI of 30–34.9 kg/m^2) for all the three groups, $14.47 \pm 1.88\,\mu g/ml$, followed by 9.47 ± 2.46 and $6.47 \pm 1.47\,\mu g/ml$ for the overweight and healthy weight women (BMI 25.0–29.9 and 18.5–24.9 kg/m^2, respectively). In summary, all the three groups' adiponectin concentrations increased with the increasing BMI group, and that for each BMI group, they were the consistently highest in the OP group. All differences were statistically significant, showing the positive association of serum adiponectin with BMI irrespective of the OP risk, P value <0.001.

Table 3 provides the relationship of serum adiponectin with the body mass index, BMD, and T-score in the three groups. A strong inverse correlation was observed between serum adiponectin and T-score in the OP and OPN groups (−0.427 and −0.301). A strong negative relationship was found between serum adiponectin and total BMD in healthy CG (−0.204). A modest positive relationship was proved between serum adiponectin with BMI in the OP and OPN subgroups (0.387, 0.201). All correlation was statistically significant, with a P value <0.001.

5. Discussion

Serum adiponectin was linked to the BMI with a positive correlation in OP and OPN; conversely, it showed a negative correlation with T-score. A strong negative relationship was confirmed between serum adiponectin and total BMD in healthy CG. Many debates exist on the effect of BMI on bone strength; some researchers confirm no association between BMI and OP, and others declared a significant correlation. Others claimed that the high BMI prevents OP by compensating for the detrimental impact of hypoestrogenic on BMD after menopause [13, 14]. Raising BMI improves bone density as mechanical loading of the bone increases. Higher adipose tissue reflected by increased BMI serves as an estrogen supply for women in menopause, and it seems to suppress osteoclast bone resorption. Interestingly, this defensive action will be missed if BMI surged into obesity, which explains the controversy in earlier research [9].

Effects of obesity on bone structure were investigated by Ibrahim et al. in a comparative study of obese Egyptian women in menopause to verify the impact of body mass index on BMD. The authors measured serum leptin and urinary C-terminal telopeptide at type 1 collagen level. They declared high serum CTX levels and low hip and spine BMD in obese postmenopausal women compared to healthy weight women [15]. The role of obesity was further cleared in Sharma et al.' study. They evaluated the impact of visceral fat as an inverse determinant for bone strength in women with OP, involving 76 participants and overweight PMW. They assessed bone turnover markers in both groups: total BMD, serum vitamin D, and parathyroid hormone levels. The authors compared visceral fat and BMI, showing the highest visceral fat values in PMW linked with low CTX, 25 (OH) D, and high BMD. All relations were statistically meaningful. The positive relationship of visceral fat with BMD, after BMI correction, showed a negative prediction of BMD $\beta = 0.368$, $P < 0.05$. Visceral fat is the most potent independent factor of BMD and bone turnover markers among all adiposity parameters. The study recommended using visceral fat and not BMI to predict bone strength in obese postmenopausal women. The estimated BMI may not represent the actual fat effect because of the diversity of fat distribution across the populace, especially in restricted areas' BMI range value [16].

Waist circumference, a commonly used parameter for visceral fat in clinical studies, showed no contribution to the critical visceral fat-based assessment of these bones. In the current study, serum adiponectin values were significantly high in OP group women and were associated with the lowest T-scores and total and lumbar BMD, across the three groups. Correlation showed significant results upon correlating serum adiponectin versus T-scores, BMI, and BMD. Therefore, we think that serum adiponectin in OP women increases in reaction to increasing demands in that category; there will be increased synthesis and excretion to safeguard the bone from OP and OPN [17, 18].

In line with our results, Al-Osami et al. reported significantly higher serum adiponectin concentration among type-2 diabetes mellitus, osteoporotic postmenopausal women compared to nondiabetic OP women. Their study investigated the effect of poor insulin control on diabetic women and its correlation to serum adiponectin versus OP risk [19].

The impact of adipocytokines on osteoporosis-related fractures was evaluated in a retrospective study. Researchers gathered data over 25 years, along with 7 years of following postmenopausal women, to determine fractures risk. The highest serum adiponectin values were associated with a higher vertebral fracture rate; the hazard ratio was 1.18, P value 0.02. Higher serum leptin levels associate a low incident of long-bone fracture; the hazard ratio was 0.70, P value = 0.03. Both parameters were recommended as an independent risk factor for predicting fractures [20]. Many researchers suggest that adiposity and OP in overweight/obese women have a complicated relationship. The local

Table 1: Baseline parameters of the studied groups.

Parameters	OP ($n = 70$) mean ± SD	OPN ($n = 70$) mean ± SD	CG ($n = 70$) mean ± SD	P value
Age (years)	60.21 ± 6.32	59.63 ± 6.21	60.96 ± 5.91	0.154^{ns}
Menopause duration (years)	12.21 ± 4.6	13.01 ± 3.54	12.31 ± 3.32	0.141^{ns}
Fat (%)	13.01 ± 2.06	12.91 ± 2.56	13.64 ± 2.97	0.136^{ns}
Waist circumference (cm)	79.54 ± 8.31	77.21 ± 8.01	79.63 ± 7.45	0.122^{ns}
BMI (kg/m^2)	27.01 ± 2.78	26.64 ± 2.97	26.45 ± 2.34	0.183^{ns}
Total BMD (g/cm^2)	0.63 ± 0.17	0.82 ± 0.19	0.89 ± 0.20	<0.001*
BMD (L2-L4) (g/cm^2)	0.67 ± 0.21	0.82 ± 0.57	1.09 ± 0.11	<0.001*
BMD F (g/cm^2)	0.41 ± 0.20	0.52 ± 0.14	0.68 ± 0.15	<0.001*
T-score (L1-L4)	−3.32 ± 0.90	−1.95 ± 0.56	0.93 ± 0.13	<0.001*
T-score F	−3.61 ± 0.98	−1.89 ± 0.11	0.90 ± 0.21	<0.001*
Calcium (mmol/L)	1.89 ± 0.49	1.90 ± 0.51	1.92 ± 0.52	0.015^{ns}
Phosphate (mmol/L)	1.42 ± 0.42	1.59 ± 0.54	1.95 ± 0.78	<0.001*
ALP (U/L)	92.48 ± 6.21	80.04 ± 7.54	78.57 ± 8.65	<0.001*
CTX (ng/mL)	1.85 ± 0.68	0.97 ± 0.45	0.45 ± 0.12	<0.001*
PICP (ng/mL)	17.47 ± 0.46	18.01 ± 0.54	19.41 ± 0.45	<0.001*
Adiponectin (μg/mL)	13.54 ± 2.54	8.21 ± 2.01	7.99 ± 2.45	<0.001*

OP, osteoporosis group; OPN, osteopenia group; CG, control group; n, no. of subjects; BMI, body mass index; BMD, bone mineral density; L, lumbar; F, femoral neck; ALP, alkaline phosphatase; CTX, serum human C-terminal telopeptides of types I collagen; PICP, serum human carboxyterminal propeptide of type I procollagen. Data are means ± SD.

Table 2: Comparison of serum adiponectin (μg/ml) in the studied groups.

Studied groups ($n = 69$)	BMI (kg/m^2) ($n = 23$)	Adiponectin (μg/ml) mean ± SD	P value
OP	BMI (18.5–24.9 kg/m^2)	10.48 ± 1.97	<0.001*
	BMI (25.0–29.9 kg/m^2)	12.87 ± 1.45	
	BMI (30.0–34.9 kg/m^2)	14.47 ± 1.88	
OPN	BMI (18.5–24.9 kg/m^2)	7.01 ± 2.47	<0.001*
	BMI (25.0–29.9 kg/m^2)	7.98 ± 2.49	
	BMI (30.0–34.9 kg/m^2)	9.47 ± 2.46	
CG	BMI (18.5–24.9 kg/m^2)	4.47 ± 1.88	<0.001*
	BMI (25.0–29.9 kg/m^2)	5.14 ± 1.87	
	BMI (30.0–34.9 kg/m^2)	6.47 ± 1.47	

BMI (18.5–24.9 kg/m^2), healthy weight $n = 7$; BMI (25.0–29.9 kg/m^2), overweight $n = 8$; BMI (30.0 to 34.9 kg/m^2), obesity $n = 8$. * P value< 0.001 (indicates a significant). The total no. of the studied groups was 69 divided as BMI (18.5–24.9 kg/m^2): 7 samples, BMI (25.0–29.9 kg/m^2): 8 samples, BMI (30.0–34.9 kg/m^2): 8 samples. ns, nonsignificant.

Table 3: The correlations of serum adiponectin (μg/ml) versus body mass index, BMD, and T-score in the studied subgroups.

Studied groups	BMI		Total BMD		T-score	
	r	P	r	P	r	P
OP	0.387	<0.001*	−0.034	<0.001*	−0.427	<0.001*
OPN	0.201	<0.001*	−0.059	<0.001*	−0.301	<0.001*
CG	−0.025	<0.001*	−0.204	<0.001*	−0.021	<0.001*

*Correlation is a significant level at 0.001.

associations and endocrine-based activity exerted by fatty tissue are accredited to alter bone strength and fracturing risk in older adults.

Jürimäe and Jürimäe [21] confirmed that serum adiponectin has an independent effect on BMD among perimenopausal women; higher levels were detected in PMW than in perimenopausal women. They suggested adiponectin to be the link between fat mass and BMD. Later studies by the same researchers highlighted the inverse relationship between serum adiponectin versus the total and areal BMD [22].

Among the study strengths, we analyzed many bone parameters: total BMD, lumbar BMD, femoral BMD, and their respective T-scores. Though serum adiponectin was linked to OP markers in earlier studies, especially for high-risk populations with medical comorbidities among elderly people, this study has addressed the relationship from a new perspective highlighting the serum adiponectin in the bone metabolism, implying its utility to measure BMD among elderly postmenopausal women with no medical comorbidities.

This study has limitations; being a single-centre study is one. Another point is its design. Since both exposure and result are measured simultaneously in cross-sectional studies, we cannot capture the long-term influence of adiponectin on bone remodelling and bone mineral density. Therefore, establishing a real cause-and-effect link is not feasible [23]. Because of the limited prediction findings associated with cross-sectional design study types, we recommend a case-control study design with longitudinal data collection to explain serum adiponectin association with OP with better predictive values.

6. Conclusion

Our analysis suggests that the serum adiponectin level serves as independent risk factors for reduced BMD among different bodyweight groups. Therefore, its levels may help predict osteoporotic fractures, which enable optimal OP prediction. Osteoporosis is best avoided than treated; having reliable markers for earlier diagnosis is vital to improving disease outcomes.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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