Genij Ortopedii. 2022. Vol. 28, no. 2. P. 249-255.

Original article

https://doi.org/10.18019/1028-4427-2022-28-2-249-255

Effect of melatonin on dyslipidemia factor in metabolic osteoarthritis

D.R. Shodiev✉, V.I. Zvyagina, M.N. Ryabova, M.N. Dmitrieva

Ryazan State Medical University, Ryazan, Russian Federation

Corresponding author: Dmitry R. Shodiev, shodiev.dima@yandex.ru

Abstract

Introduction Osteoarthritis (OA) has long been considered from the mechanical point of view of etiology and pathogenesis, as a "wear and tear" disease. However, advances in fundamental medicine have changed the way we look at this disease. The role of systemic inflammation was determined in OA progression and risk factor related clinical phenotypes were differentiated as post-traumatic OA, age associated OA, genetic OA and metabolic syndrome associated OA. The development and progression of OA in metabolic disorders envision a concept of systemic regulation of osteocartilaginous and synovial tissues, and several studies showed that dysregulation of circadian rhythms may be involved in the development of dyslipidemia and systemic inflammation associated with obesity. **The objective** was to explore the effect of melatonin on the dynamics of lipid metabolism and the severity of clinical symptoms in patients with OA and insomnia based on the role of dyslipidemia in the pathogenesis of degenerative diseases. **Materials and Methods** The study included 36 individuals including 12 healthy volunteers and 24 inpatients of experimental groups with insomnia and Kellgren-Lawrence grades 2 and 3 gonarthrosis. Standard conservative treatment consisted of drug and physical therapy. Medical history, complaints were collected from the patients and physical examination performed to evaluate edema of the joint, alignment of the lower limb, range of motion in the joints and measure waist circumference, body height, body weight; body mass index. The biochemistry blood parameters measured included total cholesterol concentration (TCC), high-density lipoprotein cholesterol, low density lipoprotein cholesterol (LDL) and triglycerides (TG). VAS and Lequesne scale were used to assess pain and function of the joints. **Results** Patients with the metabolic OA showed statistically significant ($p < 0.05$) increase in TCC (6.23 (4.28 to 6.44) mmol/L, $p < 0.0002$), LDL fractions (4.52 (3.08 to 4.92) mmol/L, $p < 0.00004$), atherogenic coefficient (CA) (4.33 (3.15–4.8) mmol/L, $p < 0.00003$) and a decrease in the HDL fraction (1.08 (0.93 to 1.4) mmol/L, $p < 0.01$) before treatment in comparison with healthy individuals. The TG level remained within the normal range (0.73 [0.62 to 0.78] mmol/L). At a month, a statistically significant ($p < 0.006$) decrease in TC (4.62 [3.71 to 5.29] mmol/L), a decrease in atherogenic fractions of LP (LDL) (2.65 [1.90 to 3.05] mmol/L) ($p < 0.002$), an increase in the HDL fraction (1.49 [1.17 to 1.72] mmol/L) ($p < 0.004$) and a decrease in CA (2.07 [1.81 to 2.34] mmol/L) ($p < 0.002$) were observed in the experimental group of patients who received melatonin at the dose of 3 mg per day as an adjunctive therapy to the basic treatment. There was no significant dynamics of lipid metabolism in patients receiving standard treatment. The Lequesne's functional index significantly ($p < 0.03$) decreased in melatonin patients after treatment from 12 [12 to 13] to 10 (8.75 to 10.25) points and showed no significant dynamics measuring 10.5 [10 to 11.75] and 10 [10 to 19.25] points in patients receiving standard treatment. Although positive dynamics in VAS scores was observed in both experimental groups a greater improvement ($p < 0.005$) was seen in the drug group with VAS score improved from 4.5 [3.75 to 5] to 2.5 [2 to 3.25] mm versus 4.5 [4 to 5] and 3.5 [3 to 4] mm in the no-drug group ($p < 0.01$). **Conclusion** Melatonin incorporated into the basic therapy was shown to exert a positive effect on pain assessment, condition of the knee joint evaluated with knee rating scales and subjective instruments, objective examination. The moderate antiatherogenic effect facilitates the therapeutic regimen to be considered in management of metabolic osteoarthritis.

Keywords: obesity, osteoarthritis, dyslipidemia, melatonin

For citation: Shodiev D.R., Zvyagina V.I., Ryabova M.N., Dmitrieva M.N. Effect of melatonin on dyslipidemia factor in metabolic osteoarthritis. *Genij Ortopedii*, 2022, vol. 28, no 2, pp. 249-255. https://doi.org/10.18019/1028-4427-2022-28-2-249-255

INTRODUCTION

Osteoarthritis (OA) has long been considered a mechanical disease etiologically and pathogenetically resulting from natural wear and tear and aging. However, fundamental research has refined the viewpoint. Now the role of systemic inflammation in the progression of OA is clearly defined with clinical phenotypes identified based on risk factors as post-traumatic, age related, genetic and OA associated with metabolic syndrome. The fact of the development and progression of OA in metabolic disorders guides the concept of systemic regulation of the osteochondral and synovial tissue of the joints. Obesity, abdominal (visceral) obesity, in particular, is the main cause of the metabolic syndrome, which includes type 2 diabetes mellitus, arterial hypertension, obstructive sleep apnea syndrome, non-alcoholic fatty liver disease (NAFLD), insulin resistance and dyslipidemia. Dyslipidemia as a link between the metabolic syndrome and an important aspect of obesity is of interest as a potential risk factor for OA. Dyslipidemia is an impaired physiological ratio of lipid blood fractions. There are various forms of dyslipidemia which are classified depending on which levels of lipids and lipoproteins are beyond the normal range. The driving force behind dyslipidaemia in metabolic syndrome is progressive insulin resistance resulting in lipolysis and lipotoxicity. In recent years, a

form of dyslipidemia resulting from the concerted action of insulin resistance and obesity has been recognized as "metabolic dyslipidemia". The condition is characterized by high concentrations of triglycerides (TG) with a decrease in the concentration of high-density lipoprotein cholesterol (HDL-C), normal or slight increase in low-density lipoprotein cholesterol (LDL-C). Patients who are overweight (BMI = 25-29.9) or obese (BMI ≥ 30) are likely to develop dyslipidemia due to changes in fat metabolism. However, there is debate about whether dyslipidemia and high cholesterol, in particular, affects the incidence of OA or not. Epidemiological studies show differing points of view [1]. A meta-analysis of "case-control" and cross-sectional studies indicated a strong relationship between dyslipidemia and OA with the relative risk of 1.37 and 1.33, respectively, but the relationship was not confirmed by cohort studies with the relative risk of 1.00 [2]. Another study showed the relative risk of dyslipidemia of 1.98 with OA than without [3], and the mean prevalence of dyslipidemia in hand OA was 37.6 ± 1.6%, much higher than the mean prevalence of 30.2 ± 0. 6% for OA in general. Clinical and epidemiological findings were reported in experiments on animals and in vitro cell cultures. Cholesterol and the esters accumulated by chondrocytes through oxidized low-density lipoprotein (LOX-1) receptors interfered with cell homeostasis provoking apoptosis and OA progression [4]. The effect of free fatty acids with different degrees of saturation (saturated fatty acids (SFA), polyunsaturated fatty acids (PUFA)) on the development of OA is of interest. Effects of fatty acids on the secretion or manifestation of pro-inflammatory factors such as interleukins, tumor necrosis factor, matrix metalloproteinases, prostaglandins, etc. were explored in local studies [5]. Overall results indicated to adverse effects of SFAs with increased production of pro-inflammatory cytokines and pro-apoptotic markers. In contrast, n-3 PUFAs were shown to reduce markers of inflammation and cartilage degradation [6]. The findings supported a systemic metabolic component of OA, where the concept of systemic inflammation has been validated, and overweight and the associated insulin resistance and dyslipidemia are now thought to be the cause of elevated circulating cytokines [7]. However, it is not clear whether systemic inflammation is a cause or a consequence of metabolic diseases. Moreover, the concept acquired more aspects to include a number of mechanisms, such as oxidative stress and the accumulation of oxidative products [8]. Finally, new trends of research demonstrated that circadian rhythm dysregulation might be involved in the development of dyslipidemia and systemic inflammation associated with obesity [9]. A recent multinational cohort study showed the melatonin levels in patients with obesity being reduced compared to patients with normal body weight [10]. And with the growing role of melatonin in the regulation of bone and cartilage metabolism the imbalance can contribute to the progression of degenerative processes in the bone and cartilage tissue.

The objective was to explore the effect of melatonin on the dynamics of lipid metabolism and the severity of clinical symptoms in patients with OA and insomnia based on the role of dyslipidemia in the pathogenesis of degenerative diseases.

MATERIAL AND METHODS

The study involved 36 people with 12 healthy subjects recruited from volunteers. Twenty-four patients of the experimental groups (1 and 2) with Kellgren-Lawrence stages 2–3 gonarthrosis and insomnia underwent inpatient treatment. Standard conservative treatment included medication (group B vitamins, non-steroidal anti-inflammatory drugs (NSAIDs) as required, pentoxifylline (4 weeks), nicotinic acid, mydocalm) and physiotherapy (massage of the lower extremities, therapeutic exercises according to the method of arthrosis, laser-, magnet-therapy). The participants were divided into 3 groups:

group 1 – volunteers without articular pathology, sleep disorders having a normal body mass index (n = 12);

group 2 – patients with metabolic phenotype of OA, insomnia who were on basic inpatient treatment (n = 12);

group 3 – patients with metabolic phenotype of OA and insomnia who were on basic inpatient treatment with melatonin administered at a dose of 3 mg per day for 4 weeks (n = 12).

An accurate medical history was obtained and a physical examination carefully performed for all patients. Edema was evaluated at the site of the affected and contralateral knee joints, the axis of the lower limb and range of motion were determined using a goniometer; height, weight, waist circumference measured and BMI calculated. Serum biochemical parameters were measured. Blood samples were collected after an overnight fasting from all participants. Venous blood samples were centrifuged at 3000 g for 30 minutes. The samples were stored frozen at -20 °C until testing for at least two months, then thawed at room temperature. Serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol

(LDL) and triglycerides (TG) were measured using commercial kits (Olveks diagnosticum, Russia) at the beginning and the end of the experiment (after blood sampling to determine biochemical parameters). The TC level was measured through the release from the composition of esters under the action of the enzyme cholesterolesterase (ChE). Then with the participation of the enzyme cholesterol oxidase (CO), cholesterol was oxidized to 4-cholesten-3-one, and the resulting hydrogen peroxide, with the participation of the enzyme peroxidase (PO), contributed to the oxidative azocoupling of 4-aminoantipyrine (4-AAP) and phenol to form a colored compound (quinonimine dye). The color intensity of the reaction medium was proportional to the cholesterol content in the test material and was determined photometrically at a wavelength of 500 (490–520) nm. The concentration of TG was based on a series of coupled enzymatic reactions catalyzed by lipase, glycerokinase (GK) in the presence of ATP, glycerol-3-phosphate oxidase (GPO) and peroxidase (PO). The hydrogen peroxide (H_2O_2) formed during these reactions promoted the oxidative azocombination of 4-AAP and phenol to form a colored compound (quinonimine). The color intensity of the reaction medium was proportional to the content of triglycerides in the test material and was measured photometrically at a wavelength of 500 (490–540) nm. HDL was determined by precipitation of chylomicrons, very low density lipoproteins (LDL) and LDL with phosphotungstic acid and Mg2+ added to the sample. HDL remained in the supernatant after centrifugation with the concentration determined in the same way as the concentration of total cholesterol. Pain assessment tool included visual analogue scale (VAS) and the Lequesne index was used for assessing severity of OA. Exclusion criteria included conditions affecting the joint under study, such as systemic inflammatory joint disease, sepsis, osteonecrosis; chronic or recent use of oral corticosteroids, lipid-lowering drugs, glucosamine or chondroitin; recent (< 3 months) intra-articular injections of corticosteroids, hyaluronic acid or other synovial fluid prostheses. Serious decompensated medical conditions such as uncontrolled diabetes, HIV, hypertension were contraindications to participation.

Ethical expertise The study was approved by the local ethics committee of the Ryazan State Medical University of the Russian Ministry of Health. All participants provided written informed consent.

Statistical analysis Statistical data processing was carried out using the Statsoft Statistica 12.0 program. The Shapiro-Wilk test was used to determine conformity of the samples to the normal distribution. With non-normally distributed variables the Mann-Whitney test was employed to determine statistical significance in independent groups and the Wilcoxon test was applied to dependent groups. The Spearman's rank coefficient of correlation was used to measure rank correlation. Differences were considered statistically significant at $p \leq 0.05$.

RESULTS

The mean age of healthy participants was 59 [57.25-65.75] years and 60.5 [59-63.5] years in the groups with the metabolic phenotype of OA. Patients were predominantly women. There were statistically significant differences in BMI ($p < 0.000001$), waist circumference ($p < 0.000003$), percentage of body fat ($p < 0.000002$) and range of motion in the knee joints ($p < 0.00001$) between a healthy group and groups with a metabolic phenotype of OA (groups 2 and 3) (Table 1). The median values of BMI in obese patients were higher by 14.9 points, waist circumference by 25.1 cm, and the percentage of body fat ratio was higher by 9.65% than in the healthy group. Patients of groups 2 and 3 showed a mixed contracture of mainly both knee joints at the initial stage of treatment. Flexion and extension deficits were 37° [25.75-62.5[and 19° [13.75-26.25], respectively. OA was graded II–III according to Kellgren-Lawrence and indicated pronounced degenerative changes in the joint accompanied by osteophytes and narrowing of the joint space. Patients of groups 2 and 3 showed statistically significant increase in the level of TC (6.23 (4.28–6.44) mmol/L, $p<0.0002$), LDL fractions (4.52 [3.08-4, 92] mmol/L, $p < 0.00004$), the atherogenic coefficient (AC) (4.33 [3.15-4.8] mmol/L, $p < 0.00003$) and a decrease in the HDL fraction (1.08 [0.93-1.4] mmol/L, $p < 0.01$) before treatment compared with healthy subjects (TC 3.51 [3.02-3.61], LDL 1.76 [1.15-1.92], TG 0.8 [0.75–0.99], HDL 1.38 [1.08-1.5], CA 1.58 [1.07-2.11]. The TG level remained within the normal range (0.73 [0.62-0.78] mmol/L). Patients of experimental group 3 who received melatonin at a dose of 3 mg per day as an addition to the basic treatment demonstrated a statistically significant decrease in TC ($p < 0.006$), decrease in atherogenic LP (LDL) fractions ($p < 0.002$), increased fraction of HDL ($p < 0.004$) and a decrease in CA ($p < 0.002$) at 1 month. There were no significant changes in lipid metabolism in the standard treatment group. Lipid spectrum parameters before and after various treatment regimens are presented in Table 2.

Table 1

Anthropometric parameters of the healthy group and groups with the metabolic phenotype of OA (groups 2 and 3)

	Healthy group	Metabolic phenotype of OA (groups 2 and 3)
BMI	21.45 [20.69–23.06]	36.35 [32.36–38.37]*
WC	86.4 [84.25–91.25]	111.5 [103.5–124.75]*
% fat	36.8 [36.23–38.13]	46.52 [43.9–49.65]*

* – $p < 0.05$ (figures clarified in the text).

Table 2

Blood lipid fractions in patients of groups 2 and 3 before and after treatment

		Group 2	Group 3
TC	before	6.38 [6.28–6.48]	5.31 [4.1–6.26]
	after	6.36 [5.41–6.48]	4.62* [3.71–5.29]
HDL	before	1.42 [1.1–1.8]	0.99 [0.85–1.13]
	after	1.32 [1.13–1.74]	1.49* [1.17–1.72]
LDL	before	4.84 [3.71–5.02]	3.75 [2.92–1.72]
	after	4.51 [3.44–4.78]	2.65* [1.90–4.98]
TG	before	0.72 [0.71–0.74]	0.75 [1.17–1.72]
	after	0.98 [0.83–1.12]	0.73 [0.62–0.78]
KA	before	3.35 [2.38–4.81]	4.42 [4.04–4.81]
	after	3.52 [2.3–4.6]	2.07* [1.81–2.34]

* – $p < 0.05$ (figures clarified in the text).

A comparative analysis of the lipid spectrum in experimental group 3 showed that the fraction of atherogenic lipoproteins decreased by 29.23 %, and total cholesterol by 13.02 %. The HDL fraction showed a positive increase of 50.5 % in the drug group, in contrast to the standard treatment group with no statistically significant differences. There were no significant changes in anthropometric parameters (BMI, % of body fat and waist circumference) in both experimental groups of the OA metabolic phenotype, since the patients were not limited to any hypocaloric diet and took meals as usual. As a result of conservative treatment, a statistically significant surplus of range of motion relative to baseline showed similar dynamics in both experimental groups (Table 3).

Table 3

Dynamics in the deficiency of range of motion of the knee joints in patients of groups 2 and 3 before and after treatment

		Group 2	Group 3
Deficiency of flexion	before	375° [25.75–62.5]	38° [23.75–54.75]
	after	25° [23–35]***	20° [14.75–40.00]*
Deficiency of extension	before	19° [10–20]	18° [10–20]
	after	10° [10–15]****	16.5° [10–19.25]**

* – $p < 0.00001$, *** – $p < 0.0007$, **$p < 0.03$, **** – $p < 0.005$.

Statistically significant differences in the Lequesne index ($p < 0.000001$) and VAS ($p < 0.000001$) were noted between healthy volunteers and patients with the metabolic phenotype of OA. The Lequesne index of the knee joints decreased from 12 [12–13] to 10 [8.75–10.25] points ($p < 0.03$) in group 3 after treatment and showed no significant dynamics in patients of group 2 measuring 10.5 [10–11.75] and 10 [10–19.25] points before and after treatment, respectively. Positive dynamics in VAS score was observed in both experimental groups with a larger amplitude ($p < 0.005$) in group 3 improving from 4.5 [3.75–5] to 2.5 [2–3.25] mm versus 4.5 [4–5] and 3.5 [3–4] mm in group 2 ($p < 0.01$). The correlation analysis between biochemical and clinical parameters showed a statistically significant ($p < 0.05$) moderate positive correlation between the level of TC ($r = 0.48$), LDL cholesterol ($r = 0.5$) and the VAS score in groups 2 and 3. A statistically significant ($p < 0.05$) moderate positive correlation was determined between the level of CA and the Lequesne index of subjective assessment of the knee function ($r = 0.52$) in the same groups (Fig. 1–3).

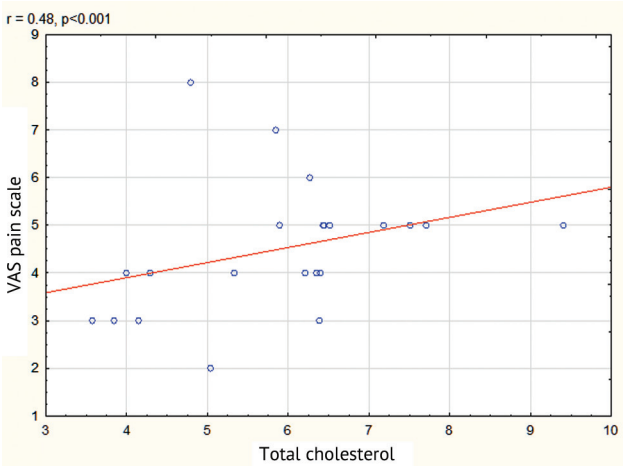

Fig. 1 Correlation analysis of the VAS score and the TC level in patients with the metabolic phenotype of OA (groups 2 and 3)

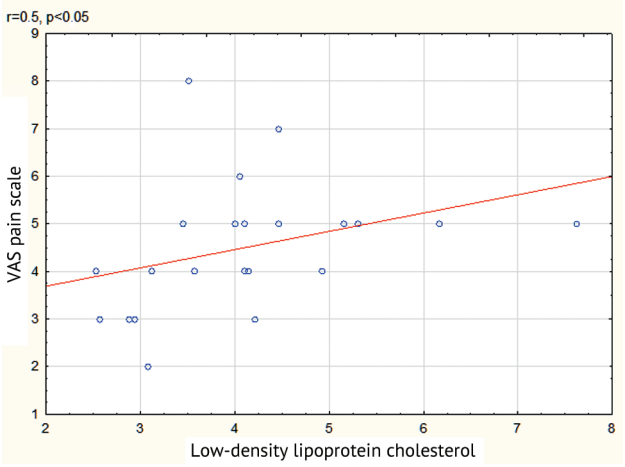

Fig. 2 Correlation analysis of the VAS scale and LDL level in patients with the metabolic phenotype of OA (groups 2 and 3)

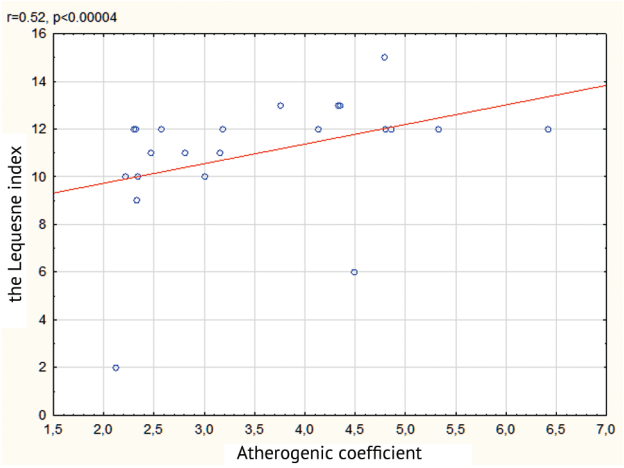

Fig. 3 Correlation analysis of the Lequesne index and the level of CA in patients with the metabolic phenotype of OA (groups 2 and 3)

DISCUSSION

Studies demonstrating the effect of melatonin on lipid metabolism in light of cardiovascular diseases report promising but contradictory results. A recent meta-analysis of the effect of melatonin supplementation on dyslipidemia and anthropometric indices reported an overall positive effect of melatonin on LDL cholesterol and TG levels compared with controls [11]. No significant effect on HDL cholesterol levels and anthropometric parameters was found. These results are generally consistent with our findings with the average physiological dose of melatonin used and the patients were not limited by calories to be consumed per day. Nevertheless, the positive effect on the level of HDL cholesterol in our series was encouraging due to the exceptional significance of the fraction in the genesis of metabolic disorders in the metabolic phenotype of OA. A review of the results of several clinical studies on the lipid-lowering effects of melatonin would allow to conclude that significant effects of melatonin on plasma lipoproteins could be found at relatively high concentrations of melatonin (6-10 mg per day) and lower doses remained ineffective [12, 13]. However, our results suggested that both lower concentrations and a relatively short duration were beneficial. The assumption of higher doses of melatonin used over longer periods of treatment resulting in significant reductions in total cholesterol and triglyceride levels are not always supported as evidenced by a meta-analysis of randomized controlled trials (RCTs) [14]. Since the mechanisms underlying the lipid-lowering effect of melatonin are very limited and debatable, the known molecular signaling pathways for the pathophysiology of dyslipidemia and OA may be a potential application point for melatonin [7, 15]. Recently published results of experiments performed on a human hepatocellular carcinoma (HepG2) cell line [16] treated with melatonin (0.1–0.3 mM) and then validated in animal models of obesity [17] showed significant inhibition in the accumulation of triglycerides and cholesterol caused by incubation of HepG2 cells with high concentrations of oleic acid. Preliminary use of melatonin induced phosphorylation of mitogen-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC) causing their activation and inactivation, respectively. Expression levels of peroxisome proliferator-activated receptor-α (PPARα) and its target gene carnitine palmitoyl-CoA transferase 1 (CPT1) which are associated with lipolysis are activated by melatonin, while expression of sterol regulatory element binding protein-1c (SREBP-1c), fatty acid synthase (FAS) and stearoyl-CoA desaturase-1 (SCD1) associated with lipogenesis were suppressed. However, melatonin did not alter the expression of genes involved in cholesterol metabolism including 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) and SREBP-2. AMPK phosphorylation and activation may play an important role in the inactivation of lipid metabolic pathways and the activation of triglyceride catabolic pathways. PPARα activation can lead to an increase in plasma HDL concentration and a decrease in LDL concentration depending on the increased expression of the LDL receptor in liver cells. However, it is not known whether these findings can be extrapolated to other cell lines, such as cartilage or bone cells.

Wan-Su Choi et al. [4] found that chondrocytes in OA elevated cholesterol levels due to increased cholesterol uptake mediated by increased levels of oxidized low-density lipoprotein receptors (LOX1), activation of cholesterol hydroxylases and increased production of oxysterol metabolites. This was most likely due to an increase in the transcriptional activity of orphan receptor alpha (RORα) by direct cholesterol binding ligands, cholesterol-25-hydroxylase (25-HC) and 25-hydroxycholesterol 7α-hydroxylase (25-HC7α). This could be associated with increased regulation of matrix metalloproteinases (MMP3, MMP9, MMP12, MMP13), disintegrin and metalloproteinases with thrombospondin motifs (ADAMTS4 and ADAMTS5) that accompanied the destruction of the cartilage

extracellular matrix. The results of other studies showed that hypercholesterolemia accelerated OA progression due to mitochondrial dysfunction in chondrocytes, partially by increasing the production of ROS [18]. Some of the effects of melatonin could be also related through these molecular pathways. Recently, more and more attention has been paid to signaling pathways that regulate transcription, for example, the hypoxia inducible factor (HIF) family. The modulating effect is explored not only in the context of the tumor process, but also in the pathogenesis of the metabolic syndrome and OA [19, 20]. The HIF protein family consists of α and β subunits that function by forming heterodimers [21], and the two main HIF isoforms (HIF-1 and HIF-2) mediate the cell response to hypoxia [22]. Several studies show that the induction of HIF-1α promotes the release of chemokines and inflammation of adipose tissue under relative hypoxia of adipocytes, [23], and the reduction of dyslipidemia and arteriosclerosis by some drugs occurs due to inhibition of the level of a number of regulated proteins through the HIF-1 signaling pathway [24]. It is worth considering and suggesting that the regulation of lipid metabolism by melatonin in the metabolic phenotype of OA, both at the systemic level and in the bone and cartilage tissue, is carried out in a similar way through HIF signaling pathways [24]. Our correlation analysis showed a moderate correlation between TC, atherogenic fractions of LA and CA with clinical pain score and function of the knee joints that is supported by the results of previous studies [3, 25] on the relationship between dyslipidemia and OA, and the need to resolve dyslipidemia in OA becomes even more obvious. The limitations of the study including a small sample of patients and the lack of blind control could have led to a limitation in the evaluation of the effectiveness of the drug. Dynamical evaluation of melatonin levels in body fluids during treatment would be practical for more accurate interpretation of causal relationships in future studies. In-depth studies of the molecular mechanisms in cell cultures and in vivo that underlie the phenomenological results of the study will be able to supplement and confirm the data obtained.

CONCLUSION

Melatonin incorporated into the basic therapy was shown to exert a positive effect on pain assessment, condition of the knee joint evaluated with knee rating scales and subjective instruments, objective examination. The moderate antiatherogenic effect facilitates the therapeutic regimen to be considered in management of metabolic osteoarthritis.

REFERENCES

1. Xie Y., Zhou W., Zhong Z., Zhao Z., Yu H., Huang Y., Zhang P. Metabolic syndrome, hypertension, and hyperglycemia were positively associated with knee osteoarthritis, while dyslipidemia showed no association with knee osteoarthritis. *Clin. Rheumatol*., 2021, vol. 40, no. 2, pp. 711-724. DOI: 10.1007/s10067-020-05216-y.
2. Xiong J., Long J., Chen X., Li Y., Song H. Dyslipidemia might be associated with an increased risk of osteoarthritis. *Biomed. Res. Int*., 2020, vol. 2020, pp. 3105248. DOI: 10.1155/2020/3105248.
3. Baudart P., Louati K., Marcelli C., Berenbaum F., Sellam J. Association between osteoarthritis and dyslipidaemia: a systematic literature review and meta-analysis. *RMD Open*, 2017, vol. 3, no. 2, pp. e000442. DOI: 10.1136/rmdopen-2017-000442.
4. Choi W.S., Lee G., Song W.H., Koh J.T., Yang J., Kwak J.S., Kim H.E., Kim S.K., Son Y.O., Nam H., Jin I., Park Z.Y., Kim J., Park I.Y., Hong J.I., Kim H.A., Chun C.H., Ryu J.H., Chun J.S. The CH25H-CYP7B1-RORα axis of cholesterol metabolism regulates osteoarthritis. *Nature*, 2019, vol. 566, no. 7743, pp. 254-258. DOI: 10.1038/s41586-019-0920-1.
5. Miao H., Chen L., Hao L., Zhang X., Chen Y., Ruan Z., Liang H. Stearic acid induces proinflammatory cytokine production partly through activation of lactate-HIF1α pathway in chondrocytes. *Sci. Rep*., 2015, vol. 5, pp. 13092. DOI: 10.1038/srep13092.
6. Loef M., Schoones J.W., Kloppenburg M., Ioan-Facsinay A. Acides gras et arthrose: différents types, différents effets [Fatty acids and osteoarthritis: different types, different effects]. *Joint Bone Spine*, 2019, vol. 86, no. 4, pp. 451-458. (in French) DOI: 10.1016/j.jbspin.2018.07.005.
7. Alvarez-Garcia O., Rogers N.H., Smith R.G., Lotz M.K. Palmitate has proapoptotic and proinflammatory effects on articular cartilage and synergizes with interleukin-1. *Arthritis Rheumatol*., 2014, vol. 66, no. 7, pp. 1779-1788. DOI: 10.1002/art.38399.
8. Matveeva E.L., Spirkina E.S., Chegurov O.K., Reva M.A. Profil lipoperoksidatsii v sinovialnoi zhidkosti sustavov u patsientov s gonartrozom, soprovozhdaiushchimsia defektami sustavnykh poverkhnostei [Profile of lipid peroxidation in the synovial fluid of the joints in patients with gonarthrosis accompanied by articular surface defects]. *Nauka Molodykh* (Eruditio Juvenium), 2020, vol. 8, no. 1, pp. 70-75. (in Russian) DOI: 10.23888/HMJ20208170-7.
9. Engin A. Circadian Rhythms in Diet-Induced Obesity. *Adv. Exp. Med. Biol*., 2017, vol. 960, pp. 19-52. DOI: 10.1007/978-3-319-48382-5_2.
10. Chowdhury-Paulino I.M., Cheng I., Valdimarsdottir U.A., Le Marchand L., Haiman C.A., Wilkens L., Mucci L.A., Markt S.C. Racial and ethnic differences in the association of body mass index (BMI) and melatonin levels among men in the Multiethnic Cohort Study. American Association for Cancer Research. Proceedings of the Twelfth AACR Conference on the Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved. San Francisco, 2019. *Cancer Epidemiol. Biomarkers Prev*., 2020, vol. 29, no. 6 Suppl_2, abstract nr C046.
11. Loloei S., Sepidarkish M., Heydarian A., Tahvilian N., Khazdouz M., Heshmati J., Pouraram H. The effect of melatonin supplementation on lipid profile and anthropometric indices: A systematic review and meta-analysis of clinical trials. *Diabetes Metab. Syndr*., 2019, vol. 13, no. 3, pp. 1901-1910. DOI: 10.1016/j.dsx.2019.04.043.
12. Raygan F., Ostadmohammadi V., Bahmani F., Reiter R.J., Asemi Z. Melatonin administration lowers biomarkers of oxidative stress and cardio-metabolic risk in type 2 diabetic patients with coronary heart disease: A randomized, double-blind, placebo-controlled trial. *Clin. Nutr*., 2019, vol. 38, no. 1, pp. 191-196. DOI: 10.1016/j.clnu.2017.12.004.
13. Anandacoomarasamy A., Leibman S., Smith G., Caterson I., Giuffre B., Fransen M., Sambrook P.N., March L. Weight loss in obese people has structure-modifying effects on medial but not on lateral knee articular cartilage. *Ann. Rheum. Dis*., 2012, vol. 71, no. 1, pp. 26-32. DOI: 10.1136/ard.2010.144725.
14. Mohammadi-Sartang M., Ghorbani M., Mazloom Z. Effects of melatonin supplementation on blood lipid concentrations: A systematic review and meta-analysis of randomized controlled trials. *Clin. Nutr*., 2018, vol. 37, no. 6, pt. A, pp. 1943-1954. DOI: 10.1016/j.clnu.2017.11.003.

15. Frommer K.W., Schäffler A., Rehart S., Lehr A., Müller-Ladner U., Neumann E. Free fatty acids: potential proinflammatory mediators in rheumatic diseases. *Ann. Rheum. Dis*., 2015, vol. 74, no. 1, pp. 303-310. DOI: 10.1136/annrheumdis-2013-203755.
16. Mi Y., Tan D., He Y., Zhou X., Zhou Q., Ji S. Melatonin modulates lipid metabolism in HepG2 cells cultured in high concentrations of oleic acid: AMPK pathway activation may play an important role. *Cell Biochem. Biophys*., 2018, vol. 76, no. 4, pp. 463-470. DOI: 10.1007/s12013-018-0859-0.
17. Ou T.H., Tung Y.T., Yang T.H., Chien Y.W. Melatonin Improves Fatty Liver Syndrome by Inhibiting the Lipogenesis Pathway in Hamsters with High-Fat Diet-Induced Hyperlipidemia. *Nutrients*, 2019, vol. 11, no. 4, pp. 748. DOI: 10.3390/nu11040748.
18. Farnaghi S., Prasadam I., Cai G., Friis T., Du Z., Crawford R., Mao X., Xiao Y. Protective effects of mitochondria-targeted antioxidants and statins on cholesterol-induced osteoarthritis. *FASEB J*., 2017, vol. 31, no. 1, pp. 356-367. DOI: 10.1096/fj.201600600R.
19. Hu S., Zhang C., Ni L., Huang C., Chen D., Shi K., Jin H., Zhang K., Li Y., Xie L., Fang M., Xiang G., Wang X., Xiao J. Stabilization of HIF-1α alleviates osteoarthritis via enhancing mitophagy. *Cell Death Dis*., 2020, vol. 11, no. 6, pp. 481. DOI: 10.1038/s41419-020-2680-0.
20. Yang Q., Zhou Y., Cai P., Fu W., Wang J., Wei Q., Li X. Up-regulated HIF-2α contributes to the Osteoarthritis development through mediating the primary cilia loss. *Int. Immunopharmacol*., 2019, vol. 75, pp. 105762. DOI: 10.1016/j.intimp.2019.105762.
21. Semenza G.L. Hypoxia-inducible factors in physiology and medicine. Cell, 2012, vol. 148, no. 3, pp. 399-408. DOI: 10.1016/j.cell.2012.01.021.
22. Smith T.G., Robbins P.A., Ratcliffe P.J. The human side of hypoxia-inducible factor. *Br. J. Haematol*., 2008, vol. 141, no. 3, pp. 325-334. DOI: 10.1111/j.1365-2141.2008.07029.x.
23. Lee Y.S., Kim J.W., Osborne O., Oh D.Y., Sasik R., Schenk S., Chen A., Chung H., Murphy A., Watkins S.M., Quehenberger O., Johnson R.S., Olefsky J.M. Increased adipocyte O2 consumption triggers HIF-1α, causing inflammation and insulin resistance in obesity. *Cell*, 2014, vol.157, no. 6, pp. 1339-1352. DOI: 10.1016/j.cell.2014.05.012.
24. Tang J.J., Li G.X., Liu Z.G., Yi R., Yu D., Zhang Y.B., Zhao S.Q., Wang S.H. Danlou Tablet improves chronic intermittent hypoxia-induced dyslipidemia and arteriosclerosis by HIF-1 α-Angptl4 mRNA signaling pathway. *Chin. J. Integr. Med*., 2020, Jul. 4. DOI: 10.1007/s11655-020-3255-8.
25. Kabalyk M.A., Suniaikin A.B. Kliniko-molekuliarnye vzaimosviazi dislipidemii i metabolicheskogo fenotipa osteoartrita [Clinical and molecular relationships between dyslipidemia and the metabolic phenotype of osteoarthritis]. *Rossiiskii Mediko-biologicheskii Vestnik im. akademika I.P. Pavlova*, 2017, vol. 25, no. 3, pp. 391-398. (in Russian) DOI: 10.23888/PAVLOVJ20173391-398.

The article was submitted 21.06.2021; approved after reviewing 27.10.2021; accepted for publication 26.01.2022.

Information about the authors:

1. Dmitry R. Shodiev – shodiev.dima@yandex.ru, eLibrary SPIN 3556-4398;
2. Valentina I. Zvyagina – Candidate of Biological Sciences, vizvyagina@yandex.ru, https://orcid.org/0000-0003-2800-5789, Scopus Author ID: 57189726173;
3. Margarita N. Ryabova – Candidate of Medical Sciences, rmn62doc@yandex.ru, eLibrary SPIN: 2077-3173, https://orcid.org/0000-0002-1707-2567;
4. Mariya N. Dmitrieva – Candidate of Pedagogical Sciences, eLibrary SPIN 1083-9650.

***Declaration of Conflicting Interests**: The authors declared no potential conflicts of interest with respect to the authorship and/or publication of this article.*