Body Weight, Insulin Resistance, and Inflammatory Biomarkers in Rats Fed Normal-Fat, High-Fat, and Ketogenic Diets Supplemented with Vitamin D

Bushra Omar Al-Badarein¹, Mousa Numan Ahmad*¹

¹ Department of Nutrition and Food Technology, Human Nutrition and Dietetics, University of Jordan, Amman, Jordan

Received on 23/10/2020 and Accepted for Publication on 4/3/2021

ABSTRACT

Ketogenic (KD) and high-fat (HFD) diets and vitamin D (VD) produce variable effects on insulin secretion and body weight (BW), but mechanisms remain unclear. We investigated the effects of normal fat diets (NFD), KD, and HFD with and without VD on BW and serum glucose, insulin, VD, insulin resistance, C-reactive protein, interleukin-6, and tumor necrosis factor-alpha in rats. Three isocaloric NFD, KD, and HFD containing respectively protein-carbohydrate-fat (NFD: 14.8%-75.7%-9.5%; KD:20.2%-10.3%-69.5%; HFD:15.2%-42.7-42.0%) and three other similar diets but with (1000 IU/kg) VD were used. Forty-five adult male Sprague-Dawley rats were used, 5 rats were sacrificed at the start, remainders were randomly divided into NFD (n=15) and HFD (n=25), and fed for 8 weeks, then 5 rats from each were sacrificed. NFD remainders were divided into 2 subgroups (n=5) and fed NFD and NFD-VD, and HFD remainders were divided into 4 subgroups (n=5) and fed HFD, HFD-VD, KD, and KD-VD for further 8 weeks, then all rats were sacrificed. BW change and FCR (-15.6± -10.13g; 0.033±0.350 respectively) of rats fed KD-VD were the lowest (P<0.05) compared to those fed KD (144.8±1.47g; 0.189±0.050), HFD-VD (143.0±8.49g; 0.187±0.100), HFD (155.8±0.3g; 0.203±0.010), NFD-VD (142.8±6.34g; 0.183±0.009), and NFD (51.0± 1.02g; 0.074±0.110) respectively. BW change correlated (P<0.01) with food intake (r=0.752), % carbohydrate (r=0.292), and % fat (r=0.341). None of the diets affected other biomarkers. Results clearly show BW-reducing effects for KD-VD that may be mediated by changes in food intake and dietary fat and carbohydrate proportion.

Keywords: Carbohydrate, Bodyweight, Insulin resistance, High-fat diet, Ketogenic diet, Obesity, Rat, Vitamin D.

INTRODUCTION

Obesity is rising worldwide at an alarming rate (Tremmel et al., 2017; Ajlouni et al., 2020). It is a risk factor for several chronic diseases such as insulin resistance, type 2 diabetes, several cancers, and cardiovascular disease (Leggio et al., 2018). Obesity is considered a state of chronic low-grade inflammation that increases the secretion of several pro-inflammatory factors mainly, C-reactive protein (CRP), interleukin 6 (IL)-6, and tumor necrosis factor-alpha (TNF)-α. This state is known to promote insulin resistance (Leggio et al., 2018). Obesity...
is often associated with remarkable deterioration in eating patterns and behavior related to dietary overload in the form of high-fat diets (HFD) in combination with high carbohydrate intake (Bradley et al., 2017).

Caloric restrictions, behavioral modification and exercise, and infrequency medication are the first-line management for obesity, but the results are not always encouraging (Wadden et al., 2012; Freire, 2020). Variability in responses to obesity treatment is well-documented, but an understanding of why some individuals respond while others do not is limited (Ahmad and Al-Badarein, 2019). Short-term (3-7 days) HFD interventions increase adipose tissue and insulin resistance (Lee et al., 2014), and continued consumption of HFD provokes adipose tissue dysfunction and inflammation state (Lee et al., 2011). However, other studies failed to confirm this (Cummins et al., 2014).

One controversial yet efficient approach to managing obesity has been the application of low-carbohydrate ketogenic diets (KD) (Lamont et al., 2016; Gomez-Arbelaez et al., 2018; Grandl et al., 2018). This diet is a severe restriction of dietary carbohydrates, with a concurrent increase in dietary fat to compensate for the energy deficit resulting in a state of metabolic ketosis. While macronutrient ratios of different KD diets may vary, a typical KD diet contained approximately 20-25% of calories from protein, 60-65% of calories from fat, and 10-15% of calories from carbohydrates (Lamont et al., 2016). This diet can lead to significant weight loss and long-term weight maintenance (Moreno et al., 2016). It targets body fat mass and induces a minor or null reduction in resting metabolic rate, thus preventing weight regain (Gomez-Arbelaez et al., 2018). Despite its beneficial effect on weight loss, KD promotes insulin resistance in humans and animals (Jornayvaz, 2011; Bielohuby et al., 2013; Grandl et al., 2018). KD also contributes to weight loss as well as improves glycemic control and metabolic parameters in type 2 diabetes (Aylward et al., 2014). The reason for this variability could be due to the different experimental protocols and models, diets, and tissue specificity. KD and HFD do not produce similar changes in insulin action or weight change (Asrih et al., 2015). Whether the change in insulin response or secretion is a direct consequence of KD and HFD or due to other factors remains to be elucidated.

There is increasing evidence that vitamin D (VD) deficiency may contribute to the onset of diabetes mellitus (Wimalawansa, 2018). The findings that relate VD receptor polymorphism to diabetes provide support for this evidence (Sentinelli et al., 2016). There are also indications that VD supplementation may prevent the onset of type 2 diabetes (Sergeev, 2016). Some work has revealed that VD inhibits the production of proinflammatory-cytokines and is positively associated with circulating an anti-inflammatory biomarker (Kim et al., 2013; Tiosano et al., 2013). Obesity is known to associate with VD deficiency (Afzal et al., 2014), although there is no consistent evidence for the causal relationship between these events (Pereira-Santos et al., 2015).

Studies demonstrating the synergistic effects of KDs and VD on body composition are limited. Wortsman et al. (2000) were the first to provide strong evidence that VD may become sequestered within adipose tissue. Chronic ketoacidosis results in increased demand for bone minerals for buffering capacity and decreased renal conversion of 25 OH vitamin D to 1, 25 (OH)2 vitamin D (Sampath et al., 2007). There is only one published report that explored the effect of KD on the developing skeleton and demonstrated reduced bone mineral content in patients on KD when followed up for 15 months (Bergqvist et al., 2008).

While KDs have received considerable attention as an effective weight-loss method, the underlined anti-adipogenic, anti-lipogenic, and anti-inflammatory mechanisms remain unclear. Studies on the combined effects of a KD and VD in human and animal models are also limited. Thus, we investigated the influence of normal-fat diets (NFD), KD, and HFD with and without VD on body weight and serum glucose, insulin, VD, insulin resistance, C-reactive protein, interleukin-6, and tumor necrosis factor in rats.
MATERIALS AND METHODS

Experimental diet preparation:

Three isonitrogenous and isocaloric diets were prepared and assigned as normal-fat (NFD), high-fat (HFD), and ketogenic (KD) diets. Three other similar diets were prepared and supplemented with (1000 IU/kg diet) vitamin D (Meerza et al., 2012; Yin et al., 2012).

Experimental diet mixtures were prepared according to Reeves (1997). The basic chemical composition of these diets is summarized in Tables (1,2)

| Parameter          | NFD     | NFD-VD  | HFD     | HFD-VD  | KD      | KD-VD   |
|--------------------|---------|---------|---------|---------|---------|---------|
| Energy (kJ/100g)   | 378.2   | 378.2   | 378.2   | 378.2   | 378.2   | 378.2   |
| Carbohydrate (%)   | 75.70   | 75.70   | 40.00   | 40.00   | 13.20   | 13.20   |
| Protein (%)        | 14.80   | 14.80   | 14.80   | 14.80   | 14.80   | 14.80   |
| Fat (%)            | 09.50   | 09.50   | 45.20   | 45.20   | 72.00   | 72.00   |

Table 1. Macronutrient and energy content of the experimental diets.

| Parameter          | NFD     | NFD-VD  | HFD     | HFD-VD  | KD      | KD-VD   |
|--------------------|---------|---------|---------|---------|---------|---------|
| Egg albumin        | 140     | 140     | 140     | 140     | 140     | 140     |
| Cornstarch         | 615.5   | 615.5   | 278     | 278     | 25      | 25      |
| Sucrose            | 100     | 100     | 100     | 100     | 100     | 100     |
| Soybean oil        | 40      | 40      | 190     | 190     | 302.5   | 302.5   |
| Cellulose          | 50      | 50      | 237.5   | 237.5   | 378     | 378     |
| Fat-soluble vitamins| 4       | 4       | 4       | 4       | 4       | 4       |
| Water-soluble vitamins| 10     | 10      | 10      | 10      | 10      | 10      |
| Mineral mixture    | 35      | 35      | 35      | 35      | 35      | 35      |
| Biotin mixture     | 3       | 3       | 3       | 3       | 3       | 3       |
| Choline bitartrate | 2.5     | 2.5     | 2.5     | 2.5     | 2.5     | 2.5     |
| Tert-Butylhydroquinone| 0.008   | 0.008   | 0.008   | 0.008   | 0.008   | 0.008   |
| VD (IU)            | -       | 1000    | -       | 1000    | -       | 1000    |

Table 2. The basic ingredient composition of the experimental diets (g/kg).

Animals’ experimentation: Adult male Sprague Dawley rats (200-250g) were used as an animal model in a randomized control design experiment. Rats (n=45) were obtained from the experimental animal unit at Jordan University, Amman, Jordan. After an adaptation period of 1 week, 5 animals were sacrificed, plasma and serum were
obtained and kept frozen at -20 °C till analyzed. Rats (n=40) were then randomly divided into 2 main groups: the NFD group (n=15) and HFD group (n=25) and fed the corresponding diets for 8 weeks. At the end of this period, 5 rats from each group were sacrificed, plasma and serum were obtained. The remaining rats in the NFD group (n=10) were divided into 2 subgroups (n=5 each), one continued on the NFD and the other was fed NFD-VD. The remaining rats in the HFD group (n=20) were divided into 4 subgroups (n=5 each), one continued on the HFD and the others were fed HFD-VD, KD, and KD-VD. The feeding period for this part of the experiment was 8 weeks (Kennedy et al., 2007).

Experimental diets and water were provided ad libitum during the study. Rats were individually housed in a well-ventilated room with a constant temperature of 25°C and a 12-hour dark/12-hour light cycle. Body weights were measured once every 2 weeks and food intake was measured every 3 days. At the end of the experimental period, rats were fasted for 8 hours and anesthetized by carbon dioxide. Blood was collected by cardiac puncture in a heparinized tube, centrifuged to obtain plasma, and kept frozen at -20°C till analysis. All the experiments involving animals were approved by the Institutional Animal Ethics Committee and carried out according to the recommended guidelines for animal care and use (National Research Council, 2011).

Biochemical analyses: Standard biochemical kits procedures were followed for the determination of glucose (glucose GOD-PAP, BIOLABS), insulin (MBS 760915 Rat Insulin ELISA Kit), vitamin D (MBS2503525 Vitamin D ELISA Kit), and the inflammatory biomarkers: C-reactive protein (Rat C-Reactive Protein ELISA 88-7501), interleukin 6 (Mouse IL-6 Uncoated ELISA 88-7064) and tumor necrosis factor-alpha (Rat Tumor Necrosis Factor ELISA Kit ®, lot number 1125150743, Ray-Bio, USA).

Insulin resistance was evaluated by the homeostasis model assessment of insulin resistance, [Insulin resistance (HOMA-IR) = fasting insulin (µ/ml) X fasting glucose (mmol/l) / 22.5] according to Wareham et al (1995). Analyses were done in duplicates following the kits manufacturer’s instructions and were performed at the nutritional biochemistry laboratories of the Department of Nutrition and Food Technology, University of Jordan, Amman, Jordan.

Statistical analysis: Statistical analyses were performed using (SAS version 9, USA). Data were presented as means ± standard deviation and differences between means were considered as significant at P ≤ 0.05. Statistical significance for differences in variable means between study groups was computed using ANOVA repeated measures (Diet and time interaction) for weight change and food intake and one-way ANOVA for other variables, followed by turkeys post-hoc test for mean separation. Spearman rank correlation coefficient (r) was used to assess the relationship in the degree of change between weight, food intake, and type of macronutrients and for all variables.

RESULTS

Bodyweight and food intake

Rats fed the NFD gained significantly (P<0.05) less weight and had less food intake after 16 weeks of the study (51.0±1.0, 691±114 g) respectively, compared to other groups (Table 3). The KD-VD rats lost (15.6±10.1 g) and had the lowest (P<0.05) food intake (469.6±226.3 g) compared to other groups. Weights of the other groups were significantly different from the beginning of the study with no significant differences (P>0.05) between groups at week 16.
Table 3. Initial, final, and weight change (g), food intake (g), and food conversion ratio of rats fed different diets for 16 weeks.

|                          | NFD     | NFD-VD  | HFD     | HFD-VD  | KD      | KD-VD   |
|--------------------------|---------|---------|---------|---------|---------|---------|
| **Initial weight**       | 228±30a | 231±35a | 233±28a | 236±32a | 237±34a | 239±32a |
| **Final weight**         | 279±36b | 373±36a | 388±36a | 379±32a | 381±24a | 223±33b |
| **Weight change**        | 51.0±1.0b | 142.8±6.3a | 155.8±0.3a | 143.0±8.5a | 144.8±1.5a | -15.6±10.1c |
| **Food intake**          | 691±114b | 780±151a | 768±163a | 773±154a | 760±148a | 470±226c |
| **FCR**                  | 0.07±0.11b | 0.18±0.09a | 0.20±0.01a | 0.19±0.10a | 0.19±0.05a | 0.03±0.35c |

Values are means ± standard deviation; FCR: food conversion ratio (weight gain/food intake); Values in rows with different superscripts are significantly different (p< 0.05), rats fed (NFD: Normal fat diet, HFD: High-fat diet, KD: ketogenic diet, -VD: supplemented with vitamin D), (n=5) groups, Repeated measures ANOVA (Diet and time interaction, P≤0.05). Post hoc test Tukey-Kramer (P≤0.05).

**Biochemical parameters**

Findings demonstrated that rats fed the NFD and HFD in the first 8 weeks did not show significant (P>0.05) differences in the mean value of serum glucose (6.1±0.1 vs. 7.4±0.1 mmol/l), insulin (15.3±4.9 vs. 16.6±7.6 µUI/ml), HOMA-IR (0.42±0.16 vs. 0.54± 0.23), vitamin D (32.7±4.6 vs. 32.1±2.9 ng/ml), and CRP (1.8±0.3 vs. 2.2±0.5 mmol/l), TNF-α (1.9±0.9 vs. 1.7±1.3 mmol/l), IL6 (1.7±0.3 vs. 1.8±0.1 mmol/l) respectively (Figure 1).

![Graphs](image_url)

Figure 1. Concentrations of fasting (A) plasma insulin (B) serum glucose(C) HOMA-IR (D) plasma vitamin D (E) plasma IL6 (F) plasma TNF (G) plasma CRP of rats fed different diets for 16 weeks.
At the end of 16 weeks of dietary interventions (Figure 1), no significant (P>0.05) differences were found between NFD, NFD-VD, HFD, HFD-VD, KD, and KD-VD respectively, in the mean values of serum glucose (6.9±0.1, 5.6±0.1, 6.9±0.1, 5.7±0.1, 5.8±0.1, 5.9±0.1 mmol/l), insulin (20.0±4.3, 22.4±3.1, 19±6.9, 18.0±6.3, 19.1±5.8, 19.7±4.7 µUI/ml), HOMA-IR (0.61±0.13, 0.56±0.11, 0.58±0.28, 0.46±0.15, 0.49±0.13, 0.52±0.15), VD (31.8±2.4, 32.6±1.5, 32.7±5.1, 32.5±6.1, 32.5±9.7, 32.7±2.2 ng/ml), CRP (2.6±0.8, 2.1±0.3, 2.6±1.3, 2.2±0.61, 3.0±0.4, 2.0±1.1 mmol/l), TNF-α (1.8±0.8, 1.5±0.7, 3.1±1.9, 2.1±1.3, 2.3±1.1, 1.6±0.9 mmol/l), and IL6 (1.8±0.1, 1.8±0.3, 1.8±0.0, 1.6±0.3, 1.8±0.2, 1.8±0.1 mmol/l). There was a 4-fold (P≤0.05) increase in the plasma insulin in rats fed NFD2 and NFD+VD2 compared control with no significant (P>0.05) differences were shown between the groups within the two experimental periods.

Correlation analyses
Correlation analyses revealed a significant positive association (r = 0.75, P<0.01) between the change in body weight and food intake (Table 4). A similar positive association was observed between the change in body weight and the proportion of carbohydrate (r = 0.292, P < 0.01) and fat (r = 0.341, P<0.01) in the die. No significant (P>0.05) correlations were found among NFD, NFD-VD, HFD, HFD-VD, KD, and KD-VD for glucose, insulin, HOMA-IR, IL6, TNF, and CRP (Table 5).

Table 4. Overall correlation coefficients among food intake, body weight change, and dietary fat and carbohydrate proportions (n=40).

| Variables          | Food intake | Carbohydrate (%) | Fat (%) |
|--------------------|-------------|------------------|---------|
| Carbohydrate (%)   | 0.495**     |                  |         |
| Fat (%)            | 0.337**     | -0.651**         |         |
| Weight change      | 0.752**     | 0.292**          | 0.341** |

** Significant at P<0.01
DISCUSSION

This research aimed to investigate the influence of NFD, KD, and HFD with and without VD on body weight, food intake, serum glucose, insulin, HOMA-IR, vitamin D, and the inflammatory biomarkers CRP, IL-6, and TNF-α in rats. These diets contained equivalent proportions of calories, protein, and micronutrients. Soybean oil was used as the primary source of fat in the experimental diets. This oil is composed of five fatty acids: palmitic acid (10%), stearic acid (4%), oleic acid (18%), linoleic acid (55%), and linolenic acid (13%), 86% of them is unsaturated fatty acids (Clement and Cahoon 2009). Compared to other diets, KD-VD was the only one to show a significant reduction in body weight, food intake, and FCR with no changes in the other variables.

The similarity in weight gain between study groups may also be attributed to the use of adult rats, while the levels of ketone bodies in such or aged rats matched those of the youngs by week 4, this perhaps indicated that adult rats take longer time to initiate ketosis (Jornayvaz et al., 2011). While the mechanism of delayed ketosis in adult or aged rats is unknown, this finding demonstrates that short-term dietary intervention may be insufficient to produce measurable physiological changes in old animals (Hernandez et al., 2020).

In this study, the ketogenic ratio of the KD was 1.4 as calculated according to Withrow's equation (Withrow, 1980). For this reason, the current KD may be a characteristic of HFD with a different macronutrient ratio that may need a longer time to induce ketosis than the intervention time. On the other hand, Lecomte et al. (2015) showed that the HFD fed rats gained more weight than controls three weeks after dietary intervention. The weight change of HFD-fed rats in this study was not significantly different from those fed NFD. The fact that daily caloric intake in all study groups over 16 weeks was not significantly different appears to be consistent with the

| Variable | Insulin | Glucose | HOMA-IR | Vitamin D | CRP | IL6 |
|----------|---------|---------|---------|-----------|-----|-----|
| Glucose  | -0.08   |         |         |           |     |     |
| HOMA-IR  | 0.95    | 0.20    |         |           |     |     |
| Vitamin D| 0.11    | 0.12    | 0.15    |           |     |     |
| CRP      | 0.30    | 0.18    | 0.36    | -0.15     |     |     |
| IL6      | -0.15   | 0.15    | -0.12   | -0.01     | 0.04|     |
| TNFα     | -0.15   | 0.22    | -0.13   | -0.01     | -0.19| 0.31|

All correlations are not significant, (P>0.05) . CRP: C reactive protein; TNF α: tumor necrosis factor; IL6: interleukin 6 Insulin resistance (HOMA-IR) = fasting insulin (µIU/ml) X fasting glucose (mmol/l)/22.5.
weight data. A possible explanation of this phenomenon might be the animals' adaptation to various HFD diets and fat sensitivity. In this context, variations in the experimental design of HFD studies with different types, fatty acid composition, and contents of dietary fats (40–60% of total energy intake), and differences in the HFD study duration (8-20 weeks) are among the reported confounding factors (Jornayvaz et al., 2011; Garbow et al., 2011; Lecomte et al., 2015; Hernandez et al., 2020). Another possible explanation may be dietary fiber and its potential as a satiating food component. It has been reported that the inclusion of insoluble dietary fiber in HFD protects against excessive body weight gain in animal models (Clark and Slavin, 2013; Trigueros et al., 2013; Rebello et al., 2014). Nonetheless, there is a lack of evidence for the long-term effects of dietary fiber in obese subjects.

It has been shown that plasma VD levels inversely correlate to several indices of obesity such as body mass index, fat mass, and waist circumference (García et al., 2009; Cheng et al., 2010). It has been also shown that increased dietary intake of VD raises its plasma levels and is associated with lower visceral adiposity (Caron-Jobin et al., 2011). In this study, plasma VD levels did not differ between different experimental groups. The fact that the adipose tissue is the main body storage site of VD and its metabolites may provide a plausible explanation for the current results. This fact has prompted the opinion that VD and its metabolites may get sequestered in the excess fat mass (Wortsman et al., 2000).

However, the physiological mechanisms underlying the above-stated opinion have not been brought forward. Nevertheless, as pointed out in the study of Drincic et al. (2012), it might just be that in individuals with a higher body mass, 25(OH) VD is simply diluted in a higher volume, so they would require higher VD input than lean individuals to achieve a sufficient 25(OH) VD status. It is presumed that the excess VD is stored in body fat as a native compound and is slowly released (Brouwer et al., 1998; Heaney et al., 2008). Thus, high VD doses may result in flatter slopes compared with those resulting from low VD doses. Therefore, this may result in a longer apparent half-life of 25(OH) VD. This mechanistic pathway may also explain the widely reported variable half-life in response to different doses of VD supplementation. For this reason, the current result showed no effect due to being supplemented rats after 8 weeks when the bodyweight increased in rats fed with VD (1000 IU/kg diet) treatment dose (Brouwer et al., 1998; Heaney et al., 2008; Drincic et al., 2012).

Furthermore, the baseline 25(OH) VD concentration has been consistently shown to make a significant contribution to the variance in 25(OH) VD response to VD supplementation (Aloia et al., 2008; Zhao et al., 2012; Mazahery et al., 2015). The hepatic hydroxylation of VD is a saturable process (Barger-Lux et al., 1998). Thus, the response of plasma VD to VD supplementation may be affected by the baseline concentration of 25(OH) VD that was in the normal range in this study. However, in the current study, experimental diets were supplemented with poly- and mono-unsaturated fatty acids-rich soybean oil. It has been found that dietary fat composition markedly affects VD response to VD supplementation (Niramitmahapanya et al., 2011). The mechanisms by which the type of fatty acids may influence vitamin D response are not known. Niramitmahapanya et al. (2011) suggested that fatty acids such as linoleic and linolenic acid may increase the solubility of VD in the micelles and increase their size. As a consequence, VD may stay longer in the micelles and may have difficulty in passing the intestinal mucosa. Decreased plasma 25(OH) VD levels could also result from VD dysmetabolism during obesity development (Niramitmahapanya et al., 2011).

Obesity is often associated with the development of insulin resistance and type 2 diabetes. Notably, as already discussed, all rat groups increased in weight, but without the concomitant occurrence of insulin resistance. Mice fed KD for 12 weeks remained euglycemic with reduced serum insulin and HOMA-IR indices and exhibited glucose intolerance, as assessed by intraperitoneal glucose tolerance tests (Garbow et al., 2011). However, Garbow et al. (2011) observed that, despite mild hepatic steatosis, systemic response to insulin was preserved, unlike in other studies. The authors explained this discrepancy by a
relatively reduced lean body mass in KD-fed mice, resulting in a higher insulin dose in insulin-tolerance tests.

Also, hepatic insulin resistance may confer a smaller contribution to overall glucose homeostasis than peripheral glucose disposal. In studies using rats, KD also induced glucose intolerance and insulin resistance (Kinzig et al., 2010; Bielohuby et al., 2013) despite reduced glucose and insulin levels. In the same studies, short-term KD feeding in rats was also associated with decreased β-cell mass, but this effect could be due to a lower lean body mass of KD-fed rats (Bielohuby et al., 2013). Interestingly, after only 6-days of KD feeding, mice showed impairments in glucose tolerance and insulin sensitivity; this was attributed to a possible adaptation to maintain blood glucose levels against insufficient amounts of carbohydrates (Murata et al., 2013). In this case, insulin signaling was impaired only in white adipose tissue but not in the liver and muscle. The authors suggested that this impairment in white adipose tissue could not be the only culprit for whole-body glucose intolerance in KD-fed mice. The possible role of KD in inducing insulin resistance is nevertheless controversial. Indeed, several authors reported that long-term KD-fed mice had normal glucose tolerance, lower baseline insulin levels, and improved insulin sensitivity (Douris et al., 2015; Holland et al., 2016).

In humans, the effect of KD on glucose homeostasis is more controversial and is notably dependent on whether or not type 2 diabetes is present (Foster et al., 2003; Westman et al., 2007; Johnstone et al., 2008). In this study, we did not assess the difference in body composition. If there is a decrease in a lean mass known to affect insulin sensitivity or organ-specific insulin resistance, the unaffected glucose and insulin levels will keep lowering glucagon levels that were also not tested. Interestingly, in a study on mice, the alpha cell mass decreased considerably in line with the reduced glucagon levels after 5-weeks of KD intervention (Jornayvaz et al., 2011). In relative terms, this decreased alpha cell mass was even more pronounced than the reduction in beta-cell mass that caused a marked decrease in the alpha-to-beta cell ratio. Low glucagon levels reduced hepatic gluconeogenesis and prevented hyperglycemia in KD-fed mice. Whether this change in alpha cell mass is a direct consequence of KD or a response to counteract glucose intolerance remains to be elucidated.

Buczinski et al. (2002) showed that long-term feeding of HFD dramatically decreased glucose turnover and clearance in mice. Glucose utilization in the presence and absence of insulin was similar in muscles isolated from different groups of studied mice, indicating that glucose clearance could be regulated by a factor distinct from insulin, like adipokines (Buczinski et al., 2002). Importantly, in the current study, none of the HFD-fed rats became insulin resistant when measured by the HOMA-IR index. Even though the diet change from HFD to KD and KD+VD did not affect HOMA-IR. The possible effect of insoluble fiber contained in the experimental diets may explain these results. In their controlled-intervention study, Weickert et al. (2011) indicated that high intakes of insoluble fiber improve insulin resistance independently of weight loss through modifications of dietary protein absorption.

In a randomized, controlled, 18-weeks trial with 111 group-matched, overweight adults with one or more further metabolic risk factors, Weickert et al. (2011) compared the effects of isoenergetic diets supplemented with varying levels of cereal fiber and plant-based protein on whole-body and hepatic insulin resistance. After six weeks of treatment, IR expressed as M-value was 25% lower in participants who consumed a high fiber diet than those who ate a high-protein diet. Supplementation of HFD with omega-3 fatty acids prevented high-fat diet-induced insulin resistance by reducing inflammasome-dependent inflammation and increasing the secretion of leptin and adiponectin, both of which exert insulin-sensitizing effects in rodents (Yan et al., 2013). Intubation of eicosapentaenoic acid reduced fasting insulin and insulin resistance without affecting blood glucose in male rats fed control and high-fat diets (Pérez-Matute et al., 2007).

Vitamin D also seems to have a direct influence on insulin sensitivity or resistance. Several studies have shown an increase in insulin sensitivity through stimulation of expression of insulin receptors on target tissues (Maestro et al., 2000) and the regulation of cellular calcium concentration in skeletal muscle cells, that might enhance glucose transport through the membrane via the
Body Weight, Insulin Resistance … Bushra Al-Badarein1, Mousa Numan Ahmad

recruitment of glucose transporter 4 (Wei et al., 2008; Muscogiuri et al., 2012). Vitamin D could also enhance insulin release by regulating the beta-cell intracytoplasmic calcium concentration (Muscogiuri et al., 2012). Vitamin D status was inversely associated with the incidence of type 2 diabetes mellitus in a longitudinal study (Mitri and Pittas, 2014). Furthermore, two meta-analyses of longitudinal observational studies confirmed these results (Afzal et al., 2013; Song et al., 2013). Nevertheless, age, diet, and lifestyle are among several confounding factors that may influence VD status and diabetes incidence (Pittas et al., 2009; Mitri et al., 2011; Mitri and Pittas, 2014).

Furthermore, no change in plasma cytokine concentrations in the current study; this result is not in line with the observation that short-term KD in mice is associated with increased inflammatory markers in the liver and adipose tissue (Badman et al., 2009) and macrophage infiltration in the liver (Garbow et al., 2011). This discrepancy may be due to the polyunsaturated fatty acid used. Rosenbaum et al. (2019) found that circulating CRP but not the inflammatory cytokine IL-6 was significantly higher on the KD. Ketosis in mice seemed to increase tissue-specific liver and white adipose tissue expression of inflammatory cytokines TNF-alpha, IL-6, and macrophage markers (Garbow et al., 2011). Outpatient studies of low-carbohydrate diets in humans have found significant increases in plasma CRP but not IL-6 (Song et al., 2016). In subjects with type 2 diabetes, the advice to follow a lower carbohydrate diet decreased IL-6 but not CRP concentrations (Jonasson et al., 2014).

In humans, several researchers have attempted to link ω3 polyunsaturated fatty acid intake with the inflammatory response without reaching consistent conclusions. A one-year dietary supplementation with ω3 polyunsaturated fatty acids did not modify the circulating cytokine levels in healthy volunteers (Blok et al., 1997). Conversely, other studies reported a marked decrease in inflammatory markers after ω3 polyunsaturated fatty acid supplementation (Cooper et al., 1993; James et al., 2000). It is important to note that the blood inflammatory profile appears to be less representative than that of the adipose tissue (Balvers et al., 2015). Furthermore, the level of nutritional ketosis may be an important factor in the regulation of adiponectin expression, knowing that ketone bodies influence adiponectin activity (Makki et al., 2013).

The authors found a negative correlation between adiponectin and pro-inflammatory cytokine TNF-α (Makki et al., 2013). Adiponectin can be a pro-inflammatory cytokine expresser, including TNF-α and IL-6. Further studies are needed to assess body ketosis and serum adiponectin (Awazawa et al., 2011; Nigro et al., 2013).

CONCLUSIONS

Rats fed the NFD, HFD in the first eight weeks did not show significant differences in the mean values of serum glucose, insulin, HOMA-IR, VD, CRP, TNF-α, IL6. Following the intervention at the end of the second 8 weeks, body weight and feed efficiency were lowest in KD supplemented with VD rats’ group. In addition to VD, the correlation showed that weight change was affected by food intake and fat and carbohydrate proportions in the diet. None of the other assessed inflammatory biomarkers or serum VD, insulin, and glucose was affected by the diets or VD supplementation. These results support that VD supplemented KD decreases body weight and feed efficiency in dietary-induced obesity in rats.

ACKNOWLEDGEMENTS

The authors would like to thank the University of Jordan, Amman, Jordan.

Conflict of interest

The authors declare that there are no conflicts of interest.
REFERENCES

Ahmad M.N., Al-Badarein B.O. (2019). Analysis of evidence linking dietary carbohydrate and fat proportions with body weight and insulin resistance. *International Journal of Applied and Natural Sciences*, 8(6): 43-60.

Afzal S., Bojesen S.E., Nordestgaard B.G. (2013). Low 25-hydroxyvitamin D and risk of type 2 diabetes: a prospective cohort study and meta-analysis. *Clinical Chemistry*, 59(2): 381–91.

Afzal S., Brøndum-Jacobsen P., Bojesen S.E., Nordestgaard B.G. (2014). Vitamin D of diabetes: A mendelian randomization study. *Lancet Diabetes Endocrinology*, 2(4): 298–306.

Ajlouni K., Khader Y., Batieha A., Jaddou H., El-Khateeb M. (2020). An alarmingly high and increasing prevalence of obesity in Jordan. *Epidemiology and Health*, 42: e2020040.

Aloia J.F., Patel M., DiMaano R., Li-Ng M., Talwar S.A., Mikhail M., et al. (2008). Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. *American Journal of Clinical Nutrition*, 87(6): 1952–8.

Asrih M., Altirriba J., Rohner-Jeannaud F., Jornayvaz F.R. (2015). A ketogenic diet impairs FGF21 signaling and promotes differential inflammatory responses in the liver and white adipose tissue. *PLoS One*, 10(5): e0126364.

Awazawa M., Ueki K., Inabe K., Yamauchi T., Kubota N., Kaneko K., et al. (2011). Adiponectin enhances insulin sensitivity by increasing hepatic IRS-2 expression via a macrophage-derived IL-6-dependent pathway. *Cell Metabolism*, 13(4): 401–12.

Barger-Lux M.J., Heaney R.P., Dowell S., Chen T.C., Holick M.F. (1998). Vitamin D and its major metabolites: serum levels after graded oral dosing in healthy men. *Osteoporosis International*, 8(3): 222–30.

Bergqvist A.G.C., Schall J.I., Stallings V.A., Zemel BS. (2008). Progressive bone mineral content loss in children with intractable epilepsy treated with the ketogenic diet. *American Journal of Clinical Nutrition*, 88(6): 1678–84.

Bielohuby M., Sisley S., Sandoval D., Herbach N., Zengin A., Fischereder M., et al. (2013). Impaired glucose tolerance in rats fed low-carbohydrate, high-fat diets. *American Journal of Physiology, Endocrinology, and Metabolism*, 305(9): E1059–70.

Blok W.L., Deslypere J-P., Demacker P.N.M., Van Der Ven-Jongeekrijg J., Hectors M.P.C., Van Der Meer J.W.M., et al. (1997). Pro- and anti-inflammatory cytokines in healthy volunteers fed various doses of fish oil for 1 year. *European Journal of Clinical Investigation*, 27(12): 1003–8.

Bradley L.E., Forman E.M., Kerrigan S.G., Goldstein S.P., Butryn M.L., Thomas J.G., et al. (2017). Project HELP: A remotely delivered behavioral intervention for weight regains after bariatric surgery. *Obesity Surgery*, 27(3): 586–98.

Brouwer D.A., van Beek J., Ferwerda H., Brugman A.M., van der Klis F.R., van der Heiden H.J., et al. (1998). Rat adipose tissue rapidly accumulates and slowly releases an orally administered high vitamin D dose. British
Journal of Nutrition, 79(6): 527–32.
Burcelin R., Crivelli V., Dacosta A., Roy-Tirelli A., Thorens B. (2002). Heterogeneous metabolic adaptation of C57BL/6J mice to a high-fat diet. American Journal of Physiology. Endocrinology, and Metabolism, 282(4): E834-42.

Caron-Jobin M., Morisset A-S., Tremblay A., Huot C., Légaré D., Tchernof A. (2011). Elevated serum 25(OH)D concentrations, vitamin D, and calcium intakes are associated with reduced adipocyte size in women. Obesity (Silver Spring), 19(7): 1335–41.

Cheng S., Massaro J.M., Fox C.S., Larson M.G., Keys M.J., McCabe E.L., et al. (2010). Adiposity, cardiometabolic risk, and vitamin D status: the Framingham Heart Study. Diabetes, 59(1): 242–8.

Clark M.J., Slavin J.L. (2013). The effect of fiber on satiety and food intake: A systematic review. Journal of American College of Nutrition, 32(3): 200–11.

Clement, T.E., Cahoon, E.B. (2009). Soybean oil: genetic approaches for modification of functionality and total content. Plant Physiology, 151(3): 1030-1040.

Cooper A.L., Gibbons L., Horan M.A., Little R.A., Rothwell N.J. (1993). Effect of dietary fish oil supplementation on fever and cytokine production in human volunteers. Clinical Nutrition, 12(6): 321–8.

Cummins T.D., Holden C.R., Sansbury B.E., Gibb A.A., Shah J., Zafar N., et al. (2014). Metabolic remodeling of white adipose tissue in obesity. American Journal of Physiology, Endocrinology, and Metabolism, 307(3): E262–77.

Douris N., Melman T., Pecherer J.M., Pissios P., Flier J.S., Cantley L.C., et al. (2015). Adaptive changes in amino acid metabolism permit normal longevity in mice consuming a low-carbohydrate ketogenic diet. Biochimica Biophysica Acta: Molecular Basis of Diseases, 1852(10): 2056–65.

Drincic A.T., Armas L.A.G., Van Diest E.E., Heaney R.P. (2012). Volumetric dilution rather than sequestration best explains the low vitamin D status of obesity. Obesity (Silver Spring), 20(7): 1444–8.

Foster G.D., Wyatt H.R., Hill J.O., McGuckin B.G., Brill C., Mohammed B.S., et al. (2003). A randomized trial of a low-carbohydrate diet for obesity. New England Journal of Medicine, 348(21): 2082–90.

Freire R. (2020). Scientific evidence of diets for weight loss: Different macronutrient composition, intermittent fasting, and popular diets. Nutrition, 69(110549): 110549.

Garbow J.R., Doherty J.M., Schugar R.C., Travers S., Weber M.L., Wentz A.E., et al. (2011). Hepatic steatosis, inflammation, and ER stress in mice maintained long term on a very low-carbohydrate ketogenic diet. American Journal of Physiology: Gastrointestinal and Liver Physiology, 300(6): G956-67.

Garcia O.P., Long K.Z., Rosado J.L. (2009). Impact of micronutrient deficiencies on obesity. Nutrition Reviews, 67(10): 559–72.

Gomez-Arbelaez D., Crujeiras A.B., Castro A.I., Martinez-Olmos M.A., Canton A., Ordoñez-Mayan L., et al. (2018). Resting metabolic rate of obese patients under very low-calorie ketogenic diet. Nutrition and Metabolism (Lond) [Internet], 15(1).

Grandl G., Straub L., Rudigier C., Arnold M., Wueest S., Konrad D., et al. (2018). Short-term feeding of a ketogenic diet induces more severe hepatic insulin resistance than an obeseogenic high-fat diet: A short-term ketogenic diet induces hepatic insulin resistance. Journal of Physiology, 596(19): 4597–609.

Heaney R.P., Armas L.A.G., Shary J.R., Bell N.H., Binkley N., Hollis B.W. (2008). 25-Hydroxylation of vitamin D3: relation to circulating vitamin D3 under various input conditions. American Journal of Clinical Nutrition, 87(6): 1738–42.

Hernandez A., Truckenbrod L., Federico Q., Campos K., Moon B., Ferekides N., et al. (2020). Metabolic switching is impaired by aging and facilitated by ketosis independent of glycogen. Aging (Albany NY), 12(9): 7963–84.
Holland A.M., Kephart W.C., Mumford P.W., Mobley C.B.,
Lowery R.P., Shake J.J., et al. (2016). Effects of a ketogenic diet on adipose tissue, liver, and serum biomarkers in sedentary rats and rats that exercised via resisted voluntary wheel running. *American Journal of Physiology: Regulatory Integration and Comparative Physiology, 311*(2): R337-51.

James M.J., Gibson R.A., Cleland L.G. (2000). Dietary polyunsaturated fatty acids and inflammatory mediator production. *American Journal of Clinical Nutrition, 71*(1): 343s–8s.

Johnstone A.M., Horgan G.W., Murison S.D., Bremner D.M., Lobley G.E. (2008). Effects of a high-protein ketogenic diet on hunger, appetite, and weight loss in obese men feeding ad libitum. *American Journal of Clinical Nutrition, 87*(1): 44–55.

Jonasson L., Guldborg H., Lundberg A.K., Nystrom F.H. (2014). Advice to follow a low-carbohydrate diet has a favorable impact on low-grade inflammation in type 2 diabetes compared with advice to follow a low-fat diet. *Annals of Medicine, 46*(3): 182–7.

Jonavyaz F.R., Birkenfeld A.L., Jurczak M.J., Kanda S., Guigni B.A., Jiang D.C., et al. (2011). Hepatic insulin resistance in mice with hepatic overexpression of diacylglycerol acyltransferase 2. *Proceedings of National Academy of Science (USA), 108*(14): 5748–52.

Kennedy A.R., Pissios P., Otu H., Xue B., Asakura K., Furukawa N., et al. (2007). A high-fat, ketogenic diet induces a unique metabolic state in mice. *American Journal of Physiology, Endocrinology, and Metabolism, 292*(6): E1724–39.

Kim M., Na W., Sohn C. (2013). Correlation between vitamin D and cardiovascular disease predictors in overweight and obese Koreans. *Journal of Clinical Biochemistry and Nutrition, 52*(2): 167–71.

Kinzig K.P., Honors M.A., Hargrave S.L. (2010). Insulin sensitivity and glucose tolerance are altered by maintenance on a ketogenic diet. *Endocrinology, 151*(7): 3105–14.

Lamont B.J., Waters M.F., Andrikopoulos S. (2016). A low-carbohydrate high-fat diet increases weight gain and does not improve glucose tolerance, insulin secretion, or β-cell mass in NZO mice. *Nutrition and Diabetes, 6*(2): e194–e194.

Lecomte V., Kaakoush N.O., Maloney C.A., Raipuria M., Huinai K.D., Mitchell H.M., et al. (2015). Changes in gut microbiota in rats fed a high-fat diet correlate with obesity-associated metabolic parameters. *PLoS One, 10*(5): e0126931.

Lee Y.S., Kim J-W., Osborne O., Oh D.Y., Sasik R., Schenk S., et al. (2014). Increased adipocyte O2 consumption triggers HIF-1α, causing inflammation and insulin resistance in obesity. *Cell, 157*(6): 1339–52.

Lee Y.S., Li P., Huh J.Y., Hwang I.J., Lu M., Kim J.I., et al. (2011). Inflammation is necessary for long-term but not short-term high-fat diet-induced insulin resistance. *Diabetes, 60*(10): 2474–83.

Leggio M., Lombardi M., Caldarone E., Mazz a A., Fusco A. (2018). High body mass index, healthy metabolic profile, and low visceral adipose tissue: The paradox is to call it obesity again. *European Journal of Internal Medicine, 52*: e15–6.

Maestro B., Campión J., Dávila N., Calle C. (2000). Stimulation by 1,25-dihydroxyvitamin D3 of insulin receptor expression and insulin responsiveness for glucose transport in U-937 human promonocytic cells. *Endocrine Journal, 47*(4): 383–91.

Makki K., Froguel P., Wolowczuk I. (2013). Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines. -139239.

Mazahery H., Stonehouse W., von Hurst P.R. (2015). The effect of monthly 50 000 IU or 100 000 IU vitamin D supplements on vitamin D status in premenopausal Middle Eastern women living in Auckland. *European Journal of Clinical Nutrition, 69*(3): 367–72.

Meerza D., Naseem I., Ahmed J. (2012). Effect of 1, 25(OH)₂ vitamin D₃ on glucose homeostasis and DNA damage in type 2 diabetic mice. *Journal of Diabetes
Complications, 26(5): 363–8.

Mitri J., Dawson-Hughes B., Hu F.B., Pittas A.G. (2011). Effects of vitamin D and calcium supplementation on pancreatic β cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. American Journal of Clinical Nutrition, 94(2): 486–94.

Mitri J., Pittas A.G. (2014). Vitamin D and diabetes. Endocrinology and Metabolism: Clinics of North America, 43(1): 205–32.

Moreno B., Crujeiras A.B., Bellido D., Sajoux I., Casanueva F.F. (2016). Obesity treatment by very low-calorie-ketogenic diet at two years: reduction in visceral fat and on the burden of disease. Endocrine, 54(3): 681–90.

Murata Y., Nishio K., Mochiyama T., Konishi M., Shimada M., Ohta H., et al. (2013). Fgf21 impairs adipocyte insulin sensitivity in mice fed a low-carbohydrate, high-fat ketogenic diet. PLoS One, 8(7): e69330.

Muscogiuri G., Sorice G.P., Ajjan R., Mezza T., Pilz S., Priololetta A., et al. (2012). Can vitamin D deficiency cause diabetes and cardiovascular diseases? Present evidence and future perspectives. Nutrition, Metabolism, and cardiovascular diseases, 22(2): 81–7.

National Research Council, Division on Earth and Life Studies, Institute for Laboratory Animal Research, Committee for the Update of the Guide for the Care and Use of Laboratory Animals. (2011). Guide for the care and use of Laboratory Animals: Eighth Edition. Washington, D.C., DC: National Academies Press.

Nigro E., Scudiero O., Sarnataro D., Mazzarella G., Sofia M., Bianco A., et al. (2013). Adiponectin affects lung epithelial A549 cell viability countering TNFa and IL-1β toxicity through AdipoR1. International Journal of Biochemistry and Cell Biology, 45(6): 1145–53.

Niramitmahapanya S., Harris S.S., Dawson-Hughes B. (2011). Type of dietary fat is associated with the 25-hydroxyvitamin D3 increment in response to vitamin D supplementation. Journal of Clinical Endocrinology & Metabolism, 96(10): 3170–3174.

Pereira-Santos M., Costa P.R.F., Assis A.M.O., Santos C.A.S.T., Santos D.B. (2015). Obesity and vitamin D deficiency: A systematic review and meta-analysis: Obesity and vitamin D. Obesity Reviews, 16(4): 341–9.

Pérez-Matute P., Pérez-Echarri N., Martínez J.A., Martí A., Moreno-Aliaga M.J. (2007). Eicosapentaenoic acid actions on adiposity and insulin resistance in control and high-fat-fed rats: role of apoptosis, adiponectin and tumour necrosis factor-alpha. British Journal of Nutrition, 97(2): 389–98.

Pittas A.G., Harris S.S., Eliades M., Stark P., Dawson-Hughes B. (2009). Association between serum osteocalcin and markers of metabolic phenotype. Journal of Clinical Endocrinology and Metabolism, 94(3): 827–32.

Rebello C., Greenway F.L., Dhurandhar N.V. (2014). Functional foods to promote weight loss and satiety. Current Opinions in Clinical Nutrition and Metabolic Care, 17(6): 596–604.

Reeves P.G. (1997). Components of the AIN-93 diets as improvements in the AIN-76A diet. Journal of Nutrition, 127(5): 838S-841S.

Rosenbaum M., Hall K.D., Guo J., Ravussin E., Mayer L.S., Reitman M.L., et al. (2019). Glucose and lipid homeostasis and inflammation in humans following an isocaloric ketogenic diet. Obesity (Silver Spring), 27(6): 971–81.

Sampath A., Kossoff E.H., Furth S.L., Pyzik P.L., Vining E.P.G. (2007). Kidney stones and the ketogenic diet: Risk factors and prevention. Journal of Childhood Neurology, 22(4): 375–8.

Sentinelli F., Bertocci L., Barchetta I., Capoccia D., Incani M., Pani M.G., et al. (2016). The vitamin D receptor (VDR) gene rs11568820 variant is associated with type 2 diabetes and impaired insulin secretion in Italian adult subjects and associated with increased cardio-metabolic risk in children. Nutrition, Metabolism, and cardiovascular diseases, 26(5): 407–13.
Sergeev I.N. (2016). 1,25-dihydroxyvitamin D3 and type 2 diabetes: Ca2+-dependent molecular mechanisms and the role of vitamin D status. *Hormones, Molecular Biology and Clinical Investigation, 26*(1): 61–5.

Song X., Kestin M., Schwarz Y., Yang P., Hu X., Lampe J.W., *et al.* (2016). A low-fat high-carbohydrate diet reduces plasma total adiponectin concentrations compared to a moderate-fat diet with no impact on biomarkers of systemic inflammation in a randomized controlled feeding study. *European Journal of Nutrition, 55*(1): 237–46.

Song Y., Wang L., Pittas A.G., Del Gobbo L.C., Zhang C., Manson J.E., *et al.* (2013). Blood 25-hydroxy vitamin D levels and incident type 2 diabetes: a meta-analysis of prospective studies. *Diabetes Care, 36*(5): 1422–8.

Tiosano D., Wildbaum G., Gepstein V., Verbitsky O., Weisman Y., Karin N., *et al.* (2013). The role of vitamin D receptor in innate and adaptive immunity: a study in hereditary vitamin D-resistant rickets patients. *Journal of Clinical Endocrinology and Metabolism, 98*(4): 1685–93.

Tremmel M., Gerdtham U-G., Nilsson P.M., Saha S. (2017). Economic burden of obesity: A systematic literature review. *International Journal of Environmental Research and Public Health [Internet], 14*(4).

Trigueros L., Peña S., Ugidos A.V., Sayas-Barberá E., Pérez-Álvarez J.A., Sendra E. (2013). Food ingredients as anti-obesity agents: A review. *Critical Review of Food Science and Nutrition, 53*(9): 929–42.

Wadden T.A., Webb V.L., Moran C.H., Bailer B.A. (2012). Lifestyle modification for obesity: new developments in diet, physical activity, and behavior therapy. *Circulation, 125*(9): 1157–70.

Wareham N.J., Phillips D.I., Byrne C.D., Hales C.N. (1995). The 30-minute insulin incremental response in an oral glucose tolerance test as a measure of insulin secretion. *Diabetes Medicine, 12*(10): 931.

Wei M.Y., Garland C.F., Gorham E.D., Mohr S.B., Giovannucci E. (2008). Vitamin D and prevention of colorectal adenoma: A meta-analysis. *Cancer Epidemiological Biomarkers Preview, 17*(11): 2958–69.

Weickert M.O., Roden M., Isken F., Hoffmann D., Nowotny P., Osterhoff M., *et al.* (2011). Effects of supplemented isoenergetic diets differing in cereal fiber and protein content on insulin sensitivity in overweight humans. *American Journal of Clinical Nutrition, 94*(2): 459–71.

Westman E.C., Feinman R.D., Mavropoulos J.C., Vernon M.C., Volek J.S., Wortman J.A., *et al.* (2007). Low-carbohydrate nutrition and metabolism. *American Journal of Clinical Nutrition, 86*(2): 276–84.

Wimalawansa S.J. (2018). Associations of vitamin D with insulin resistance, obesity, type 2 diabetes, and metabolic syndrome. *Journal of Steroid Biochemistry and Molecular Biology, 175*: 177–89.

Withrow C.D. (1980). The ketogenic diet: mechanism of anticonvulsant action. *Advanced Neurology, 27*: 635–42.

Wortsman J., Matsuoka L.Y., Chen T.C., Lu Z., Holick M.F. (2000). Decreased bioavailability of vitamin D in obesity. *American Journal of Clinical Nutrition, 72*(3): 690–3.

Yan Y., Jiang W., Spinetti T., Castilho R., Bourquin C., *et al.* (2013). Omega-3 fatty acids prevent inflammation and metabolic disorder through inhibition of NLRP3 inflammasome activation. *Immunity, 38*(6): 1154–63.

Yin Y. Yu Z., Xia M., Luo X., Lu X., Ling W. (2012). Vitamin D attenuates high fat diet-induced hepatic steatosis in rats by modulating lipid metabolism: Vitamin D attenuates high fat diet-induced hepatic steatosis in rats. *European Journal of Clinical Investigation, 42*(11): 1189–96.

Zhao L-J., Zhou Y., Bu F., Travers-Gustafson D., Ye A., Xu X., *et al.* (2012). Factors predicting vitamin D response variation in non-Hispanic white postmenopausal women. *Journal of Clinical Endocrinology and Metabolism, 97*(8): 2699–705.
وزن الجسم ومقاومة الأنسولين والمؤشرات الحيوية الالتهابية في جرذان مغذة بأنظمة غذائية دهنية طبيعية وعالية الدهون وكيتونية مزودة بفيتامين د

بشرى عمر البدارين١ وموسى نعمان أحمد١

١الجامعة الأردنية، قسم التغذية والتصنيع الغذائي، تغذية الإنسان والحيوان، عمان ١١٤٢٠، الأردن

تاريخ استلام البحث ٢٣/١٠/٢٠٢٠ وتاريخ قبوله ٤/٣/٢٠٢١

ملخص
قد تبين أن الأنظمة الغذائية الكبيرة (HFD) وعالية الدهون (KD) في هذه المسألة الأيضية غير مؤكدة، وقد تراجعت VD مع تقلبات نوع الدم والكبدة (NFD) وVD وKD في الدراسات المتباعدة لوحدها. وتتضمن ثلاثة أنظمة غذائية ذات محتوى مشابه من النبويتين والنكهة مماثل تلك في الـ KD وVD وNFD. وتحتوي على الهدوء والكيرويديات والبروتينات: ٦.٤% و٦.٠% و٦.٥%(NFD: ٦.٥% و٦.٠% و٦.١%) و KD وVD وNFD: ٦.٥% و٦.٠% و٦.٤%). وتستخرج نتائج هذه الدراسة أن الـ KD وVD وNFD: ٦.٥% و٦.٠% و٦.٤%) و KD وVD وNFD: ٦.٥% و٦.٠% و٦.٤%)

الكلمات الدالة: الكريتوديات، وزن الجسم، مقاومة الأنسولين، غذاء عالية الدهون، غذاء كيتو، السمنة، الجرذان، فيتامين (D).