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Amelioratory Effect of Vitamin D_3 on some Liver Function and Histological Alterations in Experimentally Obese Albino Rats

Osman E. Mohamed[1*], Zohour I. Nabil[1], Manal M.A. Mahmoud[2], Heba N. Gad El-Hak[1], Heba M.A. Abdelrazek[3]

[1]Department of Zoology, Faculty of Science, Suez Canal University, Ismailia, Egypt.

[2]Nutrition and Clinical Nutrition Department, Faculty of Veterinary Medicine, Suez Canal University, Ismailia, Egypt.

[3]Department of Physiology, Faculty of Veterinary Medicine, Suez Canal University, Ismailia, Egypt.

***Correspondence**
Corresponding author: Osman E. Mohamed
E-mail address: osmanabdelrazik@yahoo.com

Abstract

Obesity is a global public health issue. It is associated with a spectrum of liver abnormalities, like nonalcoholic fatty liver disease (NAFLD). The purpose of this study was to investigate the effect of Vitamin D_3 on light microscopic changes in the liver, as well as hematology and some liver enzymes in experimentally overweight albino rats. Five groups of thirty-five male albino rats were formed. For three months, Control (C) group received a standard laboratory diet. Corn oil (CO) group received normal balanced diet and given orally 20 mg/kg corn oil daily. Vitamin D (D) group received normal balanced diet and orally treated daily with 5000 IU/kg of vitamin D_3. Overweight (OW) group rats received high caloric diet. Overweight/ vitamin D (OWD) group received high caloric diet and treated with oral vitamin D_3 5000 IU/kg daily. Liver weights of animals were recorded, blood samples for hematology, some liver functions, catalase (CAT) and total antioxidant capacity (TAC) were collected. Liver samples were fixed in 10% formal saline then stained by H&E for histological examination. OW group had significantly higher liver weights, and liver function than CO group. Histologically, there was an increase of fatty degeneration in the OW group. However, OWD group was lower in all the measured and examined liver parameters than that of CO group in this study vitamin D_3 supplement could ameliorate the abnormal changes in the hepatocytes induced by obesity.

KEYWORDS
Liver, Obesity, Rats, Vitamin D, Hematology

INTRODUCTION

Obesity is a global public health issue characterized by a visceral and subcutaneous lipid accumulation and body weight gain that may impair health (Caprio *et al*., 2017). It is associated with a spectrum of liver abnormalities, known as nonalcoholic fatty liver disease (NAFLD) (Fabbrini *et al*., 2010). NAFLD is characterized by an increase in intrahepatic triglyceride content with or without inflammation and fibrosis (Caprio *et al*., 2017). Obesity can lead to increased risk of developing gallstones and Fat buildup around the liver, leading to liver damage, scar tissues, and even liver failure (Königshofer *et al*., 2019)

Therapeutic medicines and vitamins help in improvement of liver functions and reduce the risk of obesity (Milic *et al*., 2015). Vitamin D is one of the most effective dietary interventions, a non-enzymatic antioxidant, has been defined as a potent preventive and therapeutic agent for the obese subjects (Makhlouf *et al*., 2021). Moreover, vitamin D is well known for its potential role in decreasing lipid hydro peroxide (de Las Heras *et al*., 2020), beside increasing total antioxidant status and oxidative capacity in monocytes as well as its anti-inflammatory effect (Karabag-Coban *et al*., 2017).

MATERIALS AND METHODS

Vitamin D

Vitamin D_3 "Cholecalciferol"(Ossofortin Original Vitamin D_3 5000 IU 30 F.C Tablets) was used at this study, this product was purchased online from EVA PHARMA, Egypt (www.evapharma.com). All the used chemicals and reagents in this study were of high analytical grade.

Experimental animals

A total of thirty-five adult male albino rats weighing between 120 to 130 g were maintained in plastic-cages with stainless steel wire lids. They were housed for seven days, for adaptation to laboratory conditions, before the commencement of the experiments under constant temperature and humidity (25±1°C and 55.58%, respectively). Animals were provided with rat diet and clean tap water without restriction throughout the experimental duration.

Experimental groups and design of work

Five groups of thirty-five male Albino rats were formed. Control (C) group received a standard laboratory diet and tap water. Corn oil (CO) group received normal balanced diet and treated orally with 20 mg/kg corn oil daily by gavage tube (Legette *et al*., 2012). Vitamin D (D) group received normal balanced diet and treated with 5000 IU/kg of vitamin D_3 daily by gavage tube for 3 months. The selected dose of Vitamin D_3 was according to Alfawaz *et al*. (2014). Overweight (OW) group received high calories diet (25 % of fructose in water and 21.4 % fat) for 3 months. The diet was selected according to Lozano *et al*. (2016). Overweight/

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vitamin D (OWD) group received high calories diet (25 % of fructose in water and 21.4 % fat) and treated with 5000 IU/kg of vitamin D_3 daily by gavage tube for 3 months.

Blood and liver sampling

At the end of the experiment, blood samples were taken from the retro orbital plexus of all rats under light anesthesia before decapitation and after overnight fasting. Blood samples were collected in clean dry plain tubes without anticoagulant. Serum of non-hemolysis samples was thoughtfully transferred into clean dry Eppendorf tubes that were kept frozen at -20°C till used for biochemical analysis. The liver and epididymal fat were removed, excised, washed and blotted with filter paper.

Liver and fat weights

The liver and the epididymal fat were weighed by aid of digital balance. The liver and epididymal fat relative weights to body weight ratio were calculated as follow:

Organ weight/ body weight X100

Biochemical parameters and antioxidants

Cholesterol was determined using a commercial kit (Egyptian company for biotechnology (S.A.E), Egypt, REF: 230 001), triglycerides (Egyptian company for biotechnology (S.A.E), Egypt, REF: 314 001). High density lipoprotein (HDLP) was determined using a commercial kit (Vitro Scient, Egypt, REF: 1581), low-density lipoprotein (LDLP) (Vitro Scient, Egypt, REF: 1591), very-low-density lipoprotein (VLDLP) (Biocompare, U.S.A REF: IT3133), alanine aminotransferase (ALT) (SPINREACT company, Spain, REF: SP41274), aspartate aminotransferase (AST) (SPINREACT, Spain, REF: MD41264) and gamma-glutamyl transferase (GGT) (BioMed - γ- Cat. No. 30175). Total antioxidant capacity (TAC) and catalase activity (CAT) were estimated using kits that were purchased from Bio diagnostics, Egypt (CAT. No. GR 25 11 and CAT. No. MD 25 29, respectively). All procedures were carried out according to the enclosed manufacturer's pamphlet.

Histopathological examination

The liver was fixed in 10% formal saline and dehydrated. The tissues were then placed in molten soft paraffin, then hard paraffin, and cooled. The blocks were cut into thin sections and placed on glass slides. The slides were warmed, dried, and stained with Hematoxylin and Eosin stain to study the liver's structure.

Statistical analysis

One-way analysis of variance (ANOVA) was used, with Tukey post-hoc test for multiple comparisons. Data was represented as means and standard errors. P-value of the measured parameters less than 0. 05 was considered significant.

RESULTS

Effect of vitamin D_3 treatment on Boy weight, epididymal fat, and liver body weight ratio of overweight rats

Body weight, epididymal fat, and liver body weight ratio of control and different treated groups were demonstrated in Table 1. Boy weight, epididymal fat and liver body weight ratio significantly increased in OW group in comparison to CO group. While OWD group significantly decreased values of body weight, epididymal fat, and liver body weight ratio in comparison to OW group.

Table 1. Effect of Vitamin D_3 treatment on boy weight, epididymal fat, and liver body weight. ratio of overweight rats.

Parameters	Groups				
	C	CO	D	OW	OWD
Body weight (g)	281.00±1.50^{d}	280 .00±0.19^{d}	284.00±0.12^{c}	312.00±1.38^{a}	291.00±2.00^{b}
Epididymal fats/ body weight ratio (%)	4.59±0.20^{d}	4.03±0.21^{e}	4.63±0.15^{c}	5.71±0.27^{a}	5.02±0.08^{b}
Liver/ body weight ratio (%)	2.91±0.51^{c}	2.86±0.01^{d}	2.84±0.03^{d}	3.73±0.03^{a}	3.41±0.17^{b}

Data is expressed as means ± SEM, n=6. Data is statically analyzed using One-way ANOVA followed by Duncan multiple comparisons test p≤0.05. Different letters showed data of different rows which is statistically significant p≤0.05.

Table 2. Effect of Vitamin D_3 treatment on serum biochemical parameters, total antioxidant capacity (TAC) and catalase activity (CAT).

Parameters	Groups				
	C	CO	D	OW	OWD
Cholesterol (mg/dL)	102.00±0.76^{c}	98.12±0.76^{d}	103.21±0.76^{c}	162.02±0.92^{a}	116.00±0.73^{b}
Triglycerides (mg/dL)	52.30±0.53^{c}	51.15±0.56^{c}	48.01±0.73^{d}	97.02±0.93^{a}	60.00±0.92^{b}
HDLP (mg/dL)	31.20±0.21^{a}	30.50±0.23^{b}	26.58±0.41^{c}	23.61±0.15^{d}	25.71±0.48^{c}
LDLP (mg/dL)	60.31±0.67^{d}	57.34±0.92^{e}	66.91±0.67^{c}	119.00±0.98^{a}	78.32±0.10^{b}
VLDLP (mg/dL)	10.41±0.11^{c}	10.21±0.14^{c}	9.61±0.15^{d}	19.41±0.18^{a}	12.01±0.18^{b}
AST (U/L)	19.93±0.09^{c}	20.23±0.09^{c}	19.63±0.32^{d}	35.01±0.31^{a}	28.00±0.23^{b}
ALT (U/L)	22.20±0.10^{c}	22.15±0.10^{c}	18.84±0.24^{d}	29.12±0.24^{a}	28.93±0.21^{b}
GGT (U/L)	21.21±0.07^{c}	20.91±0.12^{c}	20.75±0.15^{c}	31.71±1.43^{a}	27.32±0.87^{b}
CAT (U/m)	6.65±0.05^{a}	6.68±0.01^{a}	6.69±0.12^{ab}	4.18±0.02^{d}	5.59±0.01^{c}
TAC (mM/L)	1.76±0.04^{a}	1.74±0.03^{a}	1.78±0.03^{a}	1.42±0.012^{c}	1.71±0.10^{b}

Data is expressed as means ± SEM, n=6. Data is statically analyzed using One-way ANOVA followed by Duncan multiple comparisons test P≤0.05. Different letters showed data of different rows which is statistically significant P≤0.05

Effect of vitamin D_3 treatment on biochemical parameters and antioxidants of overweight rats

Serum lipid profile, AST, ALT, GGT, TAC, and CAT were demonstrated in Table 2. Data explained that all the measured biochemical parameters except the HDLP, CAT and TAC were significantly increased in OW group compared with CO group. On the other hand, HDLP, catalase and TAC sshowed significantly decreased ($P<0.05$) levels in OW group compared with CO group.

Histopathological examination of the liver tissue

Corn oil group (Figure 1 b and g) and group received vitamin D (Figure 1c and h) had the same appearance as intact control rats' (Figure 1 a and f). Obese rats (Figure 1d and i) when compared with control showed degenerative changes in the central and portal area such as hydropic (vacuolation) and fatty degeneration. Necrotic nuclei were observed in the hepatocytes. The degenerative changes were decreased remarkably in obese rats treated with Vitamin D especially in the central areas. The fatty degeneration persisted in the peripheral region of the portal area (Figure e and j).

DISCUSSION

Diet containing high fat and fructose is the risk factor for NAFLD development. The high prevalence of NAFLD in the world raises an important concern for human health (Chen *et al*., 2023).

Feeding of rats with high calories diet (25% of fructose and 21.4% fat) in OW group resulted in a significantly body weight increased. These results coincided with Lozano *et al*. (2016) who reported that high-fat diet and high-fructose beverages increased body weight. The observed increase in the body weight of OW group may be attributed to the increased epididymal fat mass. These results confirmed with Bray *et al*. (2004) who reported that high-fat diets have caused obesity where energy from fat has a greater impact on body weight gain than energy from non-fat sources. Moreover, high-fat diet is associated with higher basal plasma insulin levels and resistance to the metabolic effects of insulin which cause inhibition of lipolysis (Ouwens *et al*., 2007). Treatment with vitamin D_3 in D group showed significantly decreased body weight compared to OW group. This result confirmed by Vanlint (2013) who reported that weight loss is associated with increased serum vitamin D_{25} concentration in overweight or obese women. The significant decrease in body weight, epididymal Fat/ body weight ratio and liver/ body weight ratio in the OWD group compared to the OW group may be attributed to vitamin D_3 reduces hepatic steatosis by reducing the free fatty acids circulation. Therefore, subsequent decrease lipid accumulation via PPAR-γ. Furthermore, vitamin D regulates hepatic inflammatory and oxidative stress genes that are causally implicated in the hepatic steatosis (Papapostoli *et al*., 2016).

Liver/ body weight ratio and epididymal fat showed a significant increase in OW group compared to CO group, these results coincided with de Castro *et al*. (2013) who reported that high fat, fructose intake caused increase in liver weight and, retroperitoneal and epididymal fat deposits. Meanwhile, treatment of rats with vitamin D_3 in OWD group compared to OW group showed significant decrease in liver /body weight ratio. This result was approved by Yin *et al*. (2012). They reported that administration of vitamin D_3 prevented high fat diet-induced body weight gain and reduced liver/ body weight ratio.

There was a significant increase of cholesterol, triglycerides, LDLP, VLDLP and significantly decreased of HDLP in OW group compared to CO group. These results coincided with Ugwor *et al*. (2022) who reported that obese rats that fed with high fructose and high lipid diets had significantly higher body weight and total body lipids (triglycerides, cholesterol, LDLP, VLDLP and free fatty acids) with significantly reduced HDLP and impaired cardiac nitric oxide signaling. These results coincided with Njelekela *et al*. (2002) who found that obese men and women had significantly higher mean serum triglycerides, cholesterol and LDLP with a higher prevalence of dyslipidemia. The previous results may be attributed to effects of a high-fat diet in cholesterol, triglycerides, LDLP and VLDL absorption, synthesis and lipoprotein processing. These findings help in the accumulation of hepatic steatosis Chung *et al*. (2013). Meanwhile, treatment of OW rats with vitamin D caused a significant decrease in cholesterol, triglycerides, LDLP while showed a significant increase of HDLP. These results were in harmony with Sepidarkish *et al*. (2019) who reported that vitamin D supplementation has beneficial effects on dyslipidemia where it reduced triglycerides, cholesterol, LDLP and VLDLP while increased serum HDLP. Vit D is associated with the promotion of calcium absorption that interns reduces absorption of fat from intestine followed by reducing cholesterol level (Wang *et al*., 2016). Also, promotion of calcium level favors the conversion of cholesterol into bile acids (Vaskonen *et al*., 2002). Furthermore, vitamin D is associated with reduction of parathormone hormone that enhances lipolysis and the peripheral removal beside the influence of vitamin D on reducing the hepatic synthesis of triglycerides with increasing VLDLP receptor expression therefore reduces triglycerides and VLDLP beside increase in HDLP (Kim and Jeong, 2019).

In the current study, there was a significant increase in serum ALT, AST, GGT of OW compared to CO group that coincided with results of Hajifathalian *et al*. (2020). They reported that overweight and obesity are significantly associated with elevated

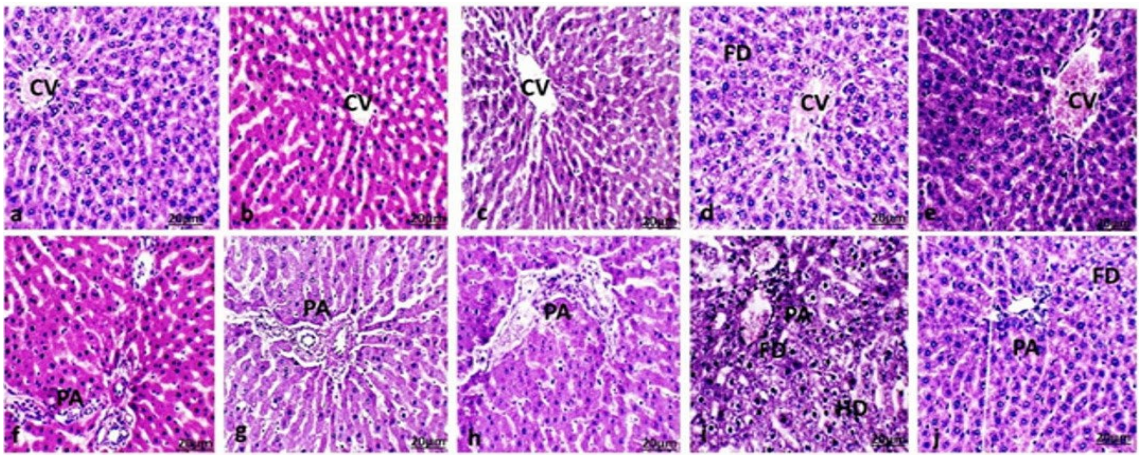

Fig. 1. Photomicrograph of (a & f) control rats, (b & g) corn oil group and group received vitamin D (c & h) showed normal hepatocytes surrounded the central veins (CV) and the portal area (PA). Obese rats (d & i) showed degenerative changes surrounding the central vein (CV) and portal area (PA) such as hydropic (HD) and fatty (FD) degeneration. Necrotic nuclei were observed in the hepatocytes. Obese rats treated with Vitamin D (e & j) showed normal hepatocytes surrounded the central vein and the fatty degeneration (FD) persisted only in the peripheral region of the portal area.

hepatic serum biochemical markers of ALT, AST and GGT. The observed increase in AST, ALT, GGT in OW group may be explained by Yang *et al*. (2014) who reported that high-fat diet cause lipid accumulation and increased infiltration of inflammatory cells in the liver evidenced by the increased plasma activities of the AST, ALT, GGT and ALP enzymes, These enzymes are considered markers of hepatic dysfunction. Meanwhile, treatment of OW rats with vitamin D showed significant decrease in ALT, AST, GGT in D group. These results were matched to those of Tavakoli *et al*. (2019) who reported that supplementation with vitamin D caused significant reductions of AST, ALT, direct bilirubin, total bilirubin, LDH, and GGT of obese rats. The significant decrease in AST, ALT, and GGT in the OWD group compared to the OW group may be attributed to the role vitamin D_3 in promoting liver function. These results harmonized with Tavakoli *et al*. (2019) who reported that there is a significant association between low level of vitamin D and liver dysfunction and mortality.

In this study induction of obesity caused a significant decrease in serum TAC and CAT. These results coincided with Noeman *et al*. (2011) who reported that high fat diet-induced obesity is accompanied by increase of oxidative stress, which is characterized by reduction of antioxidant enzymes activities like GSH, TAC and CAT levels. Moreover, Savini *et al*. (2013) reported that obesity enhanced levels of reactive oxygen or nitrogen species. The observed decrease in TAC and CAT in OW group may be explained by Kadam *et al*. (2010) who reported that decrease of TAC and CAT may be associated with increase of oxidative stress parameters-induced by NAFLD development. Whole treatment of OW rats with vitamin D showed significant increase of CAT and TAC than OW non treated group. These results were in agreement with Fathi *et al*. (2022) who showed that vitamin D promoted the activity of the antioxidant system GSH, SOD, TAC, and CAT while reducing MDA and lipid peroxidation enzymes. The significant increase in TAC and CAT in the OWD group compared to the OW group may be attributed to the role of vitamin D_3 in mitigating oxidative stress where it has a potential antioxidant effect (de Medeiros Cavalcante *et al*., 2015). This coincided with the reduced liver retrogressive changes in OWD group. Histopathological examination of obese liver illustrated marked changes in response to obesity induction and reflected in the functional measured markers. These functional and structural changes could be related to the generation of obesity oxidative damage to the liver tissue (Martínez-Martínez *et al*., 2021). The present result revealed that vitamin D significantly healed with high percentage the liver damage induced by obesity. Consistent with that result, vitamin D was found to normalize liver tissue structural in different models of hepatotoxicity (Hamouda *et al*., 2022; Lisakovska *et al*., 2017).

CONCLUSION

The published results confirmed that obesity is responsible for remarkable hepatic structural and functional abnormalities demonstrated by perturbed biochemical and pathological changes. Vitamin D enhanced the biochemical parameters and may be helpful in amelioration of obesity via promoting antioxidants. Different doses of vitamin D with more duration treatment for use to reduce fatty liver induced by obesity remain to be further elucidated.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

Alfawaz, H.A., Bhat, R.S., Al-Ayadhi, L., El-Ansary, A.K., 2014. Protective and restorative potency of Vitamin D on persistent biochemical autistic features induced in propionic acid-intoxicated rat pups. BMC Complement. Altern. Med. 14, 1-10.

Bray, G.A., Paeratakul, S., Popkin, B.M., 2004. Dietary fat and obesity: a review of animal, clinical and epidemiological studies. Physiol. Behav. 83, 549-555.

Caprio, S., Perry, R., Kursawe, R., 2017. Adolescent obesity and insulin resistance: roles of ectopic fat accumulation and adipose inflammation. Clin. Podiatr. Med. Surg. 152, 1638-1646.

Chen, L., Wang, Y., Zheng, W., Zhang, H., Sun, Y., Chen, Y., Liu, Q., 2023. Improvement of obesity-induced fatty liver disease by intermittent hypoxia exposure in a murine model. Front. Pharmacol. 14, 1097641.

Chung, R.W., Kamili, A., Tandy, S., Weir, J.M., Gaire, R., Wong, G., Meikle, P.J., Cohn, J.S., Rye, K.-A., 2013. Dietary sphingomyelin lowers hepatic lipid levels and inhibits intestinal cholesterol absorption in high-fat-fed mice. PLoS. One. 8, e55949.

de Castro, U.G.M., dos Santos, R.A.S.A.S., Silva, M.E., De Lima, W.G., Campagnole-Santos, M.J., Alzamora, A.C., 2013. Age-dependent effect of high-fructose and high-fat diets on lipid metabolism and lipid accumulation in liver and kidney of rats. Lipids. Health. Dis. 12, 1-11.

de Las Heras, N., Martín Giménez, V.M., Ferder, L., Manucha, W., Lahera, V., 2020. Implications of oxidative stress and potential role of mitochondrial dysfunction in COVID-19: therapeutic effects of vitamin D. Plant. Foods. Hum. Nutr. 9, 897.

de Medeiros Cavalcante, I.G., Silva, A.S., Costa, M.J.C., Persuhn, D.C., Issa, C.I., de Luna Freire, T.L., Gonçalves, M.d.C.R., 2015. Effect of vitamin D_3 supplementation and influence of BsmI polymorphism of the VDR gene of the inflammatory profile and oxidative stress in elderly women with vitamin D insufficiency: Vitamin D3 megadose reduces inflammatory markers. Exp. Gerontol. 66, 10-16.

Fabbrini, E., Sullivan, S., Klein, S., 2010. Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications. Int. J. Mol. Sci. 51, 679-689.

Fathi, F.E.Z.M., Sadek, K.M., Khafaga, A.F., Al Senosy, A.W., Ghoniem, H.A., Fayez, S., Zeweil, M.F., 2022. Vitamin D regulates insulin and ameliorates apoptosis and oxidative stress in pancreatic tissues of rats with streptozotocin-induced diabetes. Environ. Sci. Pollut. Res. Int. 29, 90219-90229.

Hajifathalian, K., Kumar, S., Newberry, C., Shah, S., Fortune, B., Krisko, T., Ortiz-Pujols, S., Zhou, X.K., Dannenberg, A.J., Kumar, R., 2020. Obesity is associated with worse outcomes in COVID-19: analysis of early data from New York City. Indian. J. Med. Res. 28, 1606-1612.

Hamouda, H.A., Mansour, S.M., Elyamany, M.F., 2022. Vitamin D combined with pioglitazone mitigates type-2 diabetes-induced hepatic injury through targeting inflammation, apoptosis, and oxidative stress. Inflammation 45, 156-171.

Kadam, D.P., Suryakar, A.N., Ankush, R.D., Kadam, C.Y., Deshpande, K.H., 2010. Role of oxidative stress in various stages of psoriasis. Indian journal of clinical biochemistry 25, 388-392.

Karabag-Coban, F., Hazman, O., Bozkurt, M.F., Ince, S., 2017. Antioxidant status and anti-inflammatory effects of oleuropein in streptozotocin-induced diabetic nephropathy in rats. Eur J Med Plants 18, 1-10.

Kim, M.R., Jeong, S.J., 2019. Relationship between Vitamin D Level and Lipid Profile in Non-Obese Children. Metabolites 9, 125.

Königshofer, P., Brusilovskaya, K., Schwabl, P., Reiberger, T., 2019. Animal models of portal hypertension. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease 1865, 1019-1030.

Legette, L., Ma, L., Reed, R.L., Miranda, C.L., Christensen, J.M., Rodriguez-Proteau, R., Stevens, J.F., 2012. Pharmacokinetics of xanthohumol and metabolites in rats after oral and intravenous administration. Molecular nutrition & food research 56, 466-474.

Lisakovska, O., Shymanskyy, I., Mazanova, A., Khomenko, A., Veliky, M., 2017. Vitamin D_3 protects against prednisolone-induced liver injury associated with the impairment of the hepatic NF-κB/iNOS/NO pathway. Biochemistry and Cell Biology 95, 213-222.

Lozano, I., Van der Werf, R., Bietiger, W., Seyfritz, E., Peronet, C., Pinget, M., Jeandidier, N., Maillard, E., Marchioni, E., Sigrist, S., 2016. High-fructose and high-fat diet-induced disorders in rats: impact on diabetes risk, hepatic and vascular complications. Nutrition & metabolism 13, 1-13.

Makhlouf, A.-M.A., Mahmoud, A.M., Ibrahim, R.G., Aziz, Y.S.A., 2021. Effects of vitamin D and simvastatin on inflammatory and oxidative stress markers of high-fat diet-induced obese rats. Journal of Scientific Research in Medical and Biological Sciences 2, 39-50.

Martínez-Martínez, E., V. Souza-Neto, F., Jiménez-González, S., Cachofeiro, V., 2021. Oxidative stress and vascular damage in the context of obesity: The hidden guest. Antioxidants 10, 406.

Milic, S., Mikolasevic, I., Krznaric-Zrnic, I., Stanic, M., Poropat, G., Stimac, D., Vlahovic-Palcevski, V., Orlic, L., 2015. Nonalcoholic steatohepatitis: emerging targeted therapies to optimize treatment options.

Drug Design, Development and Therapy, 4835-4845.
Njelekela, M.A., Negishi, H., Nara, Y., Sato, T., Tomohiro, M., Kuga, S., Noguchi, T., Kanda, T., Yamori, M., Matshalla, Y., 2002. Obesity and lipid profiles in middle aged men and women in Tanzania. East African medical journal 79, 58-64.
Noeman, S.A., Hamooda, H.E., Baalash, A.A., 2011. Biochemical study of oxidative stress markers in the liver, kidney and heart of high fat diet induced obesity in rats. Diabetology & metabolic syndrome 3, 1-8.
Ouwens, D., Diamant, M., Fodor, M., Habets, D., Pelsers, M., El Hasnaoui, M., Dang, Z., Van den Brom, C., Vlasblom, R., Rietdijk, A., 2007. Cardiac contractile dysfunction in insulin-resistant rats fed a high-fat diet is associated with elevated CD36-mediated fatty acid uptake and esterification. Diabetologia 50, 1938-1948.
Papapostoli, I., Lammert, F., Stokes, C.S., 2016. Effect of short-term vitamin D correction on hepatic steatosis as quantified by controlled attenuation parameter (CAP). J Gastrointestin Liver Dis 25, 175-181.
Savini, I., Catani, M.V., Evangelista, D., Gasperi, V., Avigliano, L., 2013. Obesity-associated oxidative stress: strategies finalized to improve redox state. International journal of molecular sciences 14, 10497-10538.
Sepidarkish, M., Farsi, F., Akbari-Fakhrabadi, M., Namazi, N., Almasi-Hashiani, A., Hagiagha, A.M., Heshmati, J., 2019. The effect of vitamin D supplementation on oxidative stress parameters: a systematic review and meta-analysis of clinical trials. Pharmacological research 139, 141-152.
Tavakoli, H., Rostami, H., Avan, A., Bagherniya, M., Ferns, G.A., Khayyatzadeh, S.S., Ghayour-Mobarhan, M., 2019. High dose vitamin D supplementation is associated with an improvement in serum markers of liver function. Biofactors 45, 335-342.
Ugwor, E.I., Ugbaja, R.N., James, A.S., Dosumu, O.A., Thomas, F.C., Ezenandu, E.O., Graham, R.E., 2022. Inhibition of fat accumulation, lipid dysmetabolism, cardiac inflammation, and improved nitric oxide signalling mediate the protective effects of lycopene against cardio-metabolic disorder in obese female rats. Nutrition Research 104, 140-153.
Vanlint, S., 2013. Vitamin D and obesity. Nutrients 5, 949-956.
Vaskonen, T., Mervaala, E., Sumuvuori, V., Seppänen-Laakso, T., Karppanen, H., 2002. Effects of calcium and plant sterols on serum lipids in obese Zucker rats on a low-fat diet. British Journal of Nutrition 87, 239-245.
Wang, Y., Si, S., Liu, J., Wang, Z., Jia, H., Feng, K., Sun, L., Song, S.J., 2016. The associations of serum lipids with vitamin D status. PloS one 11, e0165157.
Yang, L., Roh, Y.S., Song, J., Zhang, B., Liu, C., Loomba, R., Seki, E., 2014. Transforming growth factor beta signaling in hepatocytes participates in steatohepatitis through regulation of cell death and lipid metabolism in mice. Hepatology 59, 483-495.
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. European journal of clinical investigation 42, 1189-1196.