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MORPHOLOGICAL CONSEQUENCES OF RISK FACTORS IN THE OCCURRENCE OF GONARTHROSIS IN WOMEN WITH METABOLIC SYNDROME (ON THE EXAMPLE OF KHOREZM REGION)

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Abstract: a meta-analysis of prospective cohort studies showed that metabolic syndrome (MS) increased the risk of knee osteoarthritis in women by 23% even after adjusting for body mass index (RR 1.23; 95% CI 1.03–1.47), whereas no such association was found in men. In Uzbekistan, abdominal obesity was recorded in 55.4% of women and arterial hypertension in 38% of adults. In the Aral Sea region, 61.4% of hypertensive patients were women, among whom type 2 diabetes mellitus was twice as common as in men. Morphologically, in gonarthrosis associated with MS, synovitis and fibro-inflammatory changes in Hoffa's fat pad develop prior to cartilage degradation. Subsequently, this is confirmed by subchondral ischemia, the accumulation of lipids and glycation products in chondrocytes, and the progression of cartilage destruction.

Keywords: morphology, metabolic syndrome, knee joint, gonarthrosis, microscopic changes, women.

МОРФОЛОГИЧЕСКИЕ ПОСЛЕДСТВИЯ ФАКТОРОВ РИСКА В ВОЗНИКНОВЕНИИ ГОНАРТРОЗОВ У ЖЕНЩИН С МЕТАБОЛИЧЕСКИМ СИНДРОМОМ НА ПРИМЕРЕ ХОРЕЗМСКОЙ ОБЛАСТИ

Аннотация: мета-анализ проспективных когортных исследований показал, что метаболический синдром (МС) увеличивает риск остеоартроза коленного сустава у женщин на 23% даже после поправки на индекс массы тела (RR 1,23; 95% ДИ 1,03–1,47), в то время как у мужчин подобной связи выявлено не было. В Узбекистане абдоминальное ожирение зафиксировано у 55,4% женщин, артериальная гипертензия — у 38% взрослых. В приаральском регионе 61,4% пациентов с гипертензией составили женщины, у которых сахарный диабет 2-го типа встречался в два раза чаще, чем у мужчин. Морфологически при гонартрозе на фоне МС синовит и фиброзно-воспалительные изменения жирового тела Гоффа развиваются раньше разрушения хряща. В дальнейшем это подтверждается субхондральной ишемией, накоплением липидов и продуктов гликирования в хондроцитах, а также прогрессированием деструкции хряща.

Ключевые слова: морфология, метаболический синдром, коленный сустав, гонартроз, микроскопические изменения, женщины.

XORAZM VILOYATI MISOLIDA METABOLIK SINDROM MAVJUD AYOLLARDA GONARTROZLARNI YUZAGA KELISHIDA XAVF OMILLARINING MORFOLOGIK OQIBATLARI

Annotatsiya: Prospektiv kogort tadqiqotlarining meta-tahlilida metabolik sindrom (MS) tana vazni indeksiga muvofiqlashtirilgandan keyin ham ayollarda tizza osteoartrozi xavfini 23% ga

oshirgan (RR 1,23; 95% IO 1,03–1,47), erkaklarda esa bunday bog‘liqlik aniqlanmagan. O‘zbekistonda ayollarning 55,4% da abdominal semizlik, kattalarning 38% da arterial gipertenziya qayd etilgan. Orol bo‘yi mintaqasidagi gipertenziyali bemorlarning 61,4% qismi ayollar bo‘lib, ularda 2-tip qandli diabet erkaklarga nisbatan ikki baravar ko‘p uchragan. Morfologik jihatdan MS fonidagi gonartrozda sinovit va Goff yog‘ tanasining fibroz-yallig‘lanish o‘zgarishlari tog‘ay yemirilishidan oldin rivojlanadi. Keyinchalik subxondral ishemiya, xondrotsitlarda lipid va glikatsiya mahsulotlari to‘planishi hamda tog‘ay destruksiyasi bilan davom etishini tasdiqlaydi.

Kalit so‘zlar: morfologiya, metabolik sindrom, tizza bo‘g‘imi, gonartroz, mikroskopik o‘zgarishlar, ayollar.

Relevance of the Problem

According to the World Health Organization (WHO), the number of people suffering from obesity exceeded 1 billion in 2022. This figure indicates that every eighth person on our planet is facing this problem. Knee joint osteoarthritis (OA) is the most common form of knee joint injuries, with 365 million people worldwide suffering from this disease, followed by hand and hip joints. Considering the increase in the number of elderly people due to rising average life expectancy, as well as the increase in obesity and traumatism cases, further growth in the incidence of osteoarthritis is predicted. Recent data show that in Russia, osteoarthritis is observed in 13% of the population aged over 18. This indicator has an upward trend, with 600,000 new cases detected annually [11, 24, 26, 27].

Knee joint injuries in individuals with metabolic syndrome (MS) are becoming one of the most serious problems in healthcare. According to WHO data, around 528 million people worldwide experienced these conditions in 2019. This figure represents a 113% increase compared to 1990, demonstrating the growing relevance of this pathology [3, 8, 13, 30].

Although both the incidence and severity of metabolic syndrome-related knee joint injuries are increasing in older adult groups, more than half of all patients belong to the age group under 65 years. At the same time, regardless of age, the disease occurs 1.2 to 1.7 times more frequently in women than in men [1, 9, 14, 31].

The relevance of the problem is interpreted precisely as the extremely high rates mentioned, acting as a disease that directly impacts the socio-economic indicators of every state.

Notable aspects of the problem indicate that the post-injury process in the knee joint is irreversible, prevention and treatment measures are initiated late, and the incidence of metabolic

syndrome in women is increasing, highlighting the urgency of studying the problem and developing preventive measures [4, 17, 19, 22].

This serves as a basis for developing scientific and methodological recommendations for predicting and treatment tactics based on specific criteria for knee joint osteoarthritis in women with metabolic syndrome.

Purpose of the Study

To analyze the risk factors for gonarthrosis development and morphological consequences in the knee joints of women with metabolic syndrome in the conditions of the Khorezm region, based on literature and regional data.

Materials and Methods of the Study

As materials, intraoperative materials separated during various surgical procedures performed on the knee joints of 172 cases diagnosed with metabolic syndrome across different age groups in the "Traumatology and Orthopedics" department of the Khorezm Regional Multidisciplinary Medical Center were taken. The obtained tissues were fixed in a 10% buffered formalin solution for 72 hours, then dehydrated in ascending order through 70%, 80%, 90%, and 100% alcohols. Subsequently, the tissues were embedded in histomix paraffin blocks and placed into special cassettes. Sections of 5–7 µm\mu mµm thickness were cut using a Leica microtome and deparaffinized in xylene. Tissue sections placed on glass slides were stained using the hematoxylin-eosin method. The selection criteria for patients in analyzing the risk factors and morphological consequences of gonarthrosis in women with metabolic syndrome using the Khorezm region as an example were implemented as follows. Distribution of criteria in study groups:

Inclusion Criteria: Meta-analyses and prospective cohort studies evaluating the association between MS or its components and knee OA; clinical studies involving histological or immunohistochemical examination of knee joint tissues against the background of MS or obesity; experimental studies on models of obesity, high-fat diet, hyperglycemia, hypertension, and dyslipidemia; epidemiological, hygienic, and ecological data for Uzbekistan and the Aral Sea region. The WHO STEPS national survey (Uzbekistan, July–September 2019, 4,320 respondents, coverage 88.3%); a study screening 2,430 individuals over 40 years old in the Aral Sea region, identifying hypertension in 1,020 of them (WHO PEN protocol) [8]; results of hygienic assessment of water consumption conditions of the Aral Sea population [9]; groundwater level and salinity data collected across 2,000 monitoring wells in the Khorezm region from 1990–2006 [6, 10, 15, 32].

Method of Analysis: Information on risk factors, their effect size (relative risk, odds ratio, prevalence), and morphological changes (tissue, cellular, markers, development time) was extracted from selected sources. Morphological changes were systematized by tissues (synovial, infrapatellar fat pad, subchondral bone and microvessels, chondrocytes, hyaline cartilage) and their sequence was evaluated.

Results

The main factors influencing the effect of metabolic syndrome on the risk of gonarthrosis were interpreted as follows. The association between MS and knee OA has long been noted in cross-sectional studies. A meta-analysis conducted in 2016 associated MS with a reliable increase in the odds ratio for knee OA [2, 7, 29]. However, most studies included in this analysis were cross-sectional and unadjusted for body mass index (BMI) [12, 18, 21].

A meta-analysis that included only prospective cohort studies with multivariate analysis provided more accurate results. It included 5 cohorts (94,965 participants) from Sweden, Australia, the USA, Norway, and Finland. At baseline, 20.0% of participants (18,990 individuals) had MS. Over a mean follow-up of 14.5 years, 2,447 knee OA cases were recorded [16, 20, 23]. The results are presented in Table 1.

Effect of metabolic syndrome on the risk of knee osteoarthritis (meta-analysis of prospective cohorts, adjusted for BMI, age, sex, and physical activity)

Table 1.

Group or outcome	Relative Risk (RR)	95% Confidence Interval	p
General population, total knee OA	1.06	0.92–1.23	0.40
Severe knee OA requiring joint replacement	1.16	1.03–1.30	0.02
Symptomatic knee OA	0.84	0.65–1.08	0.18
Women	1.23	1.03–1.47	0.02
Men	0.90	0.70–1.14	0.37

As can be seen from the table, after accounting for BMI, MS did not emerge as an independent risk factor in the general population. However, in women, MS increased the risk of knee OA by 23%, and the difference between sexes was also statistically significant (p=0.04). Furthermore, MS

increased the risk of severe gonarthrosis requiring joint replacement by 16%. These data indicate that MS is significant both in the onset and severity of the disease in women.

Individual effects of metabolic syndrome components.

MS components and knee OA: evidence and underlying mechanisms

Table 2.

Component	Reliability level of evidence	Main mechanisms leading to direct knee joint damage	Source
Abdominal obesity	Strong; BMI is a confirmed risk factor	Mechanical load, adipokines (leptin, resistin), IL-6, TNF-α	[1, 4, 28]
Arterial hypertension	Moderate; association exists in meta-analysis of observational studies	Subchondral ischemia, increased intraosseous pressure, hypoxia, remodeling	[17, 30]
Dyslipidemia	Mixed; present in cross-sectional works, not confirmed in cohort studies	Ectopic lipid accumulation in chondrocytes, impaired cholesterol efflux	[18, 31]
Hyperglycemia / Type 2 DM	Mixed; independent risk not confirmed when BMI is accounted for	AGE accumulation, RAGE activation, oxidative stress, increased MMP expression	[20, 21, 29]

Cohort analysis of middle-aged women without pain symptoms studied the correlation between blood lipids and changes in knee cartilage tissue and bone marrow lesions. These results supported the role of vascular pathology in the pathogenesis of knee OA. Thus, the individual effect of each component may not be strong. However, their combination exerts a cumulative effect on the joint through low-grade systemic inflammation and vascular dysfunction.

Sex-specific risk factors in women: The higher prevalence of gonarthrosis against the background of MS in women is explained by several factors:

- **Anatomical-biomechanical:** The mechanical load on the knee joint in women is greater compared to men, while the cartilage volume is smaller.
- **Cartilage status:** In adults without clinical OA, the rate of cartilage loss and development of cartilage defects is higher in women.

• **Hormonal disorders:** Estrogen deficiency during menopause and female hormonal factors are associated with knee OA. Metabolic disorders in the postmenopausal period affect the radiological and functional state of the knee joint.

• **Metabolic changes:** In the Aral Sea region, type 2 diabetes mellitus was twice as frequent in women with arterial hypertension compared to men (13.7% vs. 7.4%; p=0.002) [8].

Risk Factors Specific to the Khorezm Region and the Aral Sea Region

National-level metabolic risk factors: According to the WHO STEPS (2019) survey, metabolic risk factors are widespread in Uzbekistan [5, 8] (Table 3).

MS components and lifestyle factors in the adult population of Uzbekistan (STEPS, 2019)

Table 3.

No.	Indicator	Prevalence
1	Overweight	32.9%
2	Obesity	23.5%
3	Abdominal obesity: women	55.4%
4	Abdominal obesity: men	64.4%
5	Blood pressure ≥140/90 mm Hg (18–69 years)	38%
6	Elevated blood glucose or taking anti-diabetes medication	8.4%
7	Impaired fasting blood glucose	13.5%
8	Non-compliance with WHO-recommended physical activity	26.1%
9	Always or frequently adding salt to food	36.6%

In Uzbekistan, more than one in every two women has abdominal obesity. This is the main foundation of MS and associated gonarthrosis.

Cardiometabolic characteristics in the Aral Sea region: 2,430 individuals over 40 years old were screened in family polyclinics of the Aral Sea region. Blood pressure ≥140/90\ge 140/90≥140/90 mm Hg was detected in 42% of them (1,020 people), of whom 61.4% were women [8, 25, 28]. The clinical profile of patients with arterial hypertension is presented in Table 4.

Cardiometabolic indicators of hypertensive patients in the Aral Sea region (n=1,020)

Table 4.

No.	Indicator	Value
1	Average age, years	57.68±8.06
2	BMI, kg/m2	29.86±5.28
3	Waist circumference, cm	104.59±11.61
4	Obesity	46.2% (49% in women, 42% in men)
5	Triglycerides, mg/dl	236.85±54.32
6	HDL cholesterol, mg/dl	41.65±6.03
7	Fasting glucose, mmol/l	5.72±1.88
8	Type 2 DM (in women / in men)	13.7% / 7.4%
9	Physical inactivity (Hypodynamia)	67.5%
10	High salt taste sensitivity threshold (in women)	85.6% (83.7%)
11	Carotid artery IMT >0.9 mm	92%
12	Left ventricular hypertrophy	96.3%
13	Microalbuminuria	76%

These indicators indicate that in the majority of hypertensive patients, MS criteria are fully or partially met. The average waist circumference is 104.6 cm, which is significantly higher than the ATP III threshold for women (88 cm). Average triglycerides are 236.9 mg/dl, exceeding the 150 mg/dl threshold. Average HDL cholesterol is 41.7 mg/dl, which is lower than the threshold for women (50 mg/dl). The fact that carotid artery intima-media thickness (IMT) is increased in 92% of cases indicates the widespread restructuring of systemic vascular adaptation mechanisms (sclerosis and atrophic processes).

Ecological and hygienic factors: Additional factors specific to the Khorezm region are summarized in Table 5.

Regional factors of the Khorezm region potentially affecting gonarthrosis development

Table 5.

Factor	Regional data	Association with gonarthrosis
Groundwater salinity	According to data from 2,000 lowland wells, groundwater is located at a depth of 0.9–1.4 m in July	Deterioration of drinking water quality, increase in salt intake
Drinking water quality	Water quality studied in terms of hardness, mineralization, sulfates, and chlorides; children's morbidity correlates with sulfates (r=0.83) and mineralization (r=0.53)	Subchondral ischemia via salt-sensitive hypertension
Salt-dust storms	Drying of the Aral Sea causes salt-dust storms in Khorezm and Karakalpakstan	Salt load, systemic inflammation
Salt sensitivity	High salt taste sensitivity threshold in 85.6% of hypertensive patients; r=0.646 between NaCl concentration and systolic BP	Hypertension, endothelial dysfunction
Public health	Health deviations in 72.6% of examined adults	High general somatic load
Hypodynamia	In 67.5% of hypertensive patients	Weakening of the musculoskeletal apparatus, obesity

Thus, in the Khorezm region, MS components (abdominal obesity, hypertension, dyslipidemia, hyperglycemia) and ecological factors (saline water, salt load) act simultaneously. This creates favorable conditions for the earlier development and more severe course of gonarthrosis against the background of MS.

Morphological Consequences in the Knee Joint

Morphological changes in gonarthrosis against the background of MS showed that changes encompass all joint tissues and develop in a specific sequence.

Synovial membrane: Synovial inflammation is the earliest morphological sign of gonarthrosis against the background of MS. When high-carbohydrate and high-fat diets were applied to Wistar rats for 8 and 16 weeks, obesity was accompanied by spontaneous local inflammation of synovial

membranes prior to cartilage degradation. Subsequently, synovitis intensified, macrophage infiltration into the synovium increased, with inflammation-prone M1 macrophages predominating. In another experiment, a high-fat diet caused a dysmetabolic state and synovial inflammation, but had almost no effect on cartilage degradation. When mechanical cartilage injury was added, synovitis intensified, numerous large osteophytes appeared, and CD68-positive cells increased in the synovial membrane and osteophytes.

Infrapatellar (Hoffa) fat pad: This tissue is located intra-articularly but extrasynovially and serves as a local "bridge" between MS and the joint. Comparing tissues harvested from patients, the infrapatellar fat pad secreted more adiponectin, adipsin, IL-6, TNF-α\alphaα, and visfatin per unit weight compared to subcutaneous fat. In mice, a 20-week high-fat diet resulted in obesity, impaired glucose tolerance, and early OA (osteophytes, doubling of the "tidemark" line). This showed that profibrotic remodeling without M1 polarization developed in the infrapatellar fat pad prior to cartilage damage.

In humans, following total knee replacement in active gonarthrosis patients in the MS group, the histological score of OA severity for cartilage and fat pad was higher compared to the non-MS group ($p<0.05p<0.05p<0.05$). The histological grade of the fat pad positively correlated with the cartilage grade. Levels of IL-17 and advanced oxidation protein products (AOPP) were also associated with histological severity. Changes in the fat pad were anatomically stratified: inflammation factors and immune cell infiltration were greater in the part facing the synovium. At the same time, in one study, high BMI was not associated with changes in immune cell number or phenotype in the fat pad. This indicates that the condition of the fat pad is determined not just by weight, but more so by metabolic disorders.

Subchondral bone and microvessels: Arterial hypertension is linked to OA via subchondral ischemia. Ischemia impairs nutrient delivery to cartilage and triggers bone remodeling. High BP increases intraosseous pressure and hypoxia, resulting in remodeling of the subchondral bone and osteochondral junction. Stasis, hypercoagulation, and microemboli in small vessels can lead to subchondral ischemia. Ischemia, in turn, weakens the bone foundation of cartilage through osteocyte death and bone resorption.

Chondrocytes: Dyslipidemia causes ectopic lipid accumulation in chondrocytes. In hyperglycemia, advanced glycation end products (AGEs) accumulate in cartilage, intensifying inflammation and catabolism through RAGE receptors in chondrocytes and synovial cells. When comparing cartilage obtained during joint replacement from patients with and without type 2 DM, the

high-glucose environment increased the inflammatory activity of chondrocytes. In isolated hypertension, hypertrophic differentiation of chondrocytes, cartilage destruction, and loss of cambial cells were determined. Meanwhile, a high-fat diet manifested as increased expression of the endoplasmic reticulum stress marker CHOP and enhanced chondrocyte apoptosis.

Sequence of morphological changes: Based on the analyzed data, the sequence of changes was summarized in Table 6.

Sequence of morphological changes in knee joint tissues in gonarthrosis against the background of MS

Table 6.

Stage	Tissue	Main morphological and immunohistochemical features
I. Earliest	Synovial membrane	Thickening of the synoviocyte layer, infiltration of CD68+ macrophages, predominance of M1 phenotype
I. Earliest	Infrapatellar fat pad	Profibrotic remodeling, enlargement of adipocytes, later inflammatory infiltrate
II. Early	Microvessels, subchondral bone	Ischemia, increased intraosseous pressure, osteocyte death, bone marrow edema, remodeling
III. Intermediate	Chondrocytes	Lipid accumulation, AGE accumulation, hypertrophy, apoptosis via CHOP
IV. Late	Hyaline cartilage	Fibrillation, loss of proteoglycans, chondrocyte clusters, tidemark duplication
IV. Late	Bone and joint margins	Subchondral sclerosis, cysts, large osteophytes

Morphological state after correction: In repeated arthroscopy performed 18 months after high tibial osteotomy, partial or complete coverage of femorotibial joint surfaces with fibrocartilage was observed in 55% of cases, while only dotted white fibrocartilage was recorded in 34%.

Cartilage regeneration after osteotomy depends on age, sex, BMI, and postoperative leg axis. In one study, multivariate analysis showed that low BMI is associated with better regeneration. In a high-fat diet experiment, weight loss did not reverse the histopathological features of OA during the studied period. Thus, morphological changes formed against the background of MS may persist long after correction.

Discussion

Women as the main risk group for gonarthrosis against the background of MS. The main finding of this analysis is that the association between MS and gonarthrosis is sex-dependent. In the meta-analysis of prospective cohorts, MS was not an independent risk factor in the general population after adjusting for BMI (RR 1.06). However, the risk increased reliably in women (RR 1.23). This difference can be explained by the greater mechanical load on the knee joint in women, smaller cartilage volume, and faster rate of cartilage loss. Sex hormones also play an important role, but their interaction with knee OA is complex and not yet fully understood.

The significance of this result for the Khorezm region is substantial. In Uzbekistan, 55.4% of women have abdominal obesity. Consequently, every second woman in the region enters the potential risk group for gonarthrosis against the background of MS. This conclusion is also supported by the fact that obesity (49%) and type 2 DM (13.7%) are more frequent in hypertensive women in the Aral Sea region compared to men.

MS as a risk factor for severe gonarthrosis. In the meta-analysis, MS was independently associated with the risk of severe knee OA requiring joint replacement (RR 1.16), but not with symptomatic OA. This indicates that MS affects the rapid progression of the disease rather than its onset. Morphological data also confirm this: the presence of MS in patients with advanced gonarthrosis was accompanied by more severe histological changes in the cartilage and fat pad.

In the experiment, a high-fat diet alone had almost no effect on cartilage. However, when combined with mechanical injury, OA symptoms clearly accelerated. This aligns with the "two-hit" hypothesis: the metabolic background prepares the joint for inflammation, while the mechanical factor initiates destruction.

"Outside-in" rather than "inside-out" model. According to traditional understanding, OA begins in the cartilage and then spreads to other tissues. In gonarthrosis against the background of MS, however, morphological changes develop largely in the reverse direction. Synovitis and changes in the fat pad appear before cartilage degradation. Systemic metabolic disorders shift macrophages toward the M1 phenotype. This process occurs through alterations in the activity of cellular nutrient sensors such as AMPK and mTORC1. Cytokines and adipokines secreted by the inflamed synovium and fat pad affect the cartilage via synovial fluid.

There are contradictions in the literature regarding the role of the infrapatellar fat pad. In some works, it is described as a focus of inflammation. In others, fibrosis predominated in the early stages rather than classic inflammation. In humans, BMI was not associated with immune cells in the fat

pad. These contradictions can be explained by differences in disease stages and metabolic status. Therefore, in future studies, stratification by MS components rather than BMI is important.

Vascular factor and Khorezm conditions. The most important regional feature for the Khorezm region is the high prevalence of salt-sensitive hypertension. A high salt taste sensitivity threshold was determined in 85.6% of hypertensive patients in the Aral Sea region. This indicator is higher even compared to hypertensive patients in Tashkent city (61.9%) [8]. The study authors associate this with the drying of the Aral Sea, salt-dust storms, and saline drinking water. Hypertension is significant in OA pathogenesis via impaired subchondral perfusion, increased intraosseous pressure, and hypoxia. Systemic activation of the renin-angiotensin and endothelin systems affects the Wnt-β\betaβ-catenin signaling pathway in the joint.

Thus, under Khorezm conditions, hypertension may be the main regional "amplifier" of gonarthrosis against the background of MS. There is also indirect evidence confirming this hypothesis. In 92% of hypertensive patients in the Aral Sea region, carotid artery intima-media thickness is increased. If systemic vascular remodeling is so widespread, subchondral microvessels of the knee joint are also likely to be damaged. Nevertheless, morphological or MRI examinations of the subchondral bone have not been conducted in the population of Khorezm, so this opinion remains a hypothesis for now.

Drinking water and mineral metabolism. Deterioration of drinking water quality in terms of hardness, mineralization, sulfates, and chlorides has been recorded in Khorezm and Karakalpakstan. There are also data that underground drinking water in Bukhara, Khorezm, and Karakalpakstan does not meet standards. There is no scientific evidence on the direct effect of mineralized water on knee OA. However, it may indirectly affect the joint through its impact on hypertension and renal function. Glomerular filtration rate was below 60 ml/min/1.73m21.73 m^21.73m2 in 24.1% of hypertensive patients in the Aral Sea region.

Impact on correction results. Regenerated cartilage after osteotomy mainly consists of fibrocartilage. BMI affects the degree of regeneration. Against the background of MS, synovial inflammation and fibrosis in the fat pad may persist even after surgery. In the experiment, histopathological changes did not reverse even after weight reduction. For women in Khorezm, this situation means that surgical correction must be carried out in conjunction with controlling the metabolic state. This includes weight reduction, blood pressure control, restricting salt intake, and stabilizing glycemia.

Recommended Indicators for a Clinical-Morphological Study to be Conducted in the Khorezm Region

Based on the analysis, it is advisable to collect data on the following indicators when studying gonarthrosis against the background of MS in the region (Table 7).

Recommended indicators for clinical-morphological study in the Khorezm region

Table 7.

Direction	Indicators	Note
Metabolic	Waist circumference, BMI, BP, triglycerides, HDL, fasting glucose, HbA1c	Assessing MS according to ATP III and IDF criteria
Regional	Salt taste sensitivity threshold (Henkin method), source of drinking water, place of residence (district)	Taking Aral Sea factors into account
Gynecological	Menopausal status and duration, number of births	Sex-specific factors
Clinical	Kellgren–Lawrence grade, WOMAC, VAS, leg axis	Disease severity
Morphological	Synovium (Krenn scale), infrapatellar fat pad, cartilage (OARSI scale), subchondral bone	In operation material
Immunohistochemical	CD68, CD86 (M1), CD206 (M2), MMP-13, RAGE/AGE	Inflammation and catabolism

Study Limitations

First, the sequence of morphological changes has been demonstrated mainly in animal models. In humans, tissue samples are usually obtained only in the late stages of the disease during surgery. Second, all cohorts included in the meta-analysis were conducted in Western countries and mainly included populations of European descent. The authors themselves emphasized the need to study this association in Asian populations as well. Third, data for the Khorezm region were mainly summarized from studies on the Aral Sea region and do not directly pertain to gonarthrosis. Fourth, evidence regarding the individual effects of MS components is contradictory.

Conclusions

1. According to prospective cohort data, metabolic syndrome independently of BMI increases the risk of knee osteoarthritis in women by 23% (RR 1.23), and the risk of severe gonarthrosis requiring joint replacement in the general population by 16% (RR 1.16). Consequently, women with MS are the highest-risk group for gonarthrosis.

2. Risk factors for gonarthrosis against the background of MS are widespread among women in the Khorezm region. In Uzbekistan, 55.4% of women have abdominal obesity. In the Aral Sea region, women account for 61.4% of hypertensive patients, and type 2 DM is twice as common in them compared to men.

3. Region-specific factors include salt-sensitive hypertension (85.6%), saline groundwater and mineralized drinking water, salt-dust storms, and hypodynamia (67.5%). These factors may contribute to the acceleration of gonarthrosis via subchondral ischemia and systemic inflammation.

4. Morphological changes in gonarthrosis against the background of MS develop in an "outside-in" direction. The earliest changes appear in the synovial membrane (M1 macrophage infiltration, synovitis) and infrapatellar fat pad (fibrosis, adipokine secretion). Then subchondral ischemia and remodeling, lipid and AGE accumulation in chondrocytes, and apoptosis are added. In the final stage, hyaline cartilage destruction, sclerosis, and large osteophytes are formed.

5. After correction, cartilage is restored mainly with fibrocartilage, and the degree of regeneration depends on BMI. Morphological changes formed against the background of MS may persist for a long time even after metabolic status improves.

REFERENCES

1. Nie D., Yan G., Zhou W. et al. Metabolic syndrome and the incidence of knee osteoarthritis: a meta-analysis of prospective cohort studies // PLoS One. 2020. Vol. 15(12). e0243576.

2. Wang H., Cheng Y., Shao D. et al. Metabolic syndrome increases the risk for knee osteoarthritis: a meta-analysis // Evid Based Complement Alternat Med. 2016. 7242478.

3. Courties A., Sellam J., Berenbaum F. Metabolic syndrome-associated osteoarthritis // Curr Opin Rheumatol. 2017. Vol. 29(2). P. 214–222.

4. Dickson B.M., Roelofs A.J., Rochford J.J. et al. The burden of metabolic syndrome on osteoarthritic joints // Arthritis Res Ther. 2019. Vol. 21. 289.

5. Yu C., Zhao S., Yue S. et al. Novel insights into the role of metabolic disorder in osteoarthritis // Front Endocrinol. 2024. 1488481.

6. Minaković I., Zvekić-Svorcan J., Smuđa M. et al. Metabolic dysregulation in postmenopause: implications for knee joint health // J Clin Med. 2025. Vol. 14(18). 6442.

7. Ministry of Health of the Republic of Uzbekistan, WHO. STEPS: Prevalence of noncommunicable disease risk factors in the Republic of Uzbekistan, 2019.

8. Fozilov X.G., Ataniyazov X.X., Xamidullayeva G.A. i dr. Ranneye viyavleniye i kontrol faktorov riska serdechno-sosudistix zabolevaniy v Priaralye: opit Uzbekistana // Kardiologiya. 2024. T. 64(1). S. 37–43.

9. Hygienic assessment of the conditions of water use of the population of the Aral region // CyberLeninka.

10. Ibrakhimov M., Martius C., Lamers J., Tischbein B. The dynamics of groundwater table and salinity over 17 years in Khorezm // Agricultural Water Management. 2011. Vol. 101(1). P. 52–61.

11. Sun A.R., Panchal S.K., Friis T. et al. Obesity-associated metabolic syndrome spontaneously induces infiltration of pro-inflammatory macrophage in synovium and promotes osteoarthritis // PLoS One. 2017. Vol. 12(8). e0183693.

12. Metabolic dysregulation accelerates injury-induced joint degeneration, driven by local inflammation; an in vivo rat study (UMC Utrecht).

13. Barboza E., Hudson J., Chang W.P. et al. Pro-fibrotic infrapatellar fat pad remodeling without M1-macrophage polarization precedes knee osteoarthritis in diet-induced obese mice // Endocrinology. 2017.

14. Inflammatory gradients in the infrapatellar fat pad of knee osteoarthritis: implications for joint damage.

15. Correlation of radiographic and histopathological changes with IL-17 and advanced oxidation protein products in knee osteoarthritic individuals with metabolic syndrome // Innov Surg Sci.

16. de Jong A.J. Immunometabolism in osteoarthritis: PhD thesis. Leiden University.

17. Ching K., Houard X., Berenbaum F., Wen C. Hypertension meets osteoarthritis — revisiting the vascular aetiology hypothesis // Nat Rev Rheumatol. 2021. Vol. 17(9). P. 533–549.

18. Zhuo Q., Yang W., Chen J., Wang Y. Metabolic syndrome meets osteoarthritis // Nat Rev Rheumatol. 2012. Vol. 8. P. 729–737.

19. Davies-Tuck M.L., Hanna F., Davis S.R. et al. Total cholesterol and triglycerides are associated with the development of new bone marrow lesions in asymptomatic middle-aged women // Arthritis Res Ther. 2009.

20. Laiguillon M.C., Courties A., Houard X. et al. Characterization of diabetic osteoarthritic cartilage and role of high glucose environment on chondrocyte activation // Osteoarthritis Cartilage. 2015. Vol. 23(9). P. 1513–1522.

21. Mendes A.F., Rosa S.C., Rufino A.T. et al. Diabetes-induced osteoarthritis: role of hyperglycemia in joint destruction // BMC Musculoskelet Disord. 2015. Vol. 16(Suppl 1). S1.

22. Ding C., Yimiti D., Sanada Y. et al. High-fat diet-induced obesity accelerates the progression of spontaneous osteoarthritis in senescence-accelerated mouse prone 8 // Mod Rheumatol. 2024. Vol. 34(4). P. 831.

23. Vliyaniye arterialnoy gipertenzii i giperlipidemii na remodelirovaniye sustavnogo xryasha i razvitiye osteoartroza (eksperimentalnoye issledovaniye) // Uspexi gerontologii. 2019. T. 32(4). S. 550–557.

24. Kanamiya T., Naito M., Hara M., Yoshimura I. The influences of biomechanical factors on cartilage regeneration after high tibial osteotomy for knees with medial compartment osteoarthritis // Arthroscopy. 2002. Vol. 18(7). P. 725–729.

25. Impact of the weightbearing line on cartilage regeneration of the medial knee compartment after open-wedge high tibial osteotomy, based on second-look arthroscopy // Cartilage.

26. Factors affecting articular cartilage regeneration after medial open-wedge high tibial osteotomy.

27. Effects of diet induced weight reduction on cartilage pathology and inflammatory mediators in the joint tissues // Front Med. 2021. 628843.

28. GBD 2021 Osteoarthritis Collaborators. Global, regional, and national burden of osteoarthritis, 1990–2020 and projections to 2050 // Lancet Rheumatol. 2023.

29. Khor A., Ma C.A., Hong C. et al. Diabetes mellitus is not a risk factor for osteoarthritis // RMD Open. 2020. Vol. 6(1).

30. Zhang Y.M., Wang J., Liu X.G. Association between hypertension and risk of knee osteoarthritis: a meta-analysis of observational studies // Medicine (Baltimore). 2017. Vol. 96(32). e7584.

31. Xiong J., Long J., Chen X. et al. Dyslipidemia might be associated with an increased risk of osteoarthritis // Biomed Res Int. 2020. 3105248.

32. Hanna F.S., Teichtahl A.J., Wluka A.E. et al. Women have increased rates of cartilage loss and progression of cartilage defects at the knee than men // Menopause. 2009. Vol. 16(4). P. 666–670.