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ORIGINAL ARTICLES

VARIATIONS IN SERUM VITAMIN D3 LEVELS AND CARDIOMETABOLIC INDICATIVE MARKERS IN FRUCTOSE-INDUCED OBESITY

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ABSTRACT

INTRODUCTION: Recent studies have linked vitamin D3 deficiency to an elevated risk of cardiovascular disease, with other risk factors including obesity, hypertension, insulin resistance, and hypercholesterolemia, which are significant pathogenic factors to metabolic syndrome. The prevalence of metabolic syndrome is significantly associated with elevated fructose consumption; nonetheless, the connection between fructose metabolism, cardiovascular disease, and hypovitaminosis D3 remains insufficiently studied.

AIM: The aim of the study was to investigate the serum levels of 25-hydroxyvitamin D3 (25(OH)D3) levels and their relationship with the principal biomarkers of metabolic syndrome and cardiomyocytes injury in fructose-induced obesity.

MATERIALS AND METHODS: We used male Wistar rats, divided into 2 groups: control and high-fructose diet (HFD) (20% fructose corn syrup for 12 weeks). Routine laboratory methods were used to measure cardiometabolic indicative markers and 25(OH)D3 serum levels. Zoometric measurements and histochemical (H&E) evaluation of heart tissue were also performed.

RESULTS: Our results showed a significant elevation of body, heart and retroperitoneal fat weight, VLDL cholesterol, glucose, triglycerides and triglyceride-glucose index (TyG), the ratio of abdominal circumference/nasoanal length, and elevated levels of hs-CRP in HFD compared to the controls. The 25(OH)D3 were significantly reduced ($p < 0.01$) and negatively correlated with increased TyG ($r = -0.82$; $p < 0.05$), accompanied by indications of left ventricular hypertrophy in the HFD group.

CONCLUSION: The study showed that a high-fructose diet leads to obesity accompanied by changes in carbohydrate and lipid metabolism and significant decrease in 25(OH)D3 levels, alongside inflammation and cardiomyocyte injury. Metabolic disorders demonstrate a functional connection between 25(OH)D3 and TyG. These initial data provide a rationale for future studies of the molecular mechanisms by which the worsened vitamin D3 status, observed in this diet, could contribute to the onset and progression of cardiovascular diseases.

Keywords: *vitamin D3, TyG index, fructose, cardiac hypertrophy, obesity*

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INTRODUCTION

In the last years, numerous epidemiological studies in humans have demonstrated that vitamin D3 deficiency is a global issue, closely associated with bone metabolic abnormalities, diabetes, cancers, inflammation, and autoimmune disorders [1]. Low serum 25-hydroxyvitamin D3 (25(OH)D3) levels are associated with an increased risk of cardiovas-

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cular disease, which is interesting because this risk is strongly tied to a number of other risk factors, including obesity, high blood pressure, insulin resistance, and high cholesterol [2,3]. Assessing the impact of these risk factors on metabolic health is essential, especially when appropriate experimental models are employed. Recent clinical practice has shown heightened interest in certain anthropometabolic indices that integrate anthropometric measurements (such as body weight, height, and waist circumference) with fundamental metabolic parameters for the identification of metabolic syndrome risk, including serum glucose and triglycerides [4]. The recent studies indicate that the triglyceride-glucose index (TyG) serves as an effective tool for clinically predicting metabolic syndrome, as it evaluates pancreatic function and insulin resistance in tissues [5]. This makes TyG an applicable indicator in the experimental modeling of obesity and other parameters assessing the metabolic syndrome.

Simultaneously, numerous studies corroborate the correlation between elevated fructose consumption worldwide and the prevalence of metabolic syndrome, dyslipidemia, metabolic dysfunction-associated steatotic liver disease (MASLD), insulin resistance, and obesity. Fructose functions as a catalyst in the advancement of hypertriglyceridemia, elevated VLDL levels, and hepatic de novo lipogenesis by activating sterol-regulatory binding protein 1 (SREBP-1c) and carbohydrate-regulated binding protein (ChREBP), ultimately resulting in insulin resistance and obesity [6]. On the other hand, insulin resistance and chronic inflammation associated with obesity are linked to endothelial dysfunction and vasoconstriction, which causes sustained elevations in blood pressure and afterload, that finally promote the development of left ventricular hypertrophy. In this regard, other studies show that vitamin D3 and its analogues suppress the pro-inflammatory cytokines in various diseases, thereby protecting the vascular endothelium from the development of endothelial dysfunction [7]. It has been found that the absence of receptors for vitamin D3 results in enhanced secretion of renin and angiotensin II, ultimately contributing to the onset of hypertension [8]. Various pathogenetic pathways connect these conditions to cardiovascular morbidity and mortality [9], but the relationship between fructose metabolism and cardiovascular damage as well as the importance of 25(OH) D3 deficiency remains inadequately researched [10]. Moreover, expanding research on the role of vitamin D3 in metabolism, cardiovascular system reactivity, and its anti-inflammatory properties would be advantageous in the creation of beneficial nutritional modulations for the improvement of the body's defenses.

AIM

The objective of our study was to investigate the serum levels of 25(OH)D3 in an animal model of metabolic syndrome and obesity caused by a high-fructose diet (HFD) as well their relationship with key biomarkers of metabolic syndrome, obesity, and cardiomyocyte injury.

MATERIAL AND METHODS

Experimental Model

Albino male Wistar rats at the age of 50 days were used. Following a two-week acclimatization period, the rats were divided into two groups (control and HFD) of 6 animals each. The control group was with an initial average group body weight of 140 g and on a standard diet and the HFD group was with an initial average group body of 136 g and on HFD, consisting of 20% fructose solution for a duration of 12 weeks. The 20% fructose solution (derived from glucose-fructose corn syrup containing 55% free fructose) was taken as a drinking solution separately from water. All animals received food (standard rodent diet) and water ad libitum. Daily monitoring of food and water intake, along with health status, was conducted, while body weight was assessed every week.

Upon the end of the experiment, venous blood was collected from the jugular vein of the rats for analysis following preliminary anesthesia with ketamine at a dosage of 15–25 mg/kg intramuscularly. The animals were euthanized with a lethal dosage of ketamine at 148 mg/kg, followed by evisceration, macroscopic assessment of the internal organs, and subsequent preparation for morphological and morphometric analysis.

The experimental procedures were approved by the Ethics Committee for Animal Experiments of Bulgaria (protocol number 272/20.07.2020) and performed with a strong consideration for ethics of an-

imal experimentation according to the International Guiding Principles for Animal Research of the EU Directive 2010/63/EU approved in Bulgaria.

Zoometric Measurements and Histological Study

- Zoometric parameters, including body weight, naso-anal distance, or NA (the distance from the nose to the anus/cm), and abdominal circumference (AC) (cm), were assessed following preliminary anesthesia with ketamine at a dosage of 15–25 mg/kg intramuscularly. After dissecting the heart and retroperitoneal adipose tissue, a macroscopic evaluation of changes and weight measurement was conducted.
- The specimens of heart tissue were preserved in a 10% formalin solution and paraffin blocks were fabricated. The sections were stained with hematoxylin and eosin (H&E) The morphometric analysis involved measuring the thickness of the left ventricle (in mm) at three distinct locations: the apex, the midsection, and the area near to the aortic valve. Each animal underwent analysis of these three separate sections at a magnification of x40, with three measurements taken for each section. The morphometric analysis and digital pictures of the scanned histology preparations were performed on Aperio Image Scope software (v12.3.3.5048).

Biochemical Analysis

- The serum concentrations of glucose, triglycerides (TGs), the cholesterol fractions (HDL and LDL) and high-sensitivity C-reactive protein (hs-CRP) were determined by routine laboratory methods on an automated biochemical analyzer OLYMPUS AU640.
- The serum concentrations of 25-hydroxyvitamin D3 (25(OH)D3) were determined by chemiluminescence, using an automated analyzer Alinity.
- The TyG was determined by the equation: TyG = Ln [(fasting triglycerides (mg/dL) x fasting glucose (mg/dL)/2]. The serum triglycerides and glucose concentrations were quantified in mmol/L and subsequently converted to mg/dL by multiplying triglycerides value in mmol/L x 88.57396 and glucose value in mmol/L x 18.0182, using MDApp platform.

Statistical Analysis

Data were analyzed using means and standard deviations (SD) for continuous variables, and results were illustrated with graphical representations where appropriate. Normality was assessed with the Shapiro–Wilk test. Group comparisons were performed using Welch's t-test, and statistical significance was set at $p < 0.05$. Correlation analysis was employed to examine the links among the indicators and assess the magnitude of their influence. The evaluation of the relationship's strength between the variables is based on the results of the Pearson coefficient (r). The degree of correlation between the variables was classified as significant when $r > 0.5 < r = 0.7$, big when $0.7 < r = 0.9$, and extremely big when $r > 0.9$ at $p < 0.05$. Statistical analyses were performed using GraphPad software (GraphPad Software, San Diego, CA, USA)

RESULTS

Study of Metabolic Status

Our results show that HFD causes statistically significant obesity ($p < 0.01$), increased retroperitoneal adipose tissue ($p < 0.05$), heart weight ($p < 0.05$), VLDL ($p < 0.01$), TGs ($p < 0.05$), glucose ($p < 0.05$) and non-significantly increased LDL levels, NA length, AC, and decreased HDL cholesterol levels compared to control rats (Table 1).

In Fig. 1 we have presented the results of the TyG index and the AC/NA length ratio. We found a

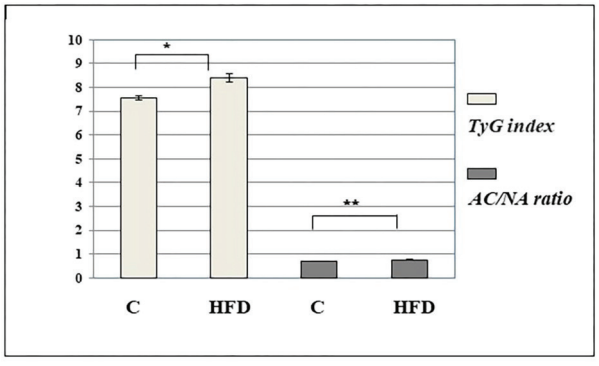


*Fig. 1. Changes in the TyG index and the AC/NA ratio. Abbreviations: C—control group, HFD—group on HFD; TyG—triglyceride-glucose index; AC/NA—the abdominal circumference/nasoanal length ratio;(N = 6). Data are expressed as mean ± SD. Statistical significance: *- p < 0.05;**- p < 0.01 vs. control group.*

Table 1. Zoometric and biochemical changes during HFD.

Metabolic Indicators	Control Group	Group on HFD
Body weight (% from first/last b.w.)	46.43% ± 5.8	57.16% ± 4.96**
Retroperitoneal fat weight (% from total body weight)	1,09% ± 0,2	1,52% ± 0,48*
Heart weight (% from total body weight)	0.48% ± 0.05	0.55% ± 0.03*
HDL cholesterol (mmol/L)	0.75 ± 0.06	0.68 ± 0.11
LDL cholesterol (mmol/L)	0.47 ± 0.07	0.54 ± 0.09
VLDL cholesterol (mmol/L)	0.21 ± 0.02	0.30 ± 0.025**
TGs Triglycerides (mmol/L)	0.48 ± 0.12	0.81 ± 0.16*
Glucose (mmol/L)	5.54 ± 0.49	7.08 ± 1.04*
NA length (cm)	23.08 ± 0.66	22.42 ± 0.31
AC (cm)	16.45 ± 0.63	17.08 ± 0.48

*Data are expressed as mean ± SD. Statistical significance: *- p < 0.05; **- p < 0.01 vs. control group.*

statistically significant increase in the TyG ($p < 0.05$) and the AC/NA ratio ($p < 0.01$) compared to the control group.

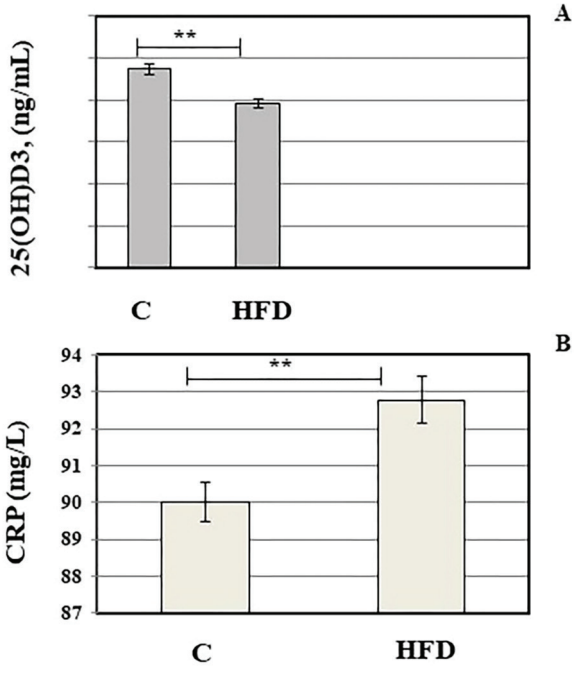


Fig. 2. Comparison of 25(OH)D3 and hs-CRP serum levels between the experimental groups.

*Abbreviations: C—control group; HFD—group on HFD. (A) 25(OH)D3—25-hydroxyvitamin D; (B) CRP—serum high-sensitivity C-reactive protein. Data are expressed as mean ± SD. Statistical significance: **- p < 0.01.*

Vitamin D Status and Evaluation of CRP as a Marker of Inflammation

The results showed significantly reduced serum levels of vitamin D3 in the HFD group ($p < 0.01$) and development of inflammation as evidenced by significantly higher levels of CRP ($p < 0.01$) compared to the control group (Fig. 2).

Associations Between 25(OH)D3 Serum Levels and Some Biochemical Parameters

Following the correlation analysis of serum 25(OH)D3 levels with the examined zoometric and biochemical parameters, a statistically significant

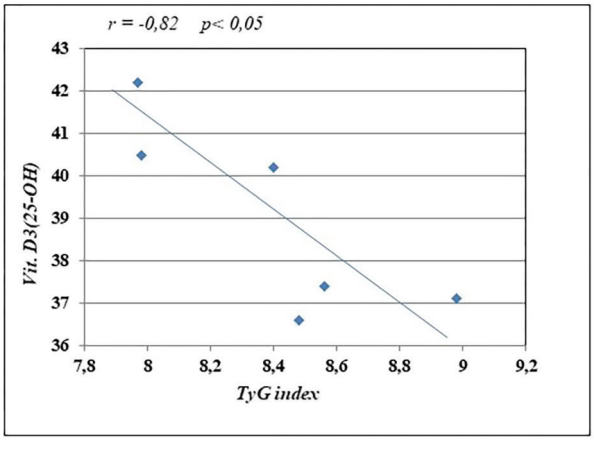


Fig. 3. Correlation between serum levels of 25(OH)D3 and the TyG assessed in the HFD group.

Abbreviations: 25(OH)D3—25-hydroxyvitamin D; TyG—triglyceride-glucose index. Statistical significance: (r = - 0.82; p < 0.05).

negative correlation was identified between lower 25(OH)D3 levels and elevated TyG in the HFD group ($r = -0.82$; $p < 0.05$) (Fig. 3).

Study of Cardiac Morphological Changes

The morphometric analysis revealed statistically significant (Fig. 4C) increase in left ventricular thickness in the HFD group (Fig. 4B) relative to the control group (Fig. 4A).

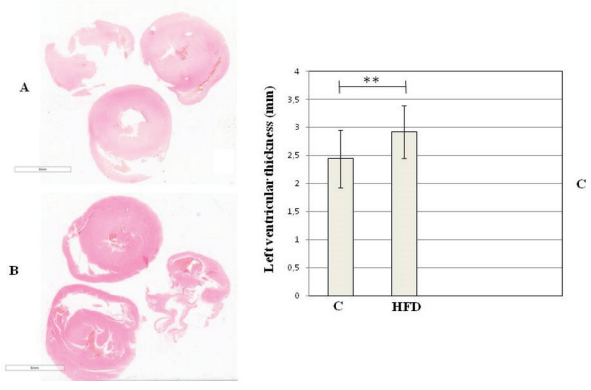


Fig. 4. Comparison of the left ventricular thickness between the experimental groups.

*Abbreviations: C—control group; HFD—group on HFD. Data are expressed as mean ± SD. Statistical significance: ** – $p < 0.01$.*

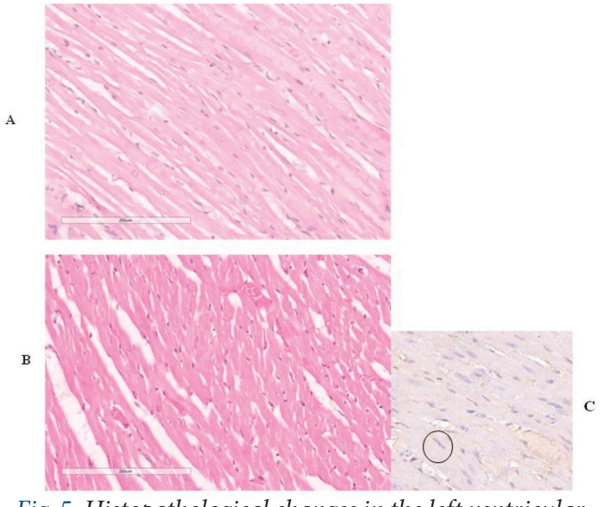


Fig. 5. Histopathological changes in the left ventricular myocardium, observed in the experimental groups.

Magnification x20. H&E. (Aperio Image scope, v12.3.3.5048) (A)—control group; (B)—group on HFD.

Histopathological alterations in the left ventricular myocardium suggest left ventricular hypertrophy. (C)—The micrograph illustrates nuclear atypism (boxcar nuclei) in the HFD group.

In contrast to the control group (Fig. 5A), changes in the cardiomyocyte architecture were detected in the HFD group (Fig. 5B). We observed signs of hypertrophy, such as an increase in cytoplasm, pronounced nucleomegaly, nuclear atypism (*boxcar nuclei*) (Fig. 5C), and growth of connective tissue, observed on H&E stained heart sections from HFD rats (Fig. 5B and C) in comparison with those of the control group (Fig. 5A).

DISCUSSION

It is well recognized that excessive fructose consumption, predominantly from added sugars in contemporary diets, is an important etiological factor in the development of metabolic disorders, as it induces visceral obesity, hyperlipidemia, and obesity-related cardiometabolic conditions. Our findings corroborate this, as after 12 weeks of administering fructose to rats, we observed obesity, significantly elevated levels of triglycerides, glucose, retroperitoneal adipose tissue and elevated LDL levels in comparison to controls (Table 1). It has been proven that the fructose-induced adipogenesis is mediated by increased levels of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) in white adipose tissue, which increases the production of glucocorticoids and hence, fat accumulation in the retroperitoneal space [11]. Fructose worsens the lipid profile by stimulating de novo lipogenesis, with the influx of free fatty acids leading to an increased accumulation of TG, VLDL and LDL (Table 1), which is indicative of possible vascular damage in our experiment as well. According to Aeberli et al. fructose increases the small dense LDL particles, which is known to increase the risk of developing endothelial dysfunction and atherosclerosis [12].

The conventional diagnostic criteria for metabolic syndrome necessitate a series of laboratory tests and clinical evaluations, which often restrict their wide use in screening initiatives. The early detection of metabolic syndrome is crucial for the implementation of measures against subsequent obesity-related cardiometabolic disorders and cardiovascular damage. In the present study, we found a significant increase in the TyG index and the AC/NA ratio in the HFD group compared to the control group (Fig. 1). According to Wan et al. the predictive efficacy of the TyG index surpasses that of existing surrogate indi-

ces, including the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) [13]. Moreover, additional indices that integrate the TyG index with anthropometric measures, including waist circumference (TyG-WC), waist-to-height ratio (TyG-WHtR), and body mass index (TyG-BMI), demonstrate considerable accuracy in assessing cardiometabolic risk [14]. Conversely, low-grade inflammation is a significant characteristic of obesity and metabolic syndrome, which is pathogenetically linked to elevated oxidative stress in visceral adipose tissue [15]. Our results indicated that the HFD group exhibited significantly elevated hs-CRP levels relative to the control group (Fig. 2B). Hs-CRP is an important inflammatory mediator and a marker of endothelial dysfunction. Numerous studies demonstrate that hs-CRP levels correlate with the severity of atherosclerosis and are directly affected by metabolic disease, establishing it as an independent predictor of cardiovascular risk [16]. Consequently, fructose consumption negatively impacts vascular homeostasis and elevates the likelihood of vascular inflammation, oxidative stress, atherosclerosis, and arterial hypertension [17,18].

The metabolism of fructose specifically enhances free radical generation by increasing uric acid levels, and reduction of endothelial nitric oxide levels [19]. Moreover, fructose metabolism produces less ATP than β-oxidation, indicating that this energy deficiency may significantly contribute to the onset of left ventricular hypertrophy and heart failure [20]. The results of our study demonstrated histological myocardial alterations in the HFD group indicative of left ventricular hypertrophy (Fig. 4 and 5), which were not present in the control group. This is supported also by the increased heart weights that we found in the HFD group versus the control group (Table 1). Brady et al. assert that metabolic dysfunction significantly contributes to the etiology of obesity-related left ventricular remodeling via the direct influence of adipokines on the extracellular matrix of cardiomyocytes [21].

The results of this study indicated also that the HFD group exhibited a significant shortage in 25(OH)D3 relative to the control group (Fig. 2A), in parallel with cardiomyocyte damage with evidence of hypertrophy (Fig. 4 and 5). Other experiments also indicate that 25(OH)D3 deficiency leads to both hypertension and cardiac hypertrophy [22,23]. Vitamin D3 metabolites are recognized for their influence on critical regulators of cardiovascular function, such as inflammation, thrombosis, and the renin-angiotensin-aldosterone system pathway [24]. This is also confirmed in the study of Dobnig et al., who found that the risk of increased cardiovascular mortality was associated with vitamin D3 deficiency [25]. Cardiac myocytes and fibroblasts are thought to express receptors for vitamin D3 and its analogues, which inhibit cardiac hypertrophy development [26]. We propose that HFD induces vitamin D3 deficiency through the mechanisms of obesity, oxidative stress, inflammation, and cellular damage. The studies by other researchers confirm that vitamin D3 levels in obese individuals are significantly lower and negatively correlated with higher BMI [27] and LDL cholesterol levels [28]. The hydrophobic characteristics of vitamin D3 facilitate its exit from the bloodstream, leading to substantial accumulation in the adipose tissue of individuals with obesity, which represents another potential cause of the inverse relationship between serum 25(OH)D3 levels and BMI [29]. Conversely, vitamin D3 shortage can cause development of obesity, as it is involved in the regulation of catabolic and anabolic adipocyte activity [30], which indicates the presence of a vicious circle between obesity and reduced vitamin D3 levels. Our model of fructose-induced obesity demonstrates a significant negative correlation between diminished 25(OH)D3 levels and elevated TyG values (Fig. 3). This indicates that these two markers exhibit a functional connection and implies that elevated TyG may significantly contribute to the onset of vitamin D insufficiency in obese patients.

While the present study was not designed to formally test causal relationships, the coexistence of 25(OH)D3 deficiency with adverse cardiac changes supports a plausible link, consistent with previous reports that connect low 25(OH)D3 status with obesity, inflammation, and cardiovascular dysfunction. These findings strengthen the rationale for further targeted studies to determine whether 25(OH)D3 deficiency directly contributes to cardiac injury in fructose-induced metabolic syndrome.

CONCLUSION

In conclusion, we observed a significant elevation in the biochemical and zoometric markers indicative of metabolic syndrome, including body weight, heart weight, retroperitoneal fat weight, VLDL cholesterol, TGs, glucose, TyG index, the AC/NA ratio in an animal model of metabolic syndrome and obesity caused by an HFD. Our investigation also demonstrated elevated levels of hs-CRP and significantly diminished serum concentrations of 25(OH)D3 and significant negative correlation between diminished 25(OH)D3 levels and elevated TyG values, alongside indications of left ventricular hypertrophy. These initial data provide a rationale for future studies of the molecular mechanisms by which the worsened vitamin D3 status, observed in this diet, could contribute to the onset and progression of cardiovascular diseases.

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